

# **MEMBRANOUS NEPHROPATHY**

**No longer 'idiopathic' but  
how should it be managed?**

**John Feehally**

# MANAGEMENT OF MEMBRANOUS NEPHROPATHY

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**Definitions**

**Aetiology & Pathogenesis**

**Predicting prognosis**

**Choosing therapy**

# MANAGEMENT OF MEMBRANOUS NEPHROPATHY

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**Definitions**

**Aetiology & Pathogenesis**

**Predicting prognosis**

**Choosing therapy**

# DEFINING MEMBRANOUS NEPHROPATHY

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**Histopathology**



**Clinical**



**Immune  
mechanisms**

# DEFINING MEMBRANOUS NEPHROPATHY

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**Histopathology**



**Clinical**

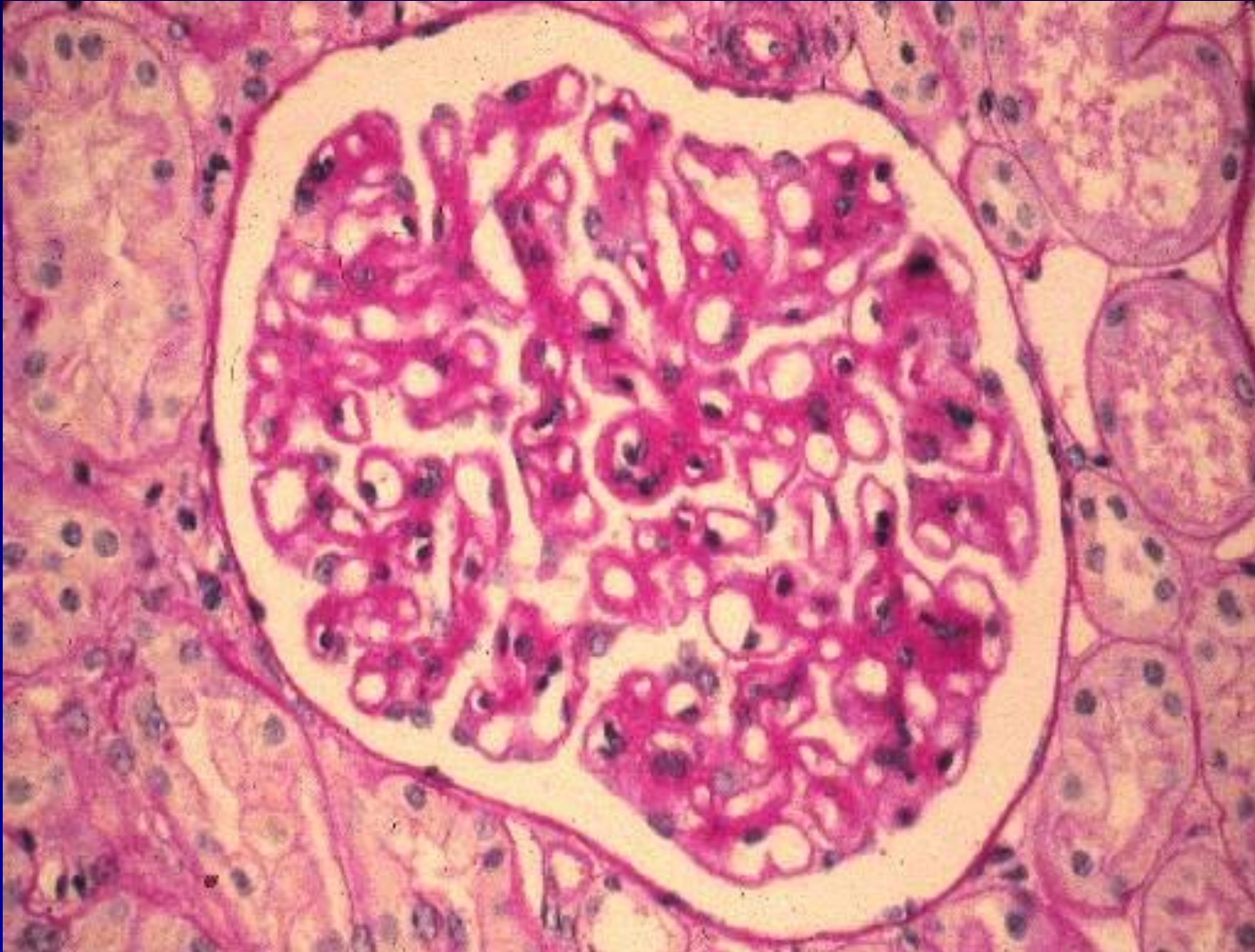


**Immune  
mechanisms**



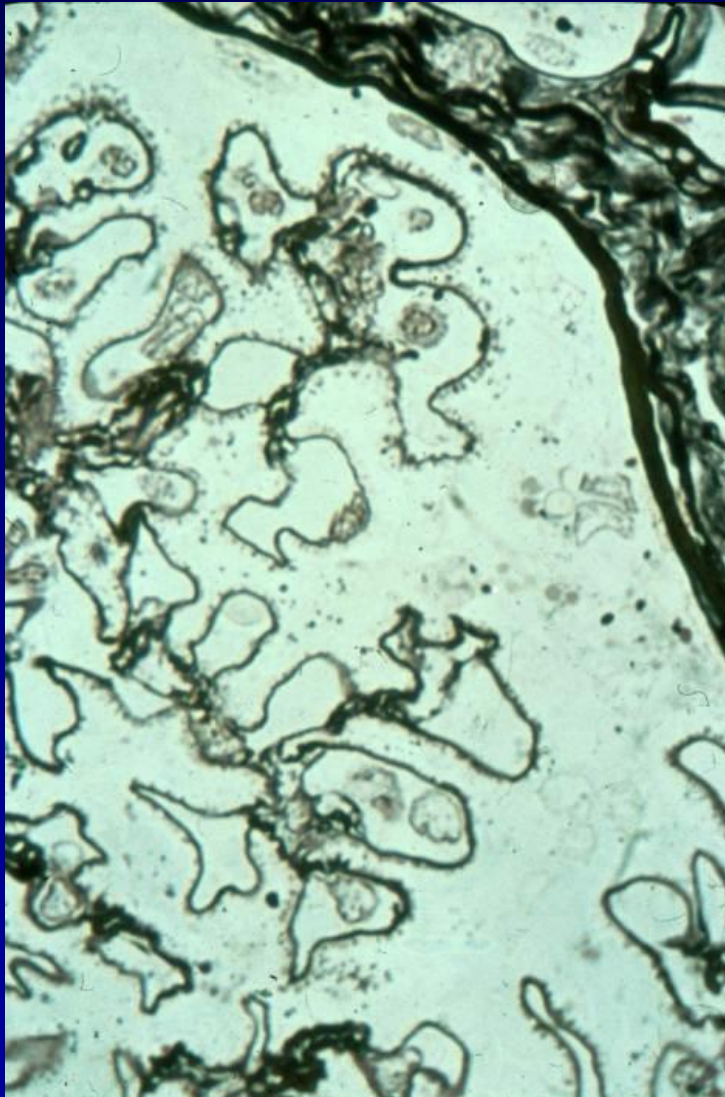
# MEMBRANOUS NEPHROPATHY

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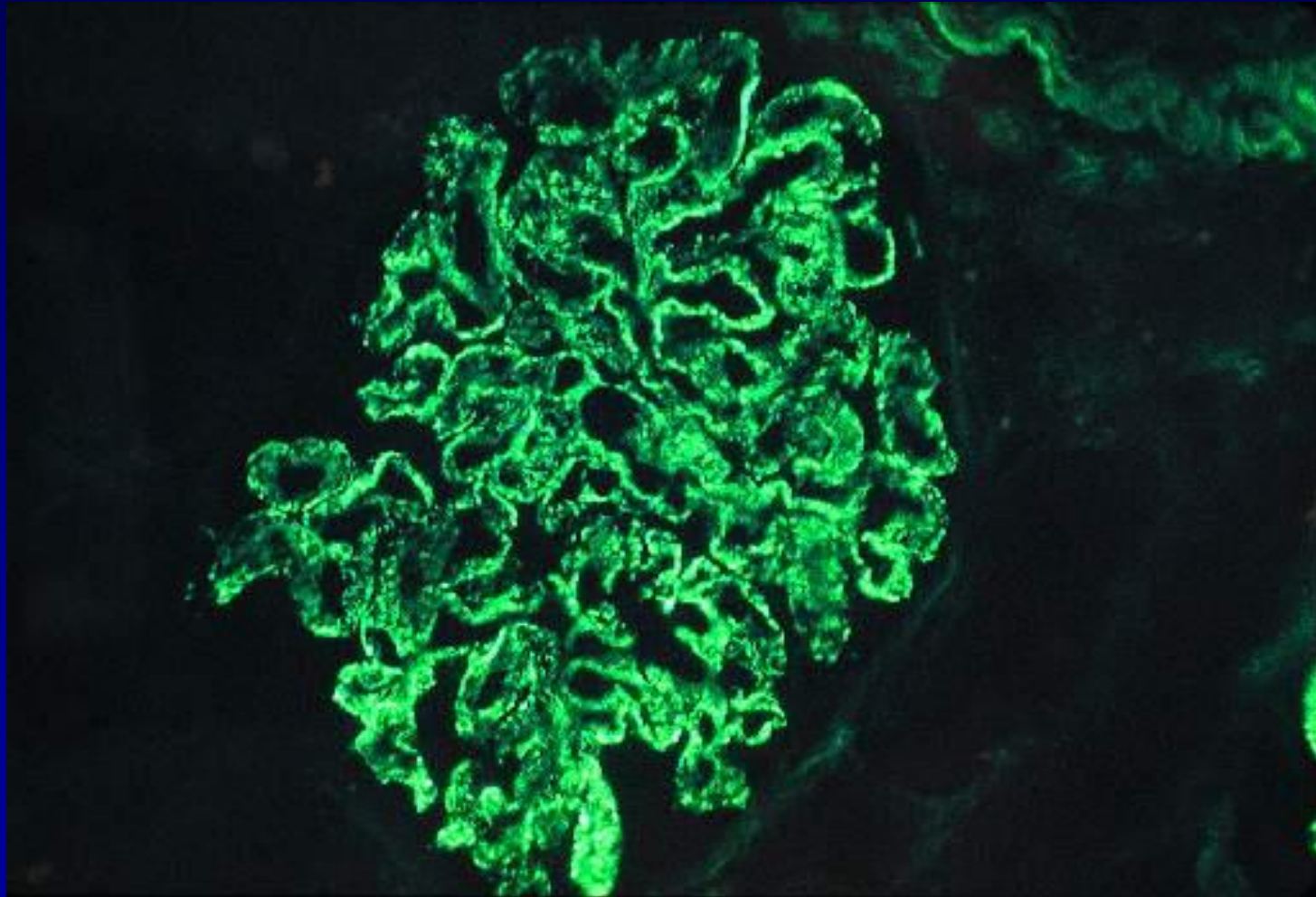
# MEMBRANOUS NEPHROPATHY

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# MEMBRANOUS NEPHROPATHY

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**Electron-dense  
deposits  
on the subepithelial  
aspect of a thickened  
GBM**

# DEFINING MEMBRANOUS NEPHROPATHY

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Histopathology

Clinical

Immune  
mechanisms

**'Pattern' *not* 'disease'**

# DEFINING MEMBRANOUS NEPHROPATHY

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**Histopathology**

**Clinical**

**Immune  
mechanisms**

*Usually*  
**nephrotic syndrome**

**'Pattern' not 'disease'**

# MANAGEMENT OF MEMBRANOUS NEPHROPATHY

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**Definitions**

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# MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE ?

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**Idiopathic**

**Secondary**

Immune disease

Infection

Drugs

Malignancy

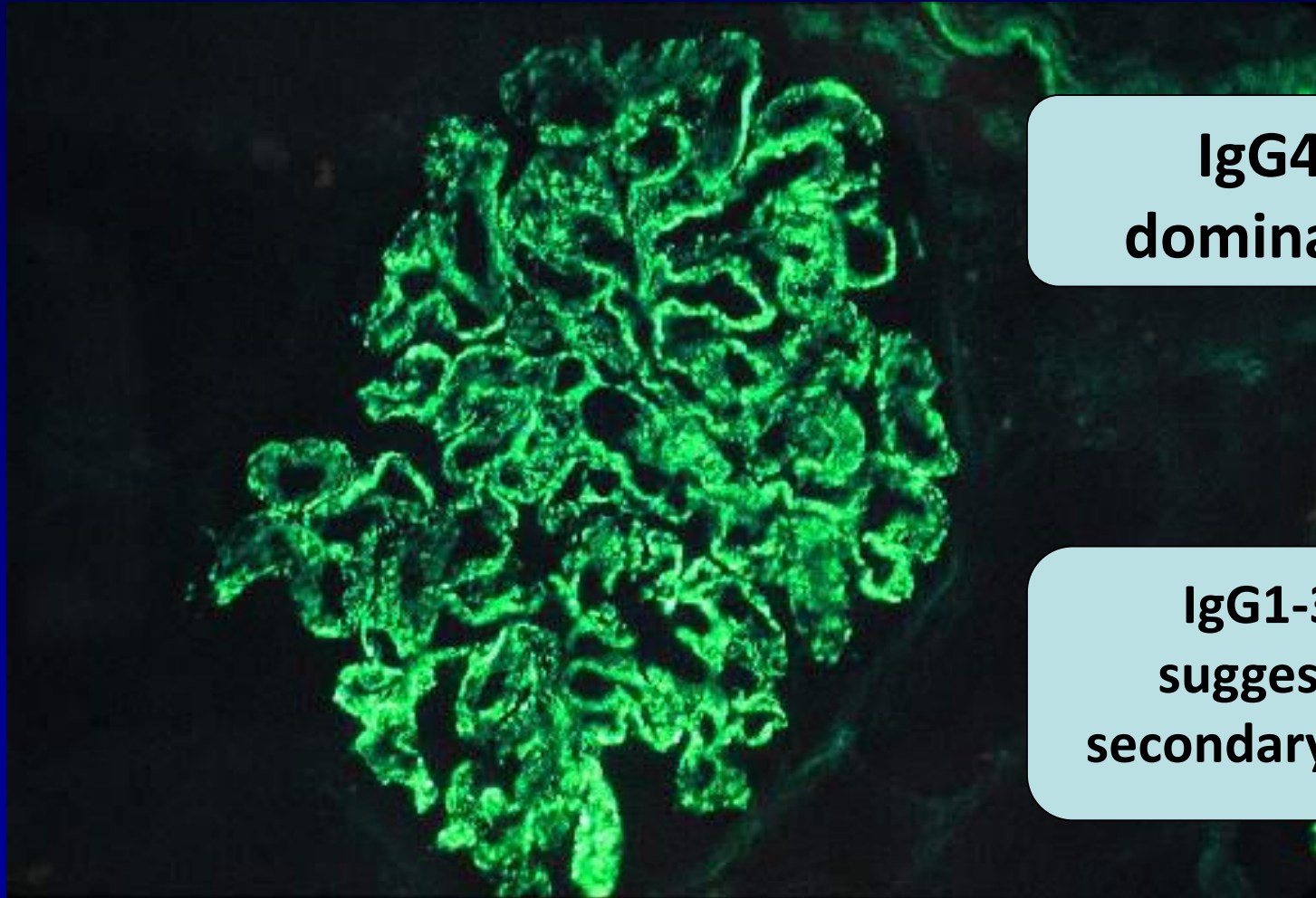
# Aetiology of Secondary Membranous Nephropathy

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Common	Uncommon
<b>IMMUNE DISEASE</b> Systemic lupus	Rheumatoid arthritis Sarcoidosis
<b>INFECTION</b> HBV HCV	Malaria, leprosy, filariasis, schistosomiasis
<b>DRUGS</b> Gold Penicillamine	Mercury, Captopril
<b>OTHER</b> Solid organ malignancies Transplant <i>de novo or recurrent</i>	Sickle cell disease

# MEMBRANOUS NEPHROPATHY

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**IgG4  
dominant**

**IgG1-3  
suggests  
secondary MN**

# DEFINING MEMBRANOUS NEPHROPATHY

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**Histopathology**



**'Pattern' not 'disease'**

**Clinical**



*Usually*  
**nephrotic syndrome**

**Immune  
mechanisms**



**The podocyte is the  
target, *but* what is the  
antigen?**

# MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE ?

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## **Idiopathic**

Diagnosis  
by exclusion

## **Secondary**

Infection

Drugs

Malignancy

# MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE ?

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**Idiopathic**

Diagnosis  
by exclusion

**Antigen unknown**

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graph TD; A[Antigen unknown] --> B[Idiopathic  
Diagnosis by exclusion]; C[Secondary  
Infection  
Drugs  
Malignancy];
```

**Secondary**

Infection

Drugs

Malignancy

# MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE ?

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**Idiopathic**

Diagnosis  
by exclusion

~~Antigen unknown~~

**Secondary**

Infection

Drugs

Malignancy

# MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE ?

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**Idiopathic**

Diagnosis  
by exclusion

**2009**

**~ 70 %  
PLA2 receptor**

**Secondary**

Infection

Drugs

Malignancy

# PLA2R and the pathogenesis of membranous nephropathy

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## TWO SEMINAL OBSERVATIONS

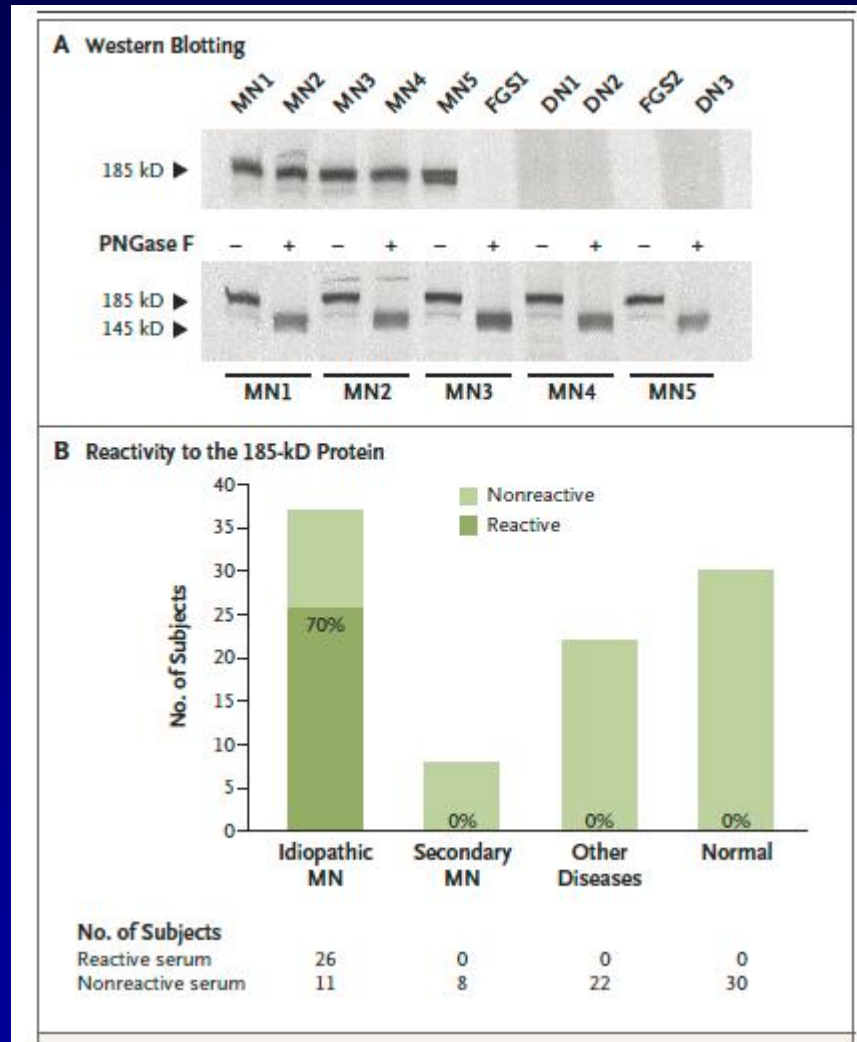
# PLA2R and the pathogenesis of membranous nephropathy

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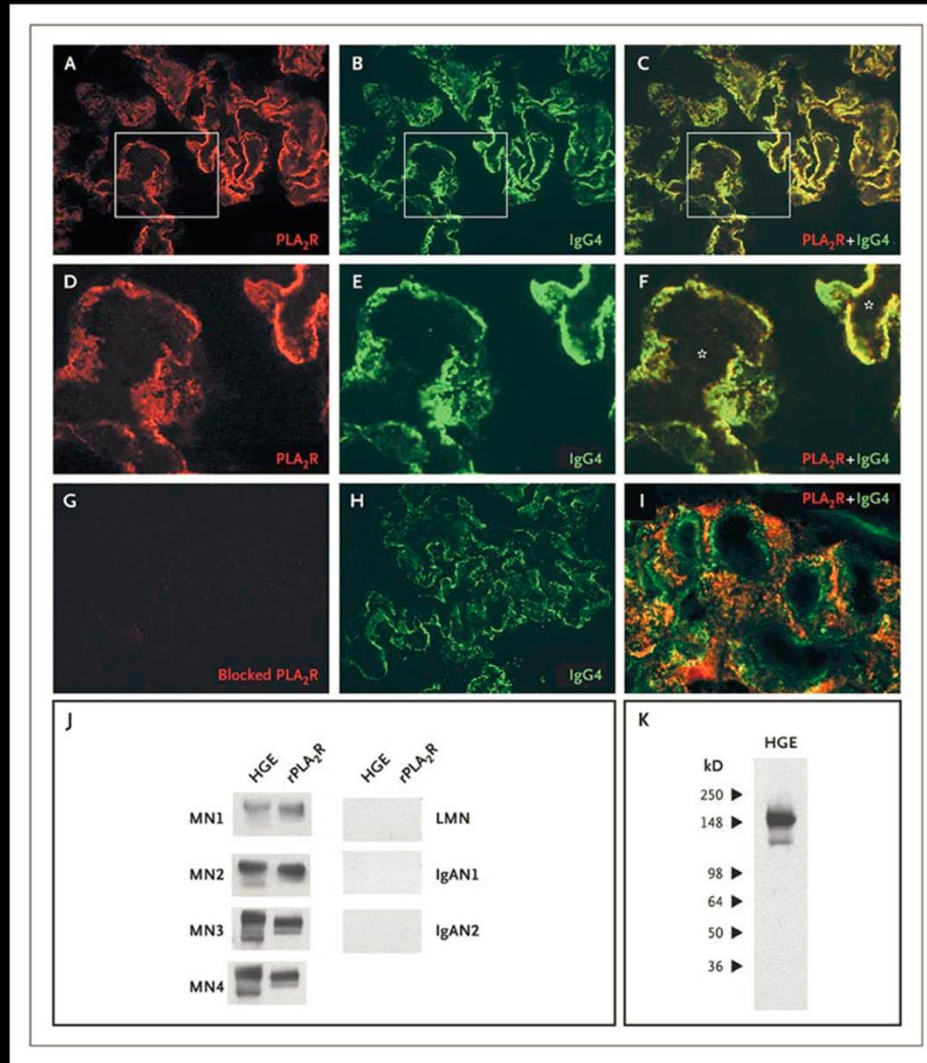
## TWO SEMINAL OBSERVATIONS

**PLA2R (M-type Phospholipase A2 Receptor)  
is the target autoantigen in MN**

# M-type PLA2 Receptor as the Target Antigen in Idiopathic Membranous Nephropathy



# Colocalization of the M-Type Phospholipase A<sub>2</sub> Receptor (PLA<sub>2</sub>R) and IgG4 and Reactivity of Eluted IgG4



Beck LH Jr et al. N Engl J Med 2009;361:11-21



The NEW ENGLAND  
JOURNAL of MEDICINE

# PLA2R and the pathogenesis of membranous nephropathy

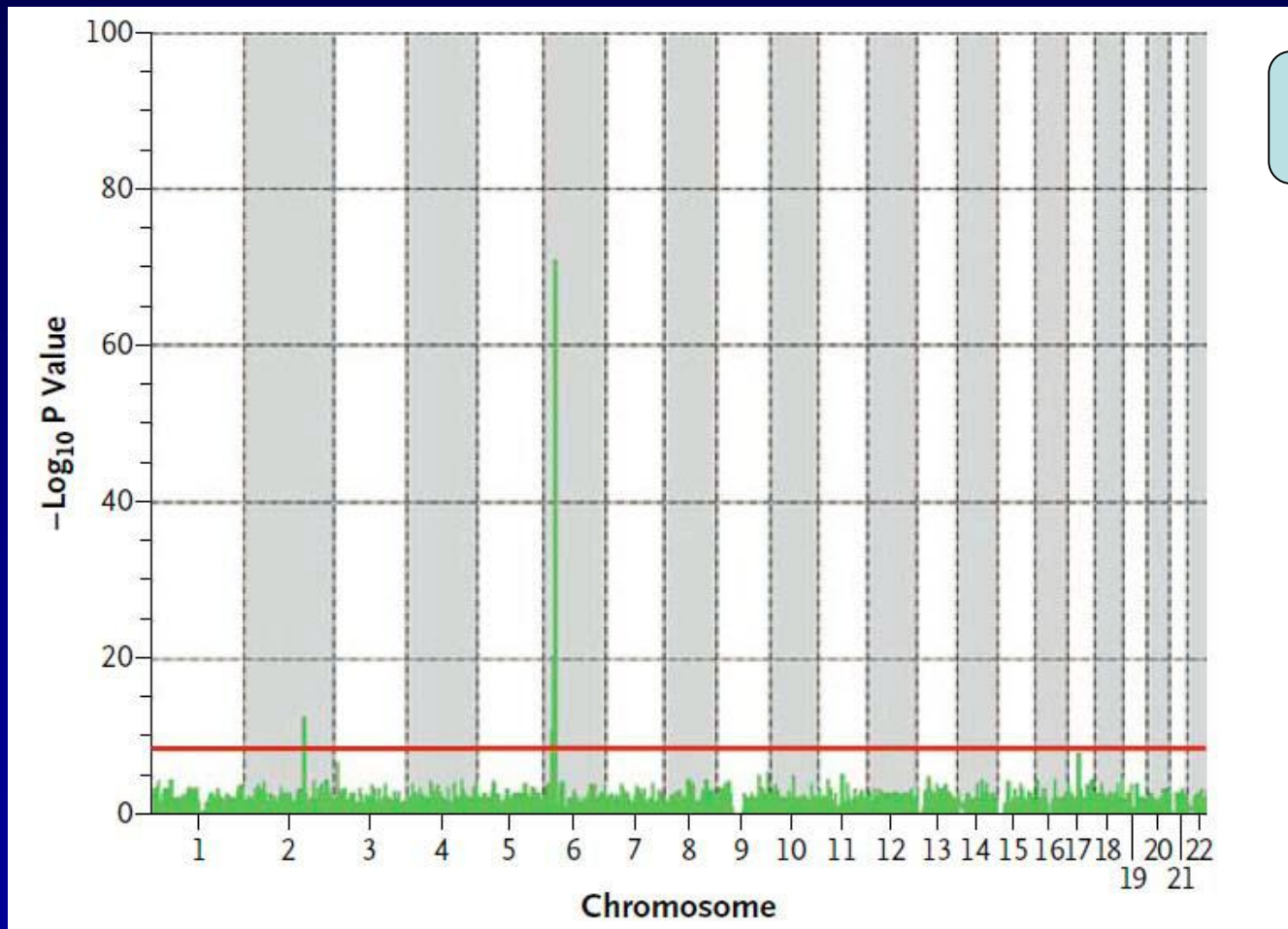
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## TWO SEMINAL OBSERVATIONS

**PLA2R** (M-type Phospholipase A2 Receptor)  
is the target autoantigen in MN

**HLA DQ1 & PLA2R1**  
are the two risk alleles

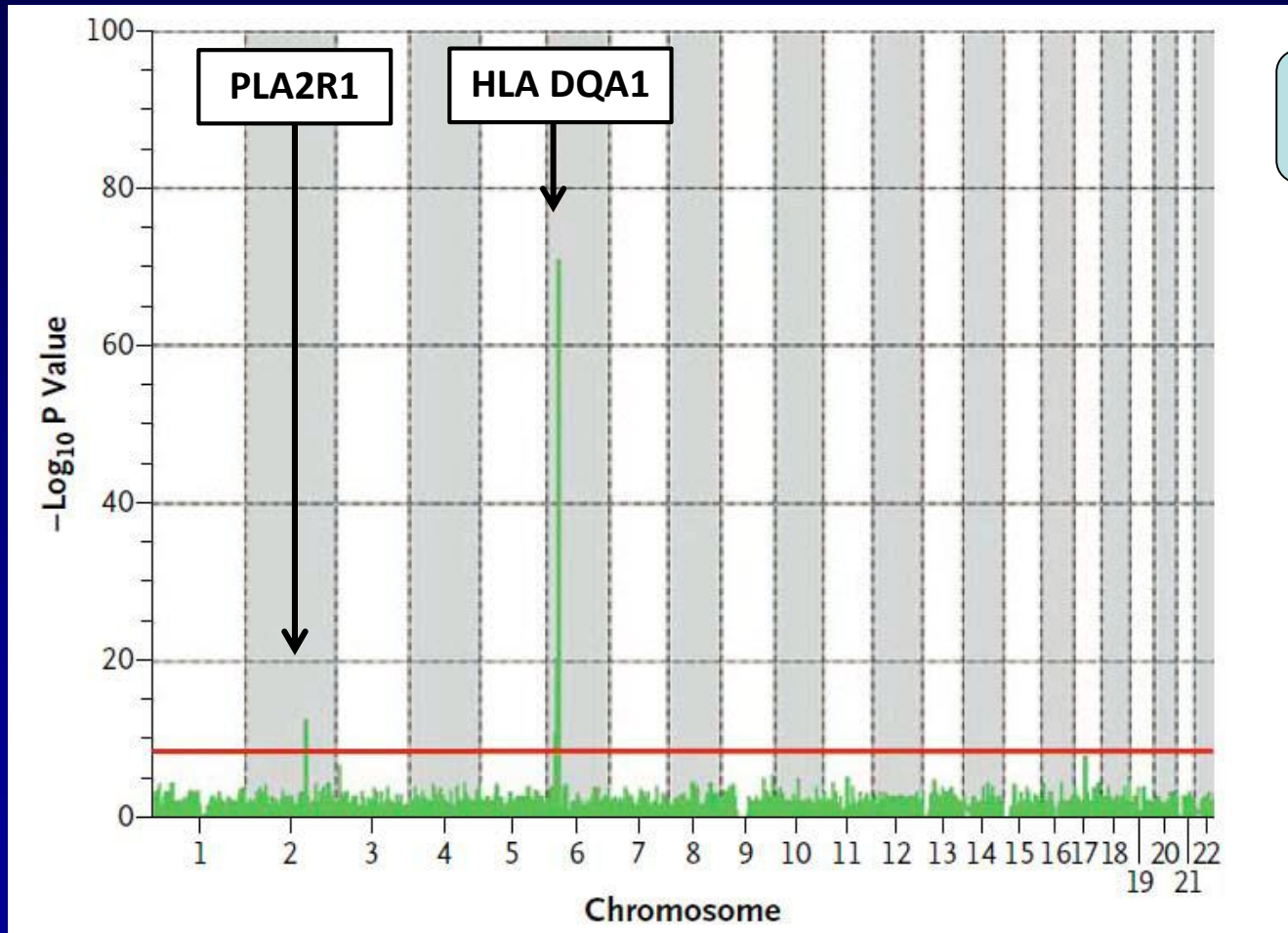
# Manhattan Plot for GWAS for Idiopathic Membranous Nephropathy



556  
cases



# Manhattan Plot for GWAS for Idiopathic Membranous Nephropathy



556 cases



## Odds ratios for Idiopathic Membranous Nephropathy according to SNP & genotype combinations

**Table 3.** Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism (SNP) and Genotype Combinations.\*

SNP rs2187668 (HLA-DQA1)	SNP rs4664308 (PLA2R1)		
	GG	GA	AA
GG			
No. of cases/total no. of subjects	14/354	79/944	97/659
Odds ratio (95% CI)	1.00	2.22 (1.24–3.97)	4.19 (2.36–7.46)
GA			
No. of cases/total no. of subjects	23/115	94/363	178/348
Odds ratio (95% CI)	6.07 (3.01–12.27)	8.49 (4.73–15.22)	25.43 (14.32–45.16)
AA			
No. of cases/total no. of subjects	5/11	23/41	42/55
Odds ratio (95% CI)	20.24 (5.51–74.38)	31.03 (13.72–70.19)	78.46 (34.55–178.17)

\* Persons who were homozygous for the low-risk allele (GG) constituted the reference category. Numbers of cases and total numbers of subjects are from the joint analysis. OR denotes odds ratio.



# MEMBRANOUS NEPHROPATHY – PATTERN OR DISEASE ?

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**Idiopathic**

Diagnosis  
by exclusion

**2009**

**70% - PLA2 Receptor**

**30% - ?**

**Secondary**

Infection

Drugs

Malignancy

# PLA2R is not the only antigen in membranous nephropathy

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- **Endogenous antigens**

- **Podocyte membrane (Primary)**

- PLA2R (70% of idiopathic MN)
- Neutral endopeptidase (NEP) (alloimmune MN in neonates)

- **Podocyte cytoplasm (Probably secondary intramolecular epitope spreading)**

- Superoxidase dismutase (SOD)
- Aldose reductase (AR)
- aEnolase

- **Exogenous antigens**

- **Cationic BSA (Debiec H *et al.* NEJM;364:2101, 2011)**
  - 4 Children <2.5 years old, Probably milk-derived

# Anti-PLA2R as a marker in 'idiopathic' MN

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# Anti-PLA2R as a marker in 'idiopathic' MN

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Is anti-PLA2R specific for 'idiopathic' MN?

# Is Anti-PLA2R specific for 'idiopathic' MN ?

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**8 published studies – 616 IMN**

**3 different methods: Indirect IF (259) ELISA (207) Western blot (150)**

Healthy controls	Other renal disease	'Idiopathic' MN Clinically active No immunosuppression	Secondary MN Tumours, lupus, viral infection
0/115 +ve	0/276 +ve	<b>72%</b>	<b>5 – 30%</b>

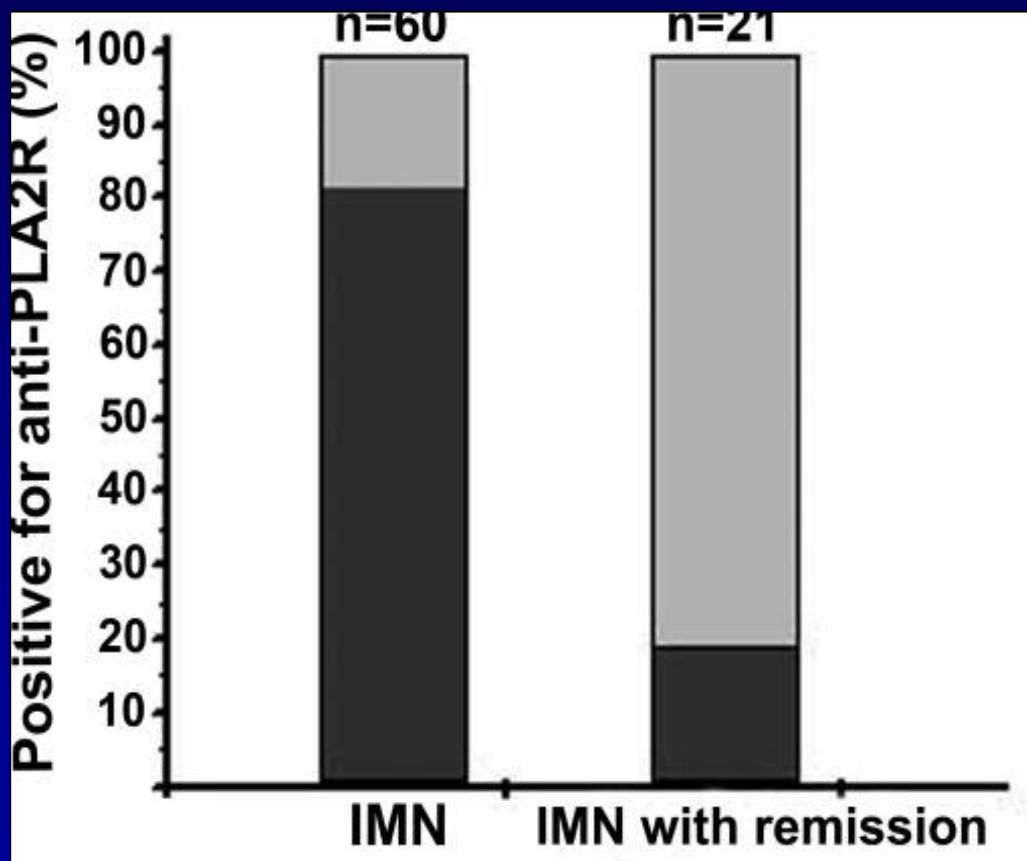
# Anti-PLA2R as a marker in 'idiopathic' MN

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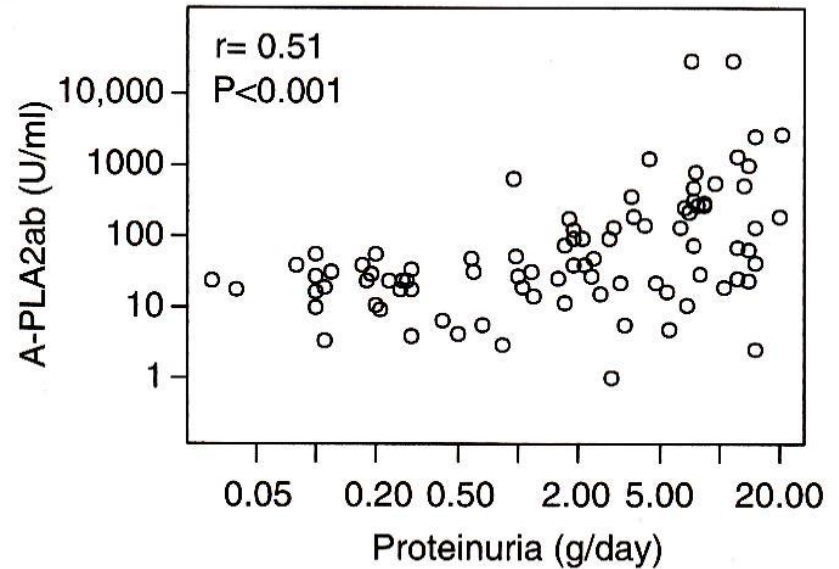
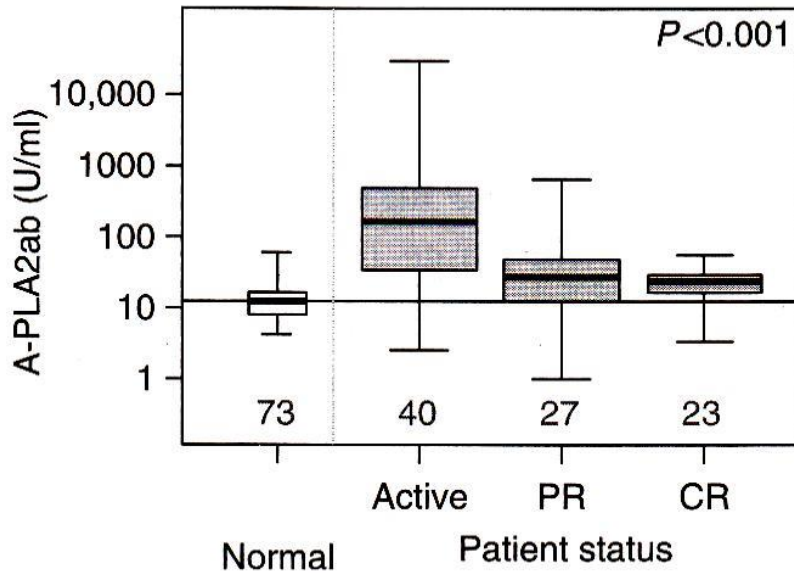
**Is anti-PLA2R specific for 'idiopathic' MN?**

**Does anti-PLA2R correlate with disease activity ?**

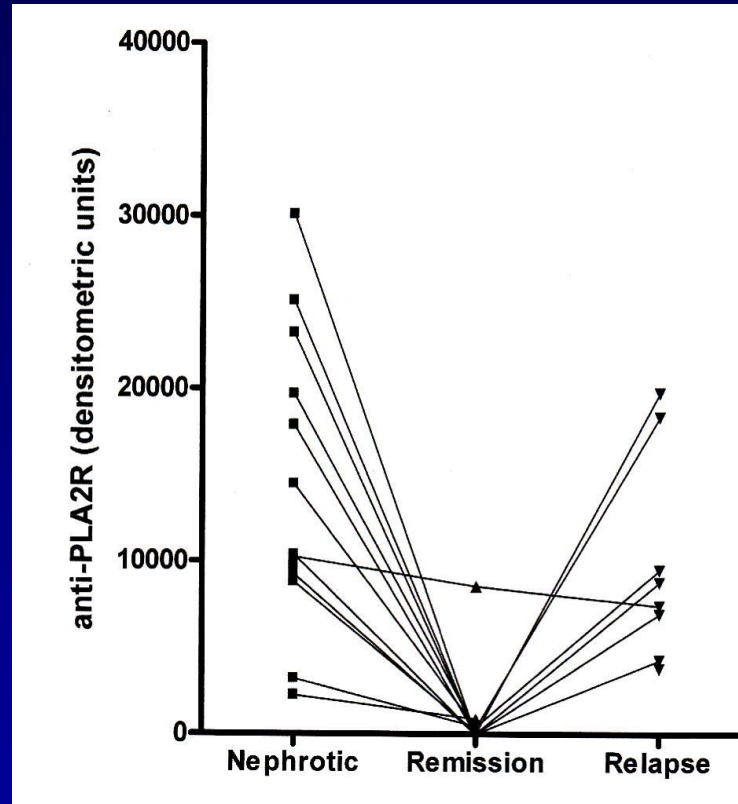
**Anti-PLA2R is elevated  
in membranous nephropathy with active disease  
and much lower or absent in remission**



# Anti-PLA2R antibodies & disease activity in Membranous Nephropathy



# Anti-PLA2R antibodies & disease activity in Membranous Nephropathy



# Anti-PLA2R as a marker in 'idiopathic' MN

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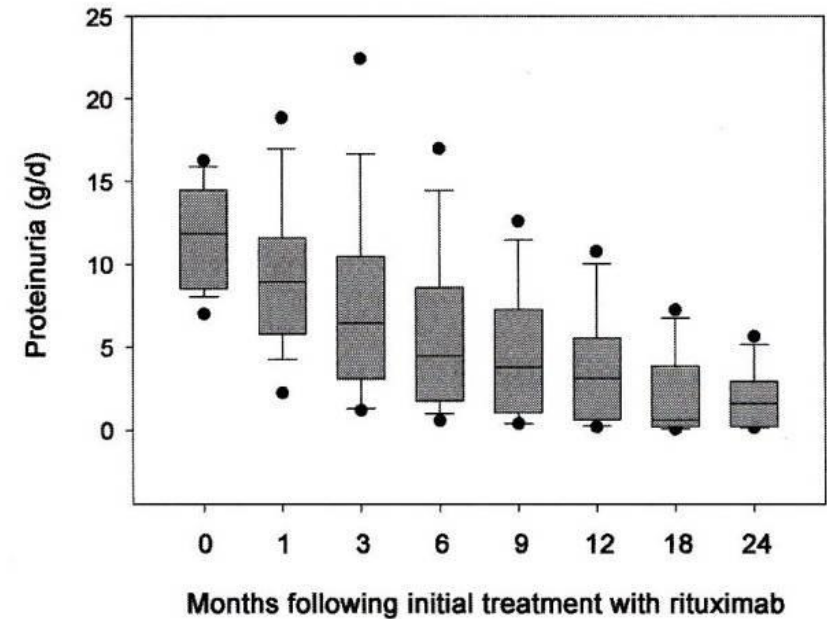
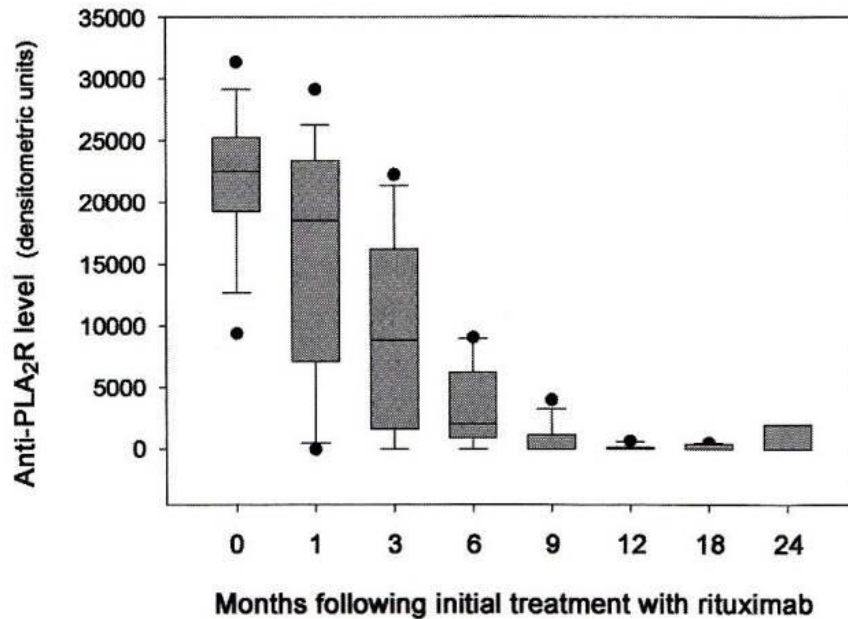
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**Does anti-PLA2R correlate with disease activity ?**

**What is the temporal association of anti-PLA2R & proteinuria in**

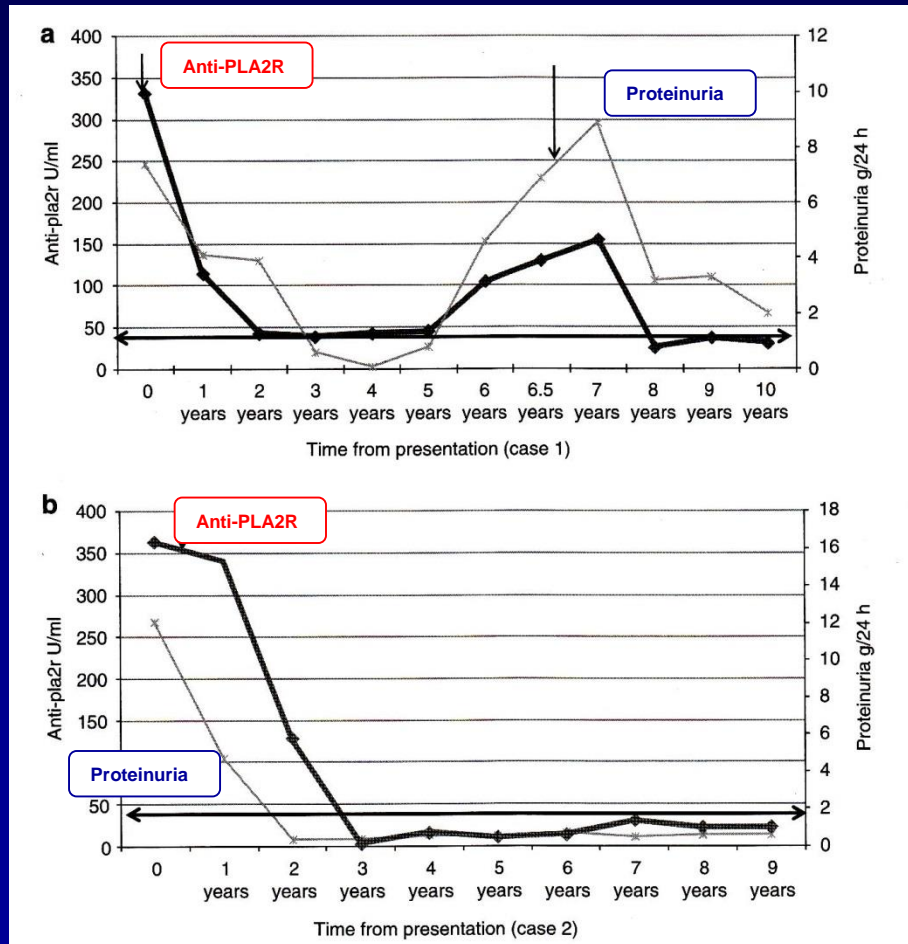
- spontaneous remission?
- therapeutic remission ?
  - relapse ?

# Rituximab-induced Depletion of anti-PLA2R Autoantibodies Predicts Response in Membranous Nephropathy



# Variable temporal relationship between anti-PLA2R antibodies & disease activity in Membranous Nephropathy

Cyclosporin x 2



Spontaneous remission

# Anti-PLA2R as a marker in 'idiopathic' MN

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**Is anti-PLA2R specific for 'idiopathic' MN?**

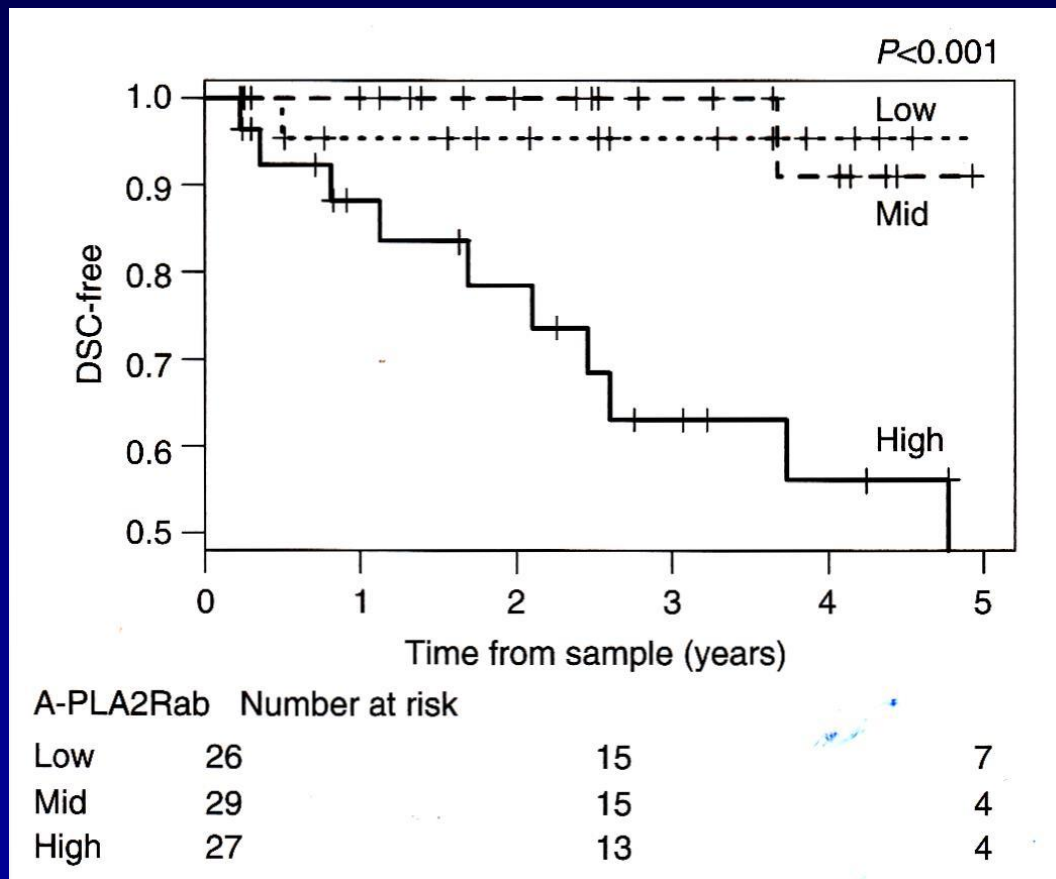
**Does anti-PLA2R correlate with disease activity ?**

**What is the temporal association of anti-PLA2R & proteinuria in**

- spontaneous remission?
- therapeutic remission ?
  - relapse ?

**Does anti-PLA2R correlate with clinical outcome ?**

# Anti-PLA2R levels & time to doubling of serum creatinine in membranous nephropathy



# Anti-PLA2R levels & outcome in membranous nephropathy

N = 79

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Anti-PLA2R levels *did not* predict:

Complete remission

Partial remission

Renal failure

Anti-PLA2R levels in lower tertile *did* predict:

Spontaneous remission

# Anti-PLA2R as a marker in 'idiopathic' MN

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**Is anti-PLA2R specific for 'idiopathic' MN?**

**Does anti-PLA2R correlate with disease activity ?**

**What is the temporal association of anti-PLA2R & proteinuria in**

- spontaneous remission?
- therapeutic remission ?
  - relapse ?

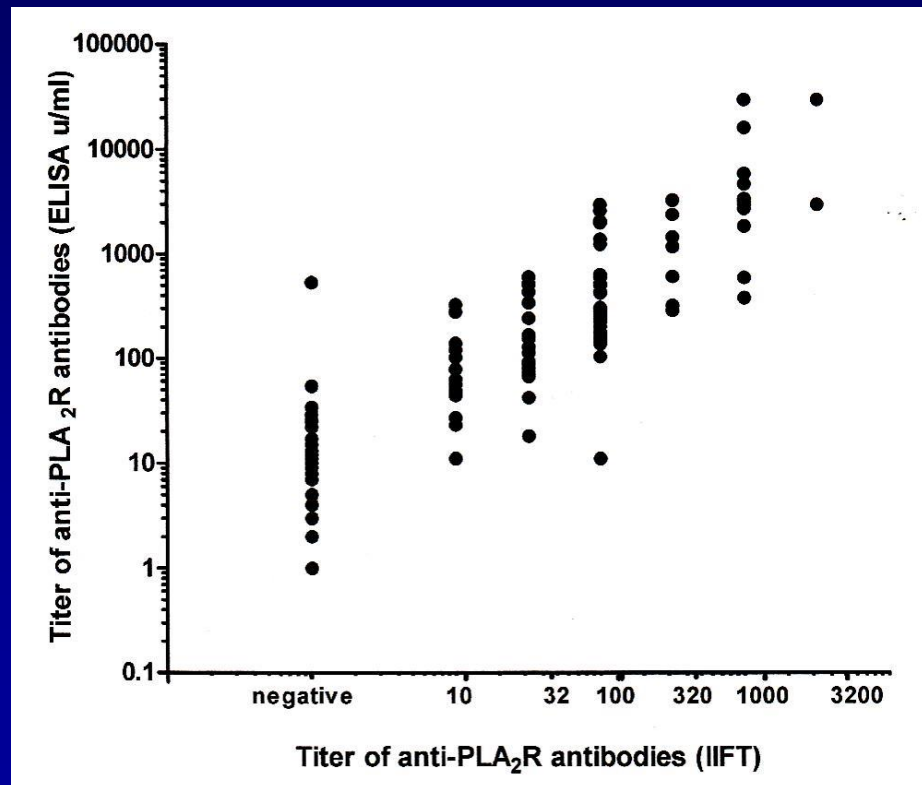
**Does anti-PLA2R correlate with clinical outcome ?**

**How should anti-PLA2R be measured ?**

# How should anti-PLA<sub>2</sub>R antibodies be measured?

Which antibody: rabbit? guinea pig?

Which technique: Western blot? ELISA? Indirect IF?



# Anti-PLA2R & Membranous Nephropathy

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Should we measure anti-PLA2R routinely

... for diagnosis?

.... to guide therapy ?

....not yet .....

# MEMBRANOUS NEPHROPATHY

## Terminology

---

~~Idiopathic~~

Primary ?

Secondary

Infection

Drugs

Malignancy

# MANAGEMENT OF MEMBRANOUS NEPHROPATHY

---

**Definitions**

**Aetiology & Pathogenesis**

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**Choosing therapy**

# MEMBRANOUS NEPHROPATHY

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Can we predict prognosis at presentation ?

Pathological features ?

Clinical features ?

Serology ?

# MEMBRANOUS NEPHROPATHY

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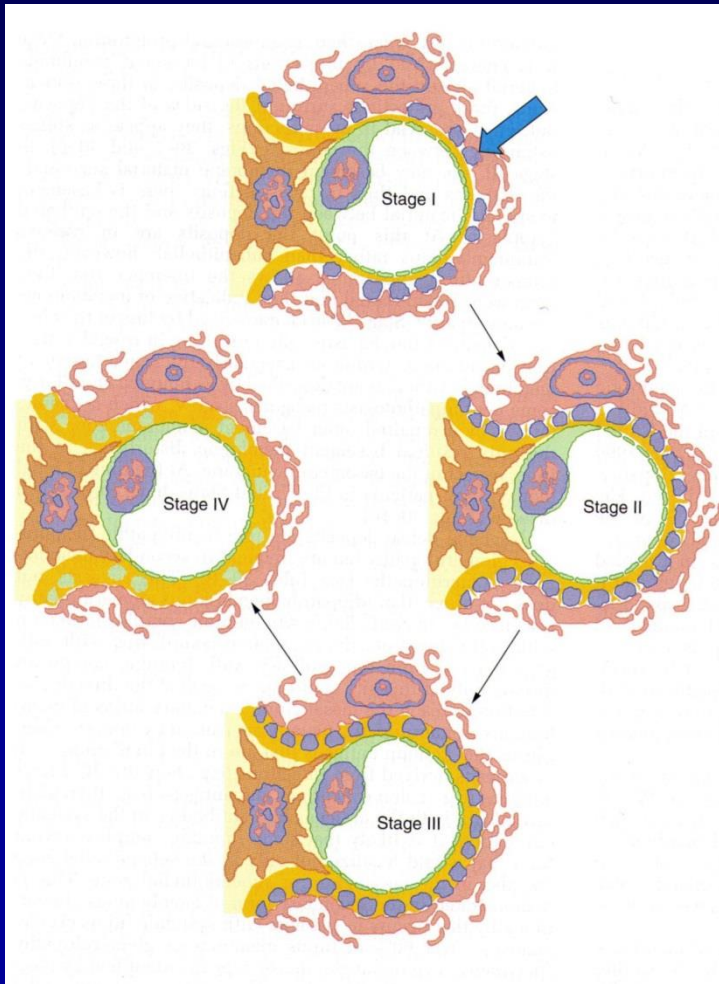
Can we predict prognosis at presentation ?

**Pathological features ?**

***Glomerulosclerosis***

***Tubular atrophy & interstitial fibrosis***

# PATHOLOGICAL CLASSIFICATION OF MEMBRANOUS NEPHROPATHY



## ELECTRON MICROSCOPY

**Stage 1: subepithelial EDDs, no BM reaction**

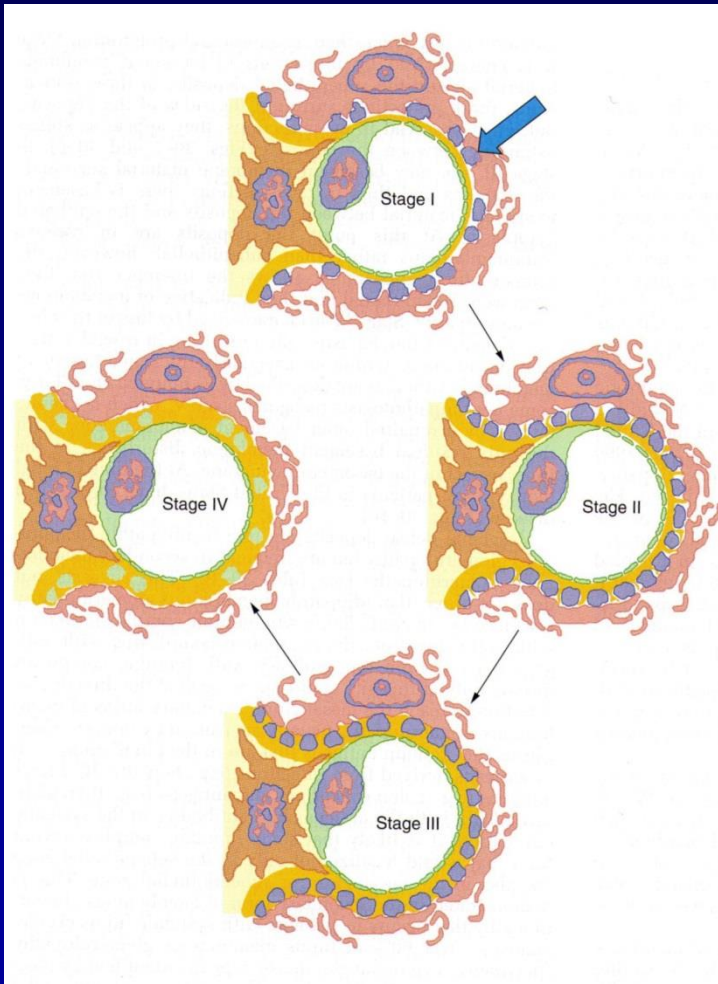
**Stage II: 'spikes'**

**Stage III: EDDs surrounded by BM**

**Stage IV: lucency of deposits**

# PATHOLOGICAL CLASSIFICATION OF MEMBRANOUS NEPHROPATHY

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- Logical & systematic
- Covers 'progression' of lesions

*BUT*

11 reports 1979-1992

8/11 suggested this classification  
did not predict outcome or duration of disease

Ehrenreich & Churg, 1968

# MEMBRANOUS NEPHROPATHY

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Can we predict prognosis at presentation ?

Pathological features ?

Clinical features ?

Serology ?

# NATURAL HISTORY of “IDIOPATHIC” MEMBRANOUS NEPHROPATHY with NEPHROTIC SYNDROME

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- **ONE THIRD**: spontaneous complete remission in 3 to 5 years  
25% who enter remission subsequently relapse
- **ONE THIRD**: Partial remission (24hr uProt < 2g) with persistent proteinuria but no loss of GFR
- **ONE THIRD**: ESRD over 5 to 10 years
- Remission or maintain normal GFR for > 3 years - prognosis is excellent

# NATURAL HISTORY of "IDIOPATHIC" MEMBRANOUS NEPHROPATHY with NEPHROTIC SYNDROME

---

- **ONE THIRD**: spontaneous complete remission in 3 to 5 years

25%

There is now no such thing as:

'the natural history of membranous nephropathy'

- **ONE** pers

- **ONE**

BP control

Renin-angiotensin blockade

Salt restriction

- Remission rate is high - prognosis is excellent

# PREDICTING RISK IN MEMBRANOUS NEPHROPATHY – Toronto Registry

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## **LOW RISK**

normal renal function  
proteinuria < 4g/day for 6/12

## **MEDIUM RISK**

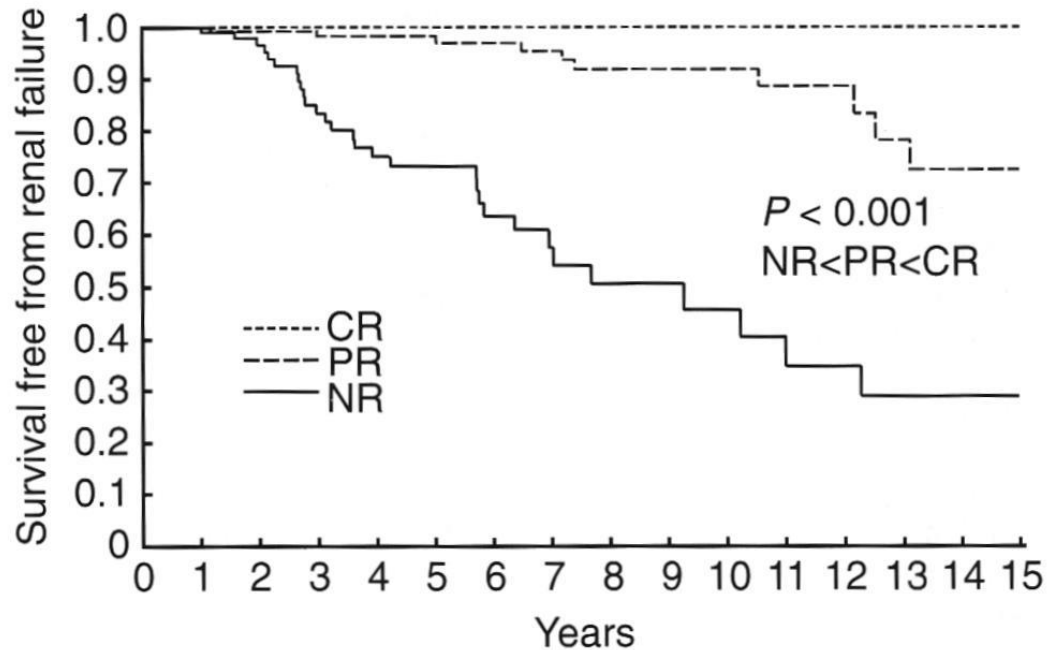
normal renal function  
proteinuria > 4g/d < 8g/d for 6/12

## **HIGH RISK**

abnormal renal function or/and  
persistent proteinuria >8g/d for >6/12

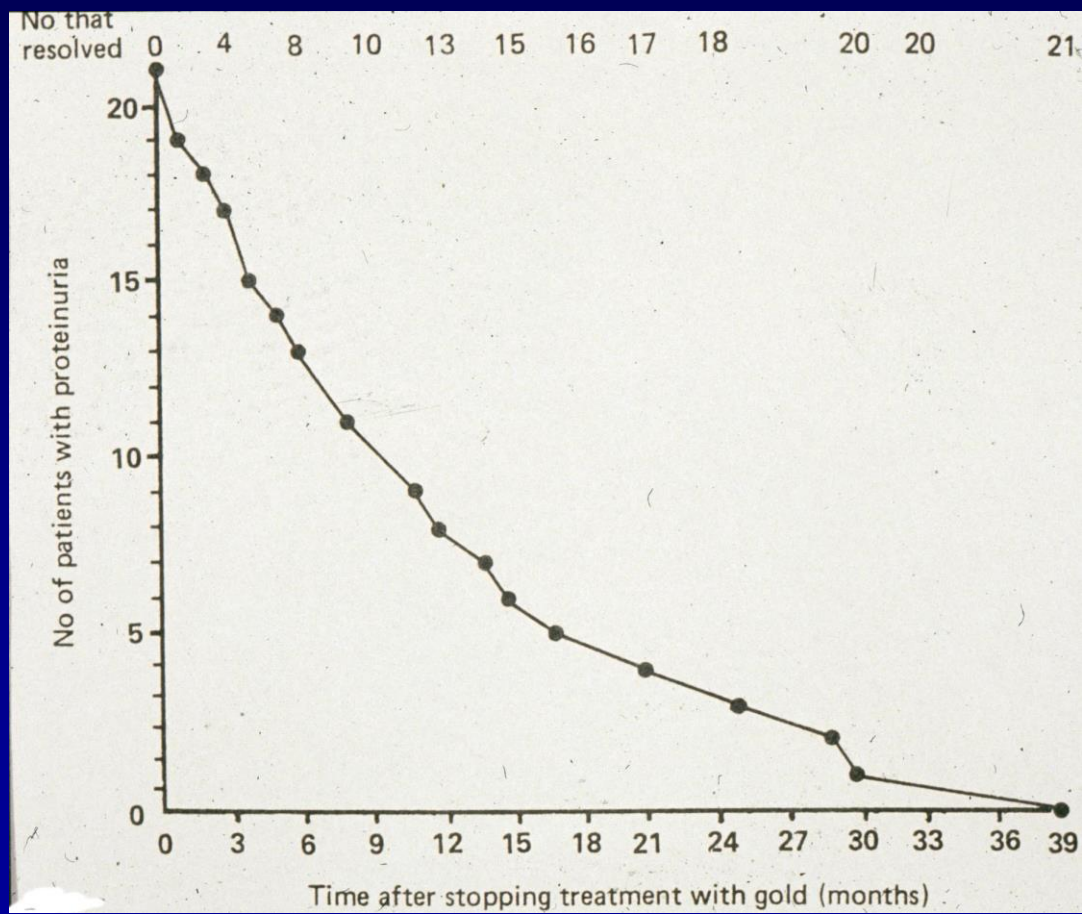
# VALUE OF PARTIAL REMISSION IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

TORONTO GN REGISTRY - 343 patients



CR	102	67	33	12
PR	135	74	32	9
NR	106	34	9	4

# NATURAL HISTORY OF GOLD-INDUCED MEMBRANOUS NEPHROPATHY



Hall CL et al. Adv Exp Med Biol. 1989;252:247-56

# MEMBRANOUS NEPHROPATHY

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Can we predict prognosis at presentation ?

Pathological features ?

Clinical features ?

**Serology ?**

# MEMBRANOUS NEPHROPATHY

---

Can we predict prognosis at presentation ?

Pathological features ?

Clinical features ?

**Serology ?**

*Anti-PLA2R antibodies are promising, but not of proven value*

# MANAGEMENT OF MEMBRANOUS NEPHROPATHY

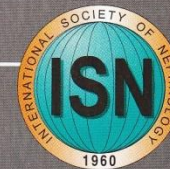
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**Definitions**

**Aetiology & Pathogenesis**

**Predicting prognosis**

**Choosing therapy**



# kidney

INTERNATIONAL  
*supplements*

KI Supplements 2012  
2(2): 1-274



CLINICAL PRACTICE GUIDELINE FOR  
GLOMERULONEPHRITIS

# Examples of Rating Guideline Recommendations

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QUALITY of Supporting Evidence is shown as A, B, C or D

Level 1	We recommend....	1A
<p><b>Of 19 recommendations or suggestions for 'idiopathic' Membranous Nephropathy only 3 (16%) are 1A or 1B</b></p>		
Le	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them	No RCTs Supported by limited observational data

# Examples of Rating Guideline Recommendations

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QUALITY of Supporting Evidence is shown as A, B, C or D

Level 1	We recommend....	1A
Level 2	Each patient needs help to arrive at a management decision appropriate for them	Supported by limited observational data

The recommendations or suggestions *only apply to nephrotic syndrome* *not to asymptomatic proteinuria*

# Examples of Rating Guideline Recommendations

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QUALITY of Supporting Evidence is shown as A, B, C or D

Level 1	We recommend....	1A
<p><b>NONE</b> of the available RCT evidence has relevant information about <b>anti-PLA2R status</b></p>		
Le	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them	No RCTs Supported by limited observational data

# **Basics of treatment in idiopathic membranous nephropathy**

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**Exclude secondary causes**

**Anti-proteinuric therapy**

**BP control; RAS blockade**

**Disease-specific immunotherapy**

# TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

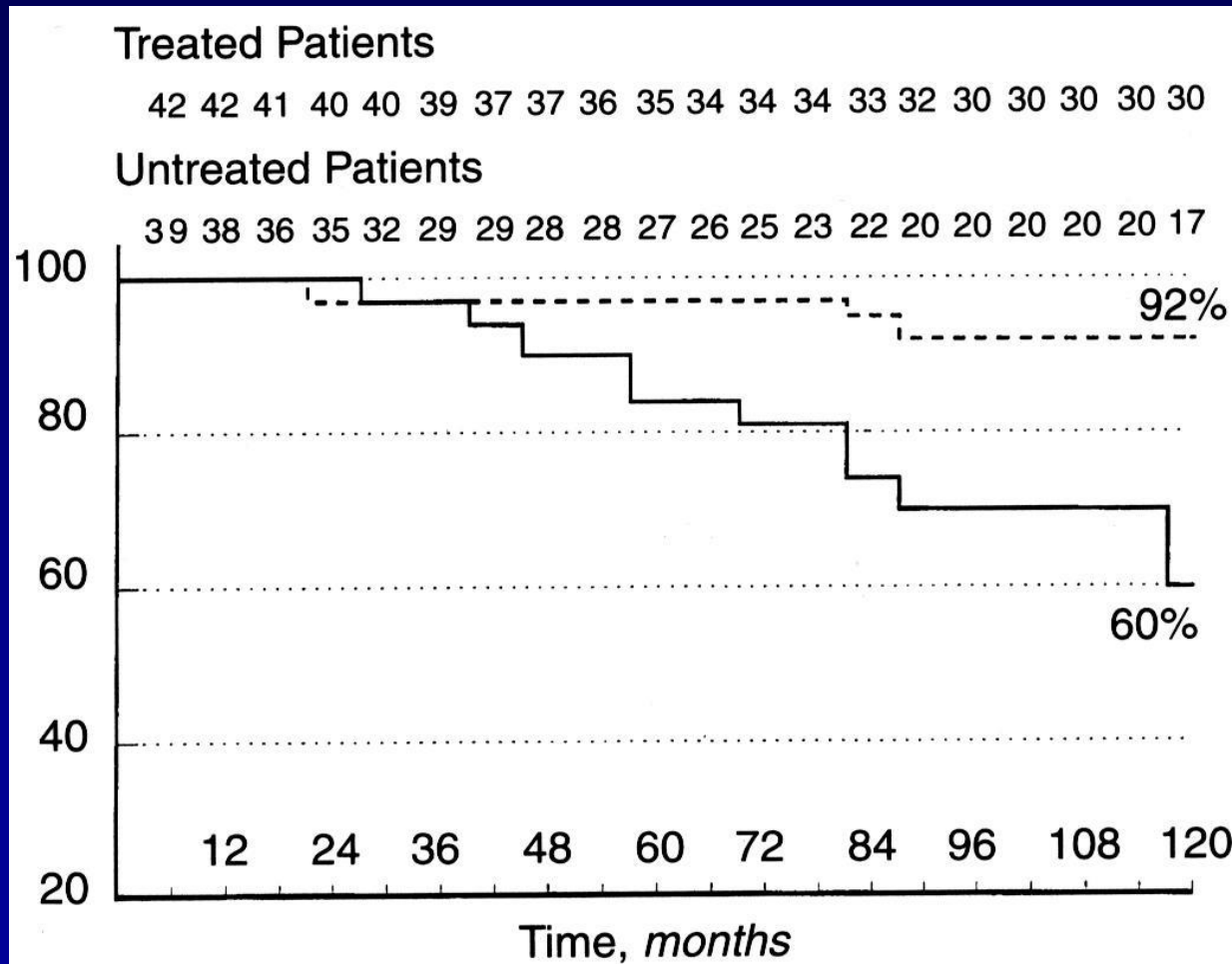
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**“ Should I treat this patient ? ”**

**“ Should I treat this patient  
with an immunosuppressive regimen  
with a significant adverse event profile ? ”**

**BP control  
Renin-angiotensin blockade  
Salt restriction  
Statin**

# 10 YEAR FOLLOW UP OF 'PONTICELLI REGIMEN' FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME



**'PONTICELLI REGIMEN'  
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY  
WITH NEPHROTIC SYNDROME**

---

**Why is there controversy ?**

**'PONTICELLI REGIMEN'  
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY  
WITH NEPHROTIC SYNDROME**

---

**Why is there controversy ?**

**Toxicity**

**Are old trials relevant to modern practice ?**

**Does ethnicity matter ?**

**Is it necessary to treat *all* patients ?**

# **'PONTICELLI REGIMEN' FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME**

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**In 6 months the patient receives:**

**9 grams Methylprednisolone  
*and* oral Prednisolone 0.4mg/kg/alt day for 3 months**

***plus***

**Chlorambucil 0.2 mg/kg/day for 3 months**

***or***

**Cyclophosphamide 2.5 mg/kg/day**

# CALCINEURIN INHIBITORS FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

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## Cyclosporine

Cattran D et al. ....

## Tacrolimus

Praga M et al.

**Both are effective**

**BUT not been compared 'head to head' with 'Ponticelli'**

**'PONTICELLI REGIMEN'  
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY  
WITH NEPHROTIC SYNDROME**

---

**Why is there controversy ?**

**Toxicity**

**Are old trials relevant to modern practice ?**

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# ARE OLDER RCTs RELEVANT TO MODERN MANAGEMENT OF GN ?

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**BP targets**

**Renin-angiotensin system blockade**

# 10 YEAR FOLLOW UP OF 'PONTICELLI REGIMEN' FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

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**Blood pressure defined as > 160/90**

**Renin-angiotensin blockade ?**

# RCT OF CORTICOSTEROIDS AND CYCLOPHOSPHAMIDE FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

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## Significant benefit of steroid/cyclo regimen

Median BP	
Baseline	113/78
10 years	132/83

Not different between treatment groups

**'PONTICELLI REGIMEN'  
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY  
WITH NEPHROTIC SYNDROME**

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**Why is there controversy ?**

**Toxicity**

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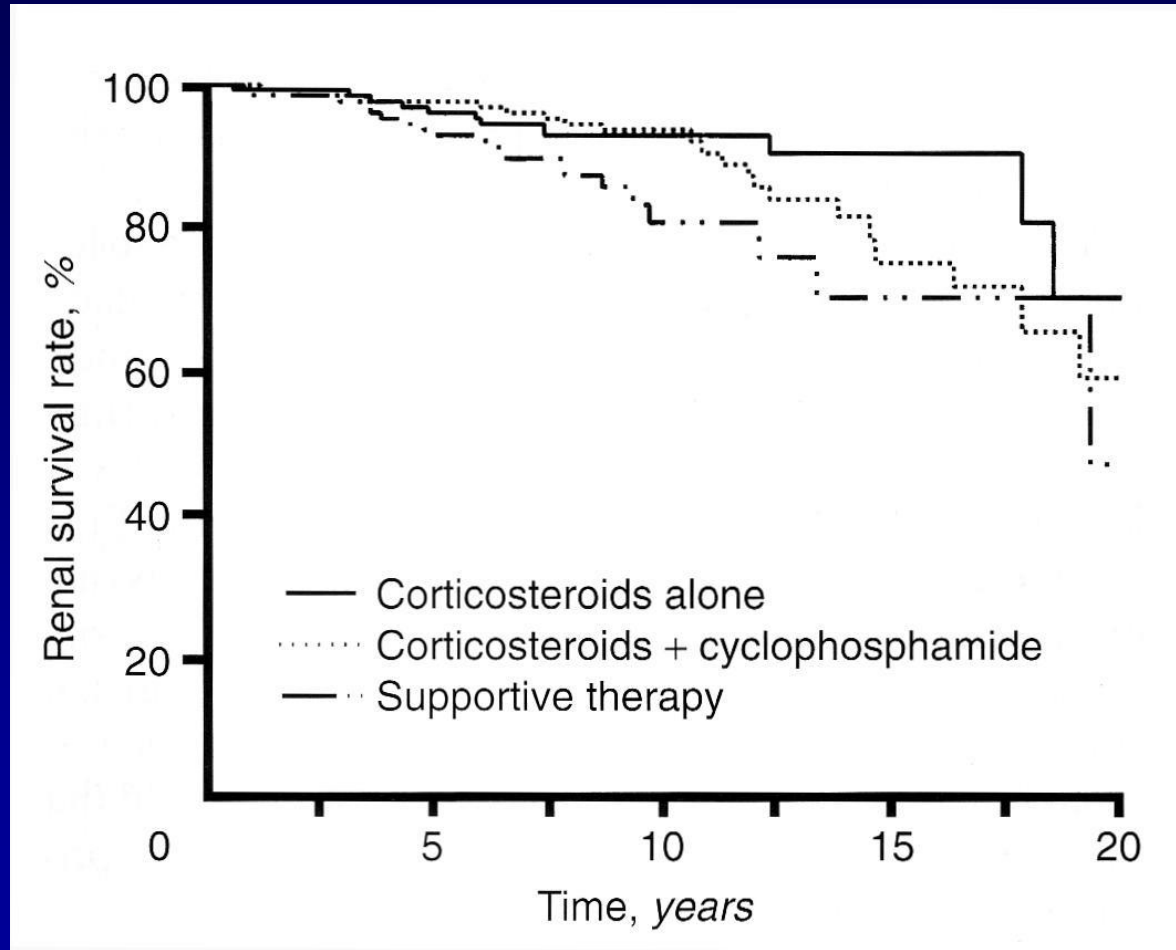
# PROGNOSIS OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN JAPAN

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**949 patients followed for up to 20 years**  
**No RCTs**

**374 corticosteroids**  
**257 alkylating agents**  
**157 other immunosuppressives**  
**161 'supportive therapy'**

# PROGNOSIS OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN JAPAN



**'PONTICELLI REGIMEN'  
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY  
WITH NEPHROTIC SYNDROME**

---

**Why is there controversy ?**

**Toxicity**

**Are old trials relevant to modern practice ?**

**Does ethnicity matter ?**

**Is it necessary to treat *all* patients ?**

# EARLY vs. LATE START OF IMMUNOSUPPRESSIVE TREATMENT IN IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

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**RCT**

**Prednisolone/cyclophosphamide**

**Immediately or delayed until renal function declined**

**EARLY TREATMENT**

**Earlier remission**

**Shorter duration of nephrotic syndrome**

**No difference at 6 years**

**in**

**Remission**

**Renal function**

**Relapse rate**

**Adverse events**

# TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

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Select high risk patients

‘Head to head’

Is ‘Ponticelli’ or CNI more effective ?

**Tight BP control**

**125/75**

**Full renin-angiotensin  
blockade**

**Statin**

**Tight BP control**

**125/75**

**Full renin-angiotensin  
blockade**

**Statin**



**Deteriorating renal function or intractable nephrotic syndrome**

**Tight BP control**

**125/75**

**Full renin-angiotensin  
blockade**

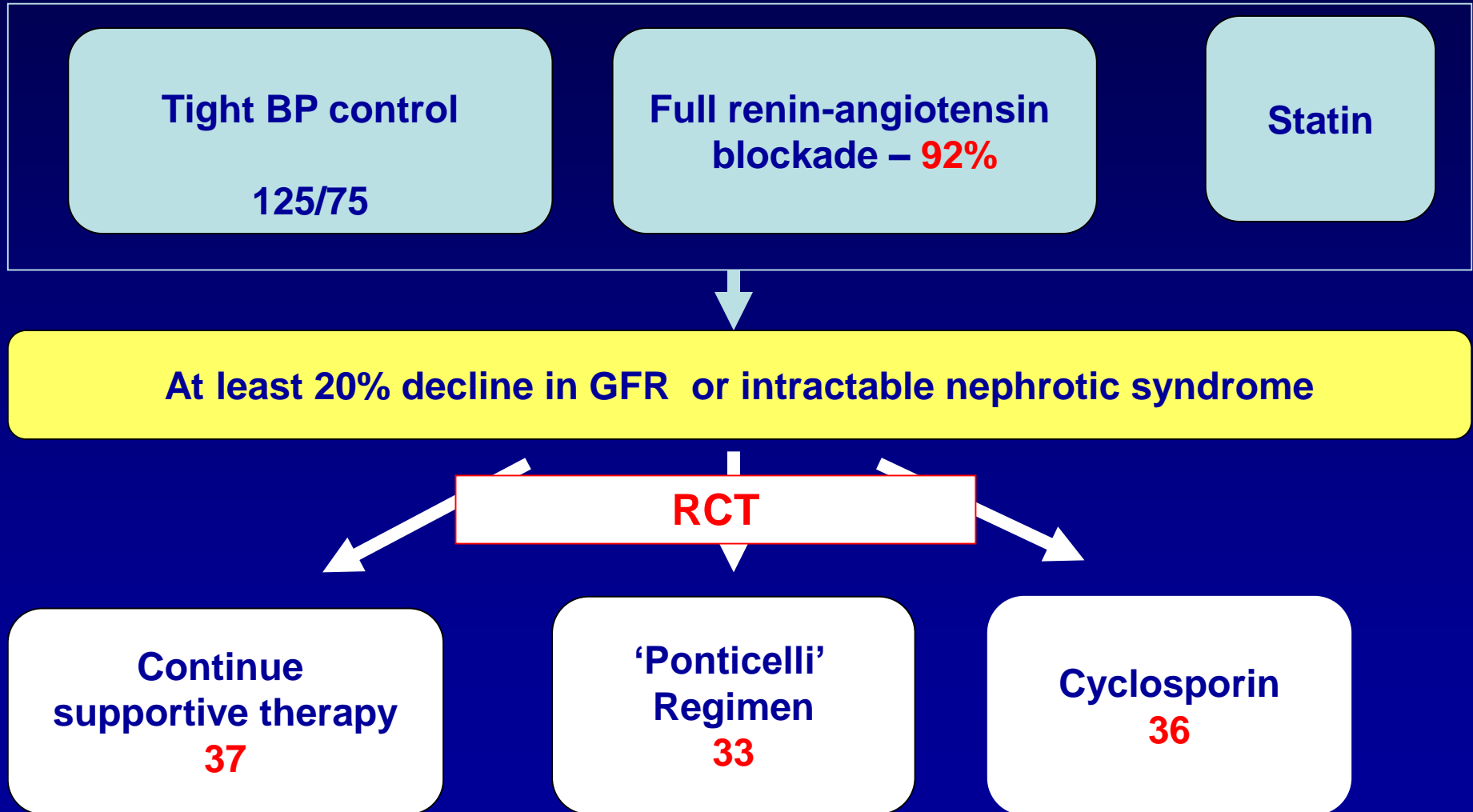
**Statin**



**Deteriorating renal function or intractable nephrotic syndrome**

**What is the evidence that immunosuppressive regimens  
give additional benefit ?**

# THE UK RANDOMISED CONTROLLED TRIAL OF IMMUNOSUPPRESSION FOR PROGRESSIVE MEMBRANOUS NEPHROPATHY



# THE UK RANDOMISED CONTROLLED TRIAL OF IMMUNOSUPPRESSION FOR PROGRESSIVE MEMBRANOUS NEPHROPATHY

Tight BP control

125/75

Full renin-angiotensin  
blockade – 92%

Statin

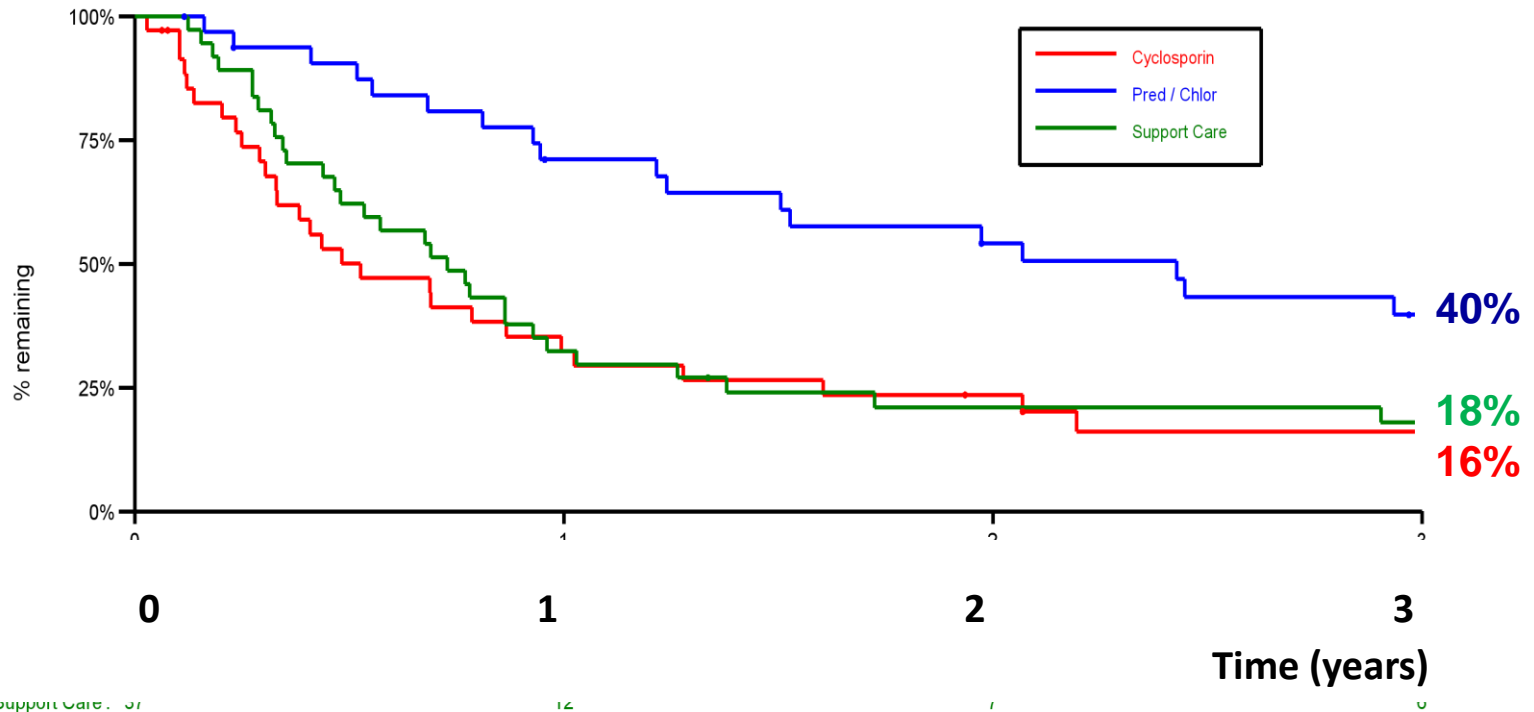
At least 20% decline in GFR or intractable nephrotic syndrome

Primary end point: further 20% decline in GFR

Intention to treat analysis

su

# Time to 20% fall in GFR



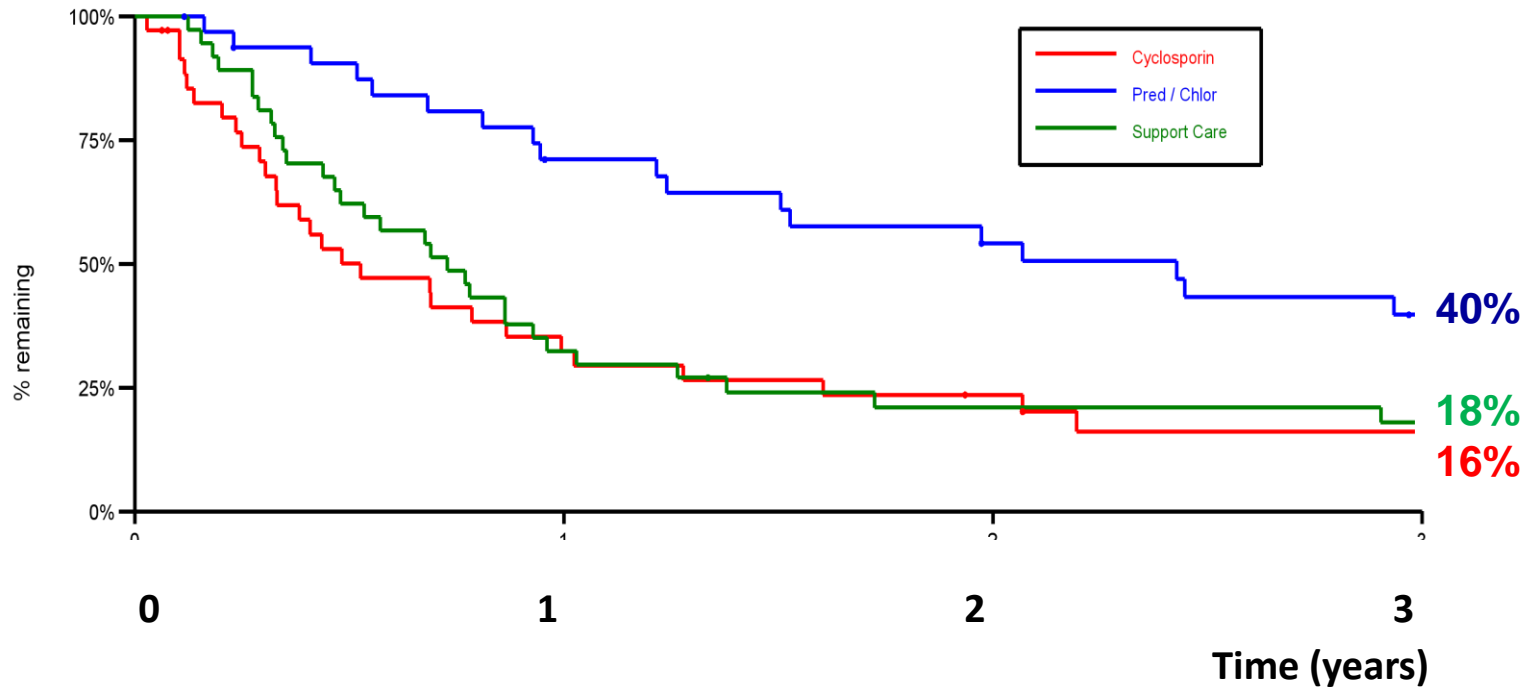
Support Care: 31

16

7

0

# Time to 20% fall in GFR



**Hazard Ratio (95% CI):**

**Pred/Chlorambucil vs Supportive care: HR 0.44 (0.24, 0.78), 2p=0.0042**

# RITUXIMAB FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY

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**2003-2012**

**90 references on PubMed**

**Hundreds of patients treated**

# RITUXIMAB FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY

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2003-2012

90 references on PubMed

Hundreds of patients treated

No RCT

# **RITUXIMAB FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME**

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**n = 100**

**Persistent uP >3.5g/d after 6 months ACE inhibitor**

**10 year experience, at least 6 months follow up**

**32% previous immunosuppression**

**RITUXIMAB - most had 2 doses,  
second dose when peripheral blood B cells recovering**

# RITUXIMAB

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**Perception –**

**A powerful B-cell specific targeted therapy**

**Replacing more toxic agents**

**Remarkably safe**

## **ADVERSE EFFECTS OF RITUXIMAB**

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**Up to 10% infusion reaction**

**Short term infection risk < 'Ponticelli regimen'**

**Increased tumour risk in rheumatology studies**

**Progressive multifocal leucoencephalopathy in nephrotic children**

**? relates to extent of other immunosuppressive exposure**

# COST OF RITUXIMAB

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**1 dose of rituximab: \$4,000**

**Ponticelli regimen for 6 months: \$ 600**

Does avoiding one hospital admission for a septic episode save the cost of rituximab ?

# MEmbranous Nephropathy Trial Of Rituximab (MENTOR)

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**Mayo Clinic**

**3 months run in ....**

**Cyclosporine for 6 months**

**vs.**

**Rituximab – minimum 2 doses**

**ClinTrials.gov: NCT01180036**

# ECULIZUMAB [C5 COMPLEMENT INHIBITOR] IN MEMBRANOUS NEPHROPATHY

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**Logical treatment**

**Prevents assembly of C5b-9 membrane attack complex**

**RCT**

**No benefit**

**Incomplete complement inhibition**

# TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

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**“ Should I treat this patient ? ”**

# TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

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**“ Should I treat this patient ? ”**

**“ Should I treat this patient  
with an immunosuppressive regimen  
with a significant adverse event profile ? ”**

# TREATMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

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**Do the simple things properly**

**Minimise adverse effects of treatment**

**Use guidelines with judgment**

**Wait for evidence**

**Help create the evidence**