Primary & Secondary Glomerular Disease

John Feehally

GLOMERULONEPHRITIS

Immune disease which mainly affects glomeruli

Renal biopsy required to make the diagnosis

ISSUES IN GLOMERULONEPHRITIS

Terminology

Classification

Aetiology

Natural History

Treatment

ISSUES IN GLOMERULONEPHRITIS

Terminology

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Natural history

Treatment

TERMINOLOGY IN GLOMERULONEPHRITIS

Glomerulonephritis

or

Glomerular disease

TERMINOLOGY IN GLOMERULONEPHRITIS

Primary ?

Secondary ?

TERMINOLOGY IN GLOMERULONEPHRITIS

Different names for the same thing…..

Minimal change nephrotic syndrome

Minimal change disease

Lipoid nephrosis

Idiopathic nephrotic syndrome

Minimal change glomerulonephritis

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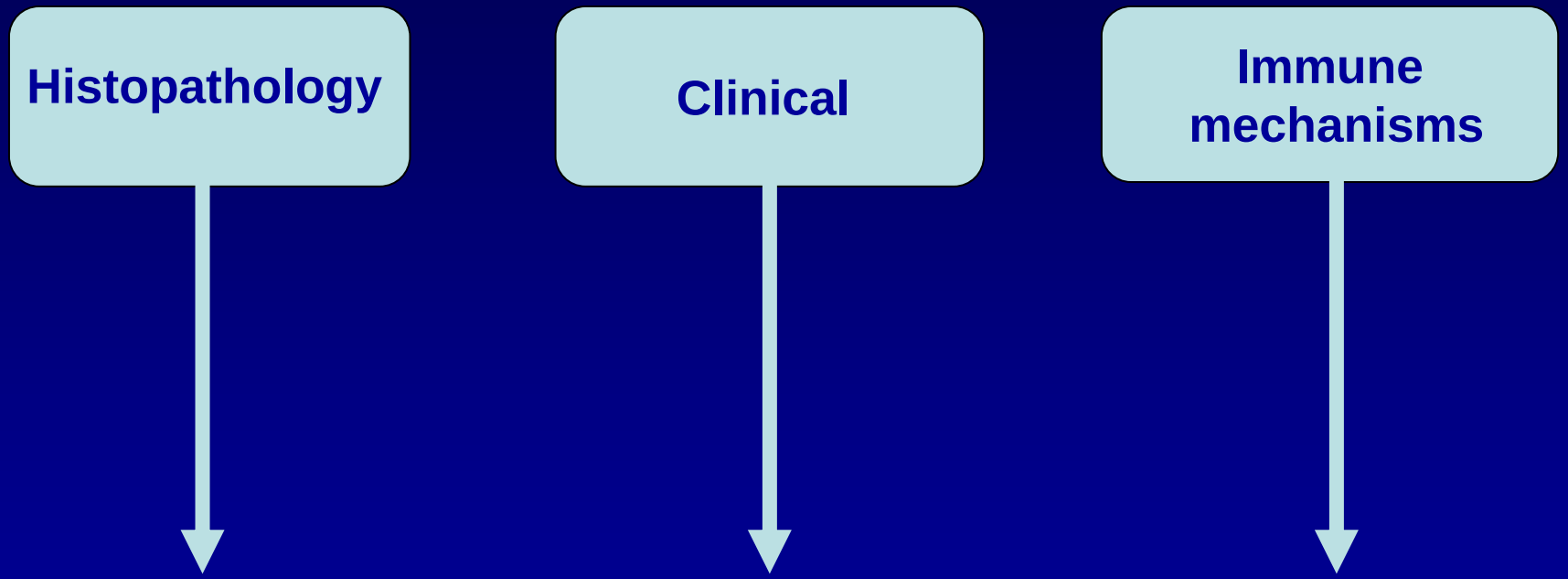
CLASSIFICATION OF GLOMERULONEPHRITIS



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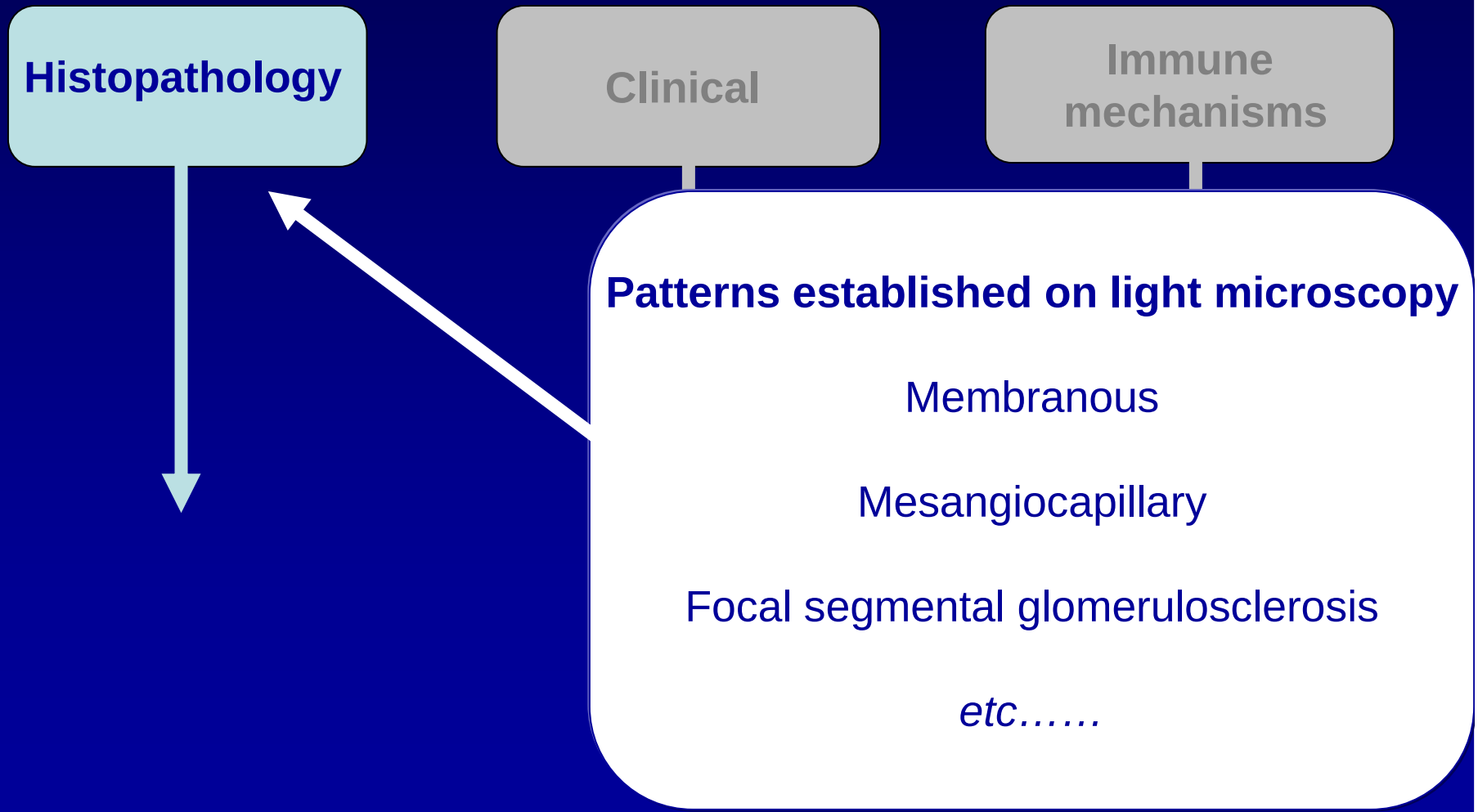

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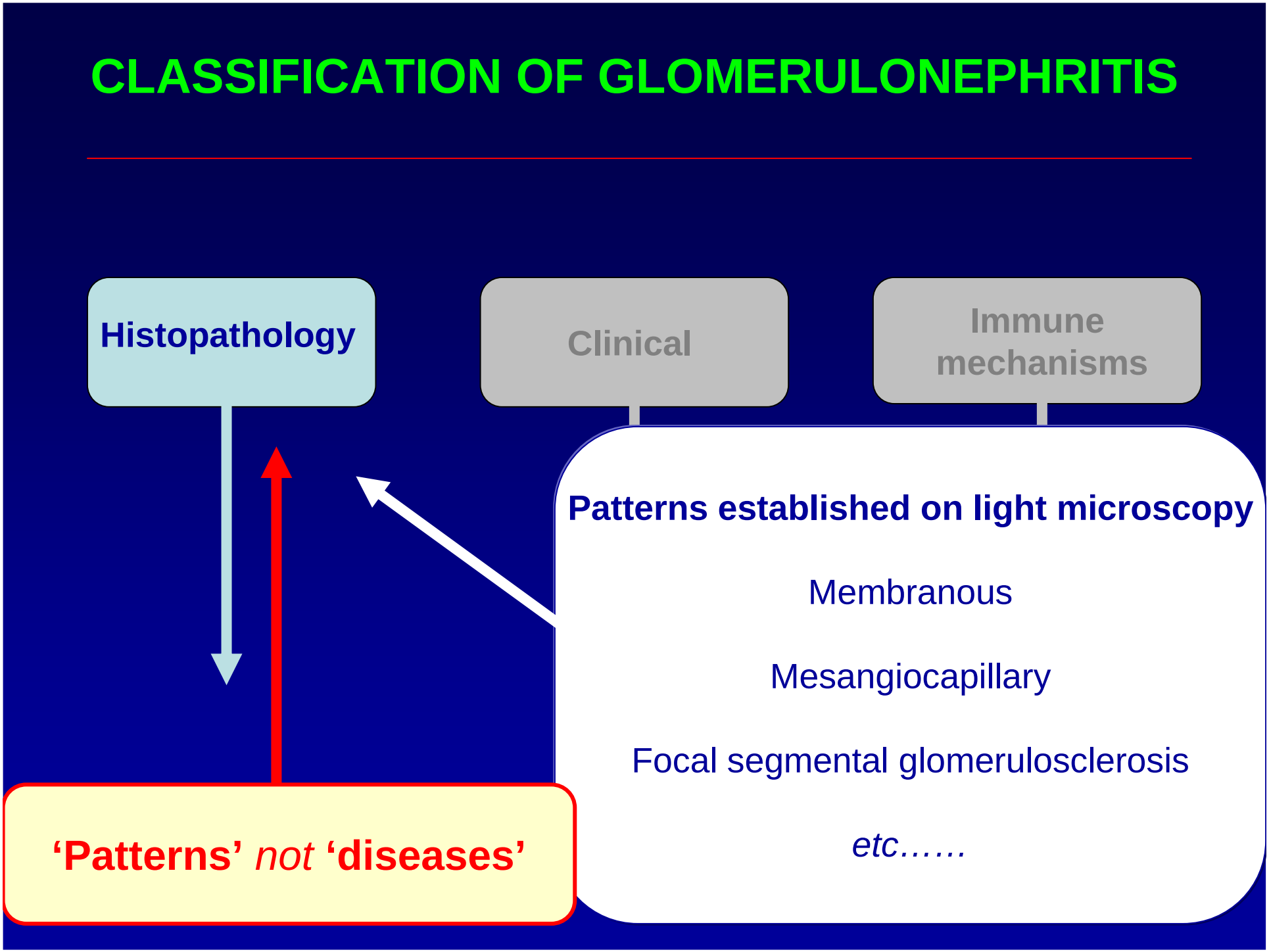

PATHOLOGICAL CLASSIFICATION OF GLOMERULONEPHRITIS

Light microscopic appearance
e.g.
MEMBRANOUS NEPHROPATHY

Type of immune deposits
e.g.
IgA NEPHROPATHY

ISSUES IN GLOMERULONEPHRITIS

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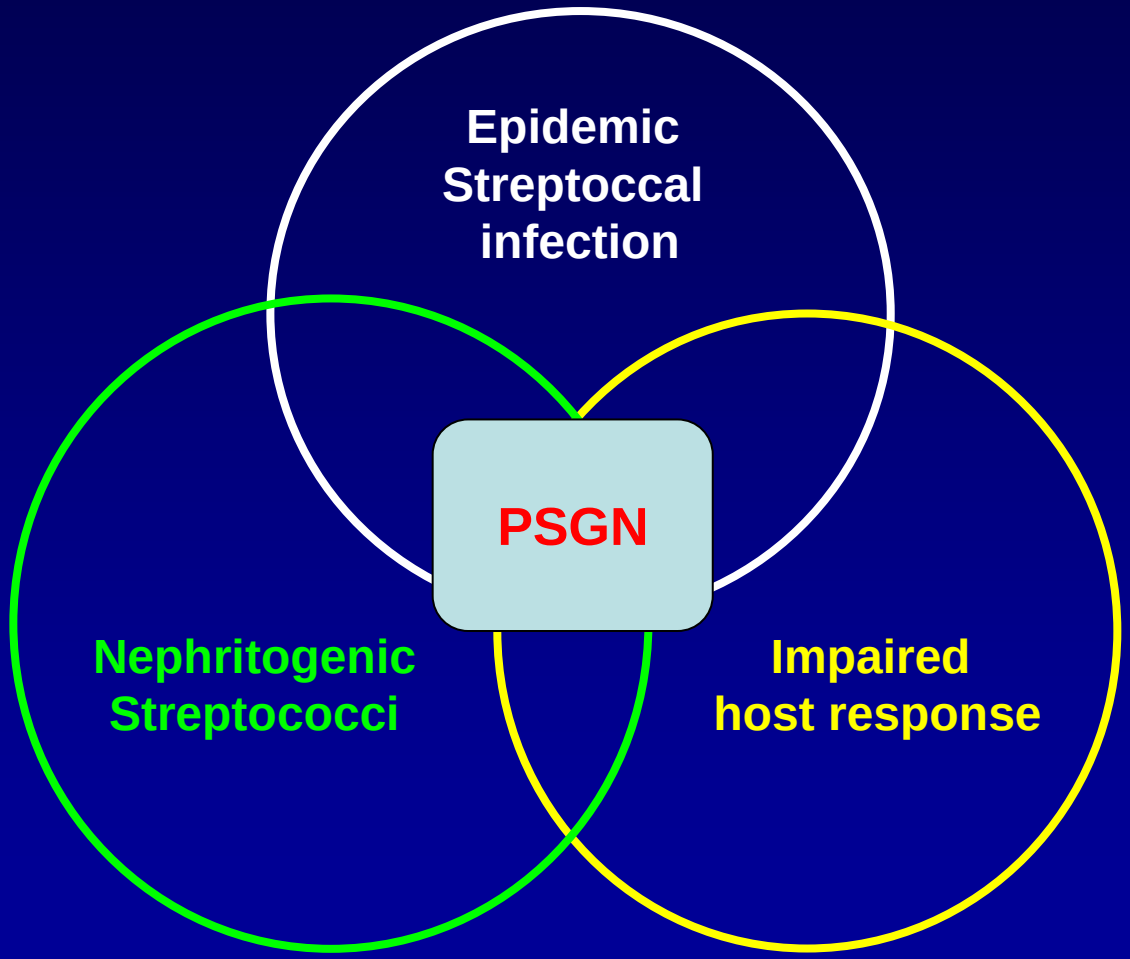
AETIOLOGY OF GN

INFECTION

- the dominant aetiological agent for GN in the developing world

- Bacterial
- Viral
- Parasitic

POST-STREPTOCOCCAL GLOMERULONEPHRITIS



MEMBRANOUS NEPHROPATHY

DEVELOPING WORLD

HBV

Leprosy

Syphilis

Hydatid disease

Malaria

Schistosomiasis

DEVELOPED WORLD

Idiopathic

Drugs

Malignancy

Lupus

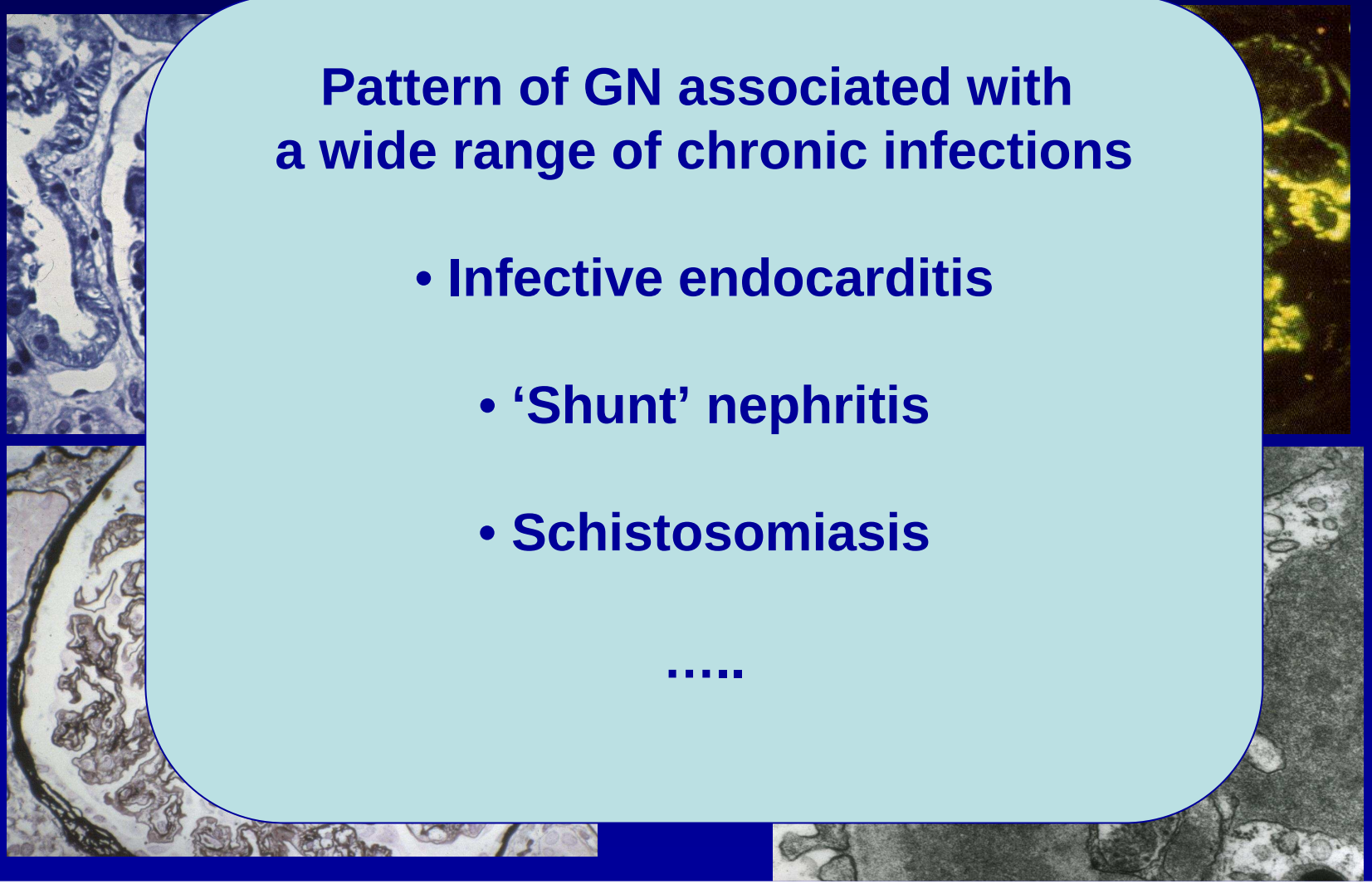
.....

Infections

CHRONIC INFECTION AND GN

Commonest histological pattern

Mesangiocapillary [membranoproliferative] GN type 1

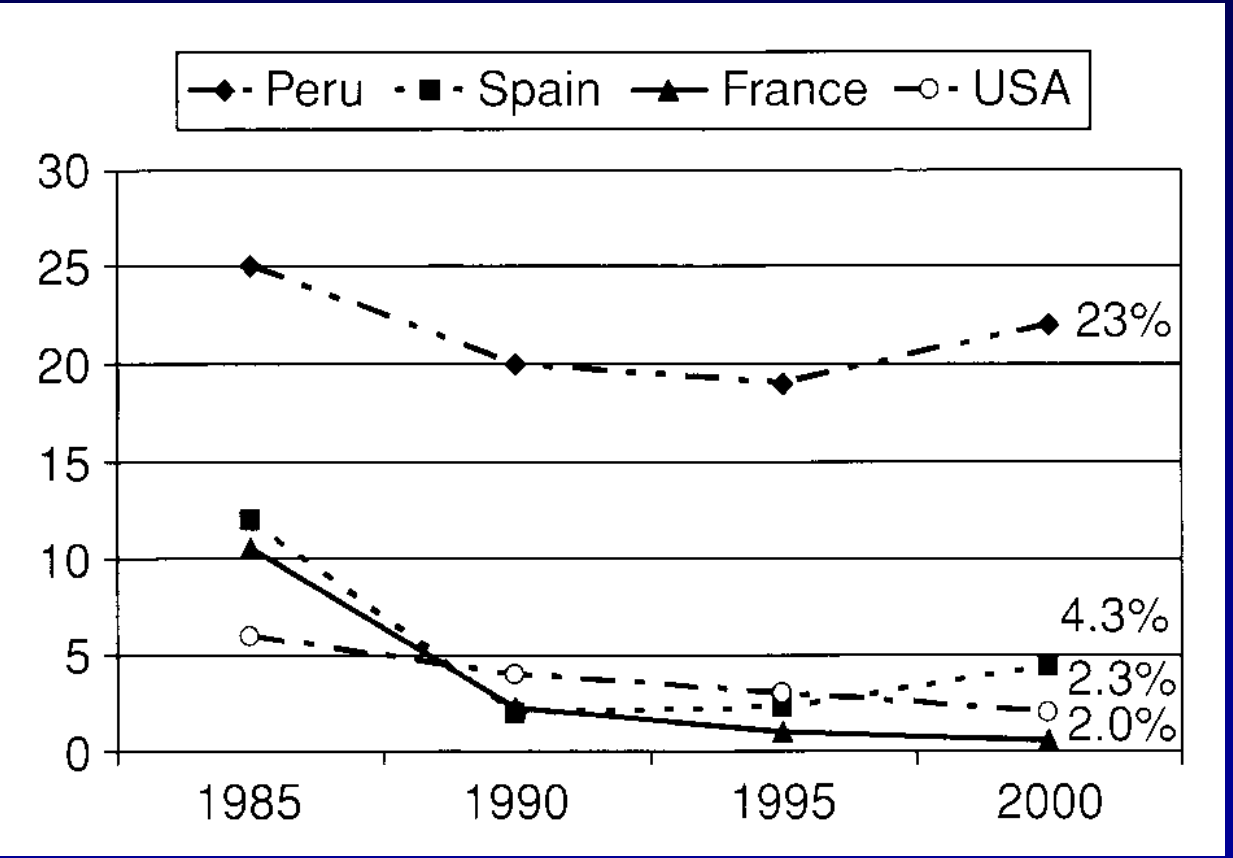


Pattern of GN associated with a wide range of chronic infections

- **Infective endocarditis**
- **‘Shunt’ nephritis**
- **Schistosomiasis**

…..

CHANGING PREVALENCE OF MCGN

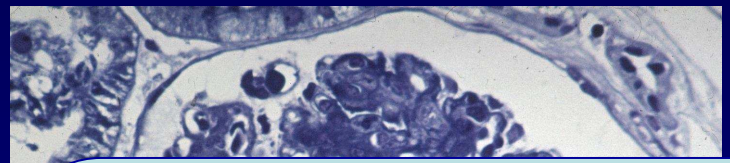


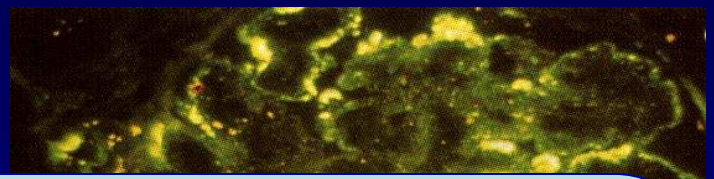
Hurtado A, Johnson RJ. KI 2005; Suppl 97: S62-S67

CHRONIC INFECTION AND GN

Commonest histological pattern

Mesangiocapillary [membranoproliferative] GN type 1

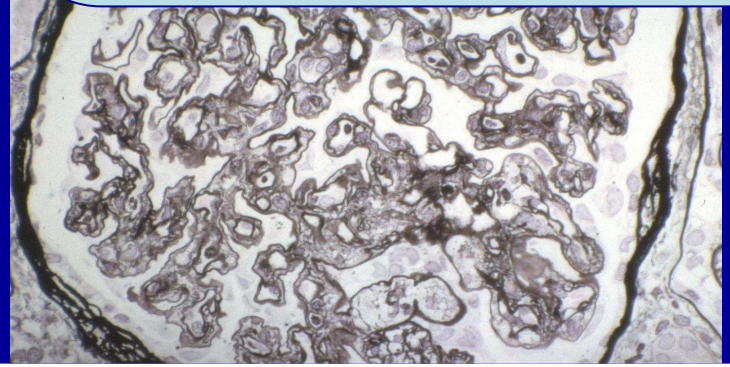


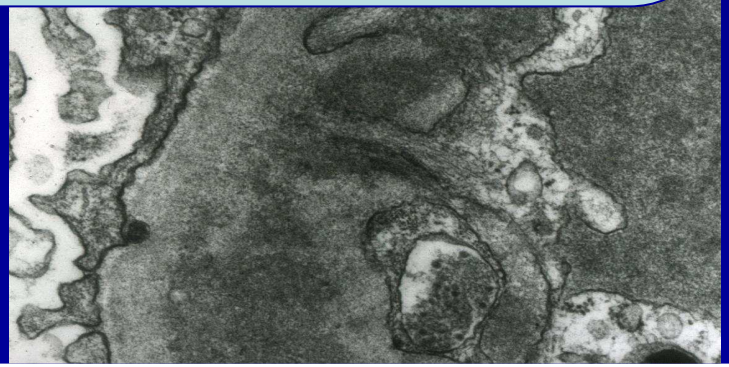


DEVELOPED WORLD

Incidence falling

Emergence of HCV as a causative agent





AETIOLOGY OF GN

INFECTION

Dominant aetiological agent for GN in the developing world

VARIED HOST RESPONSE

↓

Same infection → different patterns of GN

Same pattern of GN ← different infection

AETIOLOGY OF GN

The developed world

Are the common patterns of GN caused by infections we have not yet identified ?

Are other enviromental antigens involved ?

Do changing patterns of GN reflect changing patterns of host immunity in urbanised culture ?

AETIOLOGY OF GN

Infection

Other identifiable environmental antigens

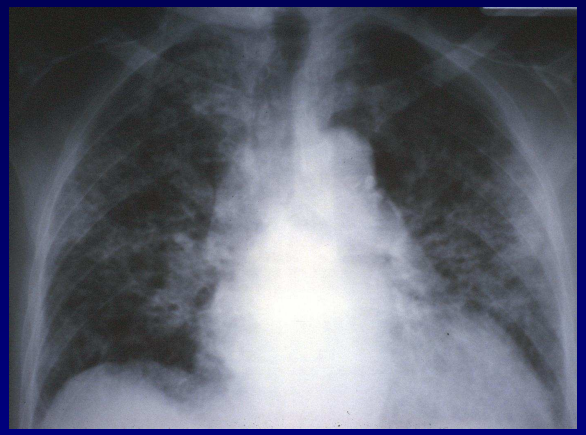
AETIOLOGY OF GN

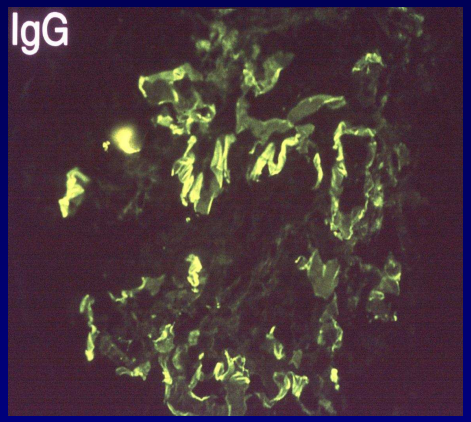
Infection

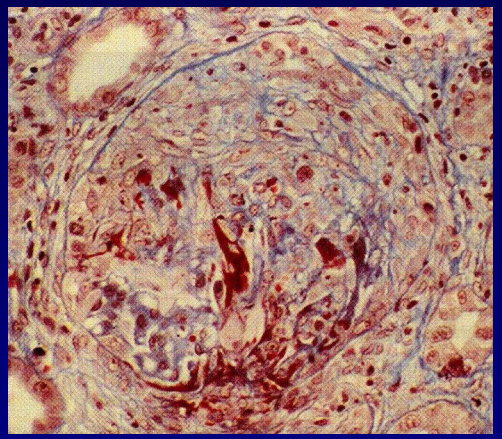
Other identifiable environmental antigens

Auto-immunity

GOODPASTURE'S DISEASE – ANTI-GBM DISEASE







The circulating anti-GBM IgG antibody is directly pathogenic

Transfer experiments

Depletion of antibody is therapeutic

LUPUS NEPHRITIS

The archetypal ‘immune complex’ disease

…. although the antigens involved in the complexes remain incompletely defined

Highly variable expression of renal disease

AETIOLOGY OF GN

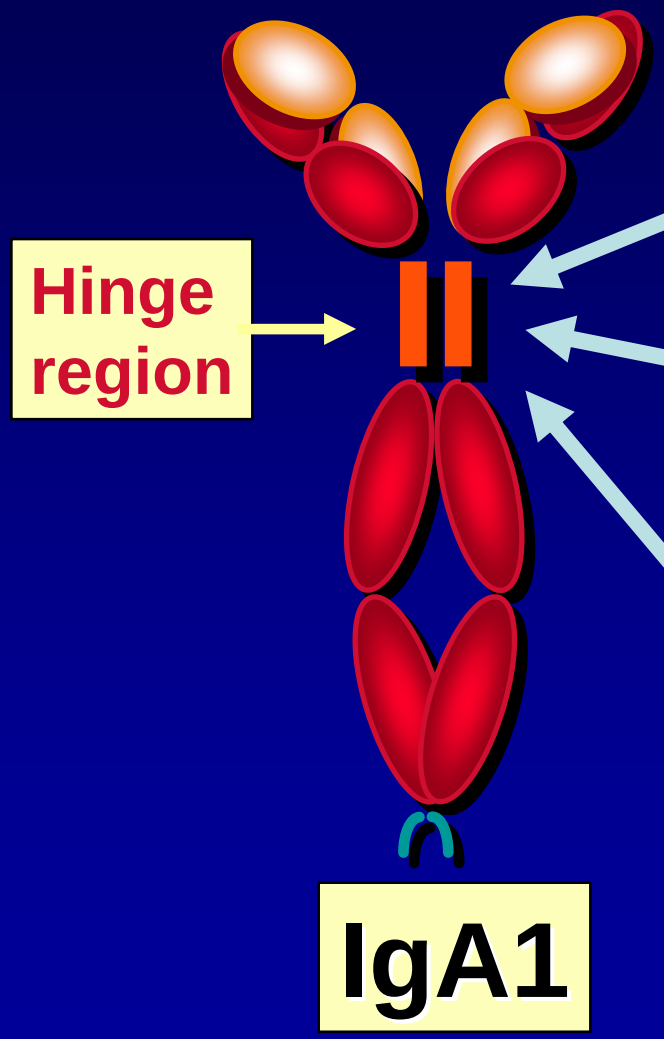
Infection

Other identifiable environmental antigens

Auto-immunity

Other

ALTERED IgA1 O-GLYCOSYLATION IN IgA NEPHROPATHY



A plausible site for a pathogenic abnormality

Hinge has unusual O-glycosylation

Hinge O-glycosylation abnormal in:

Serum IgA1 & mesangial IgA1 in IgAN

AETIOLOGY OF GN

Infection

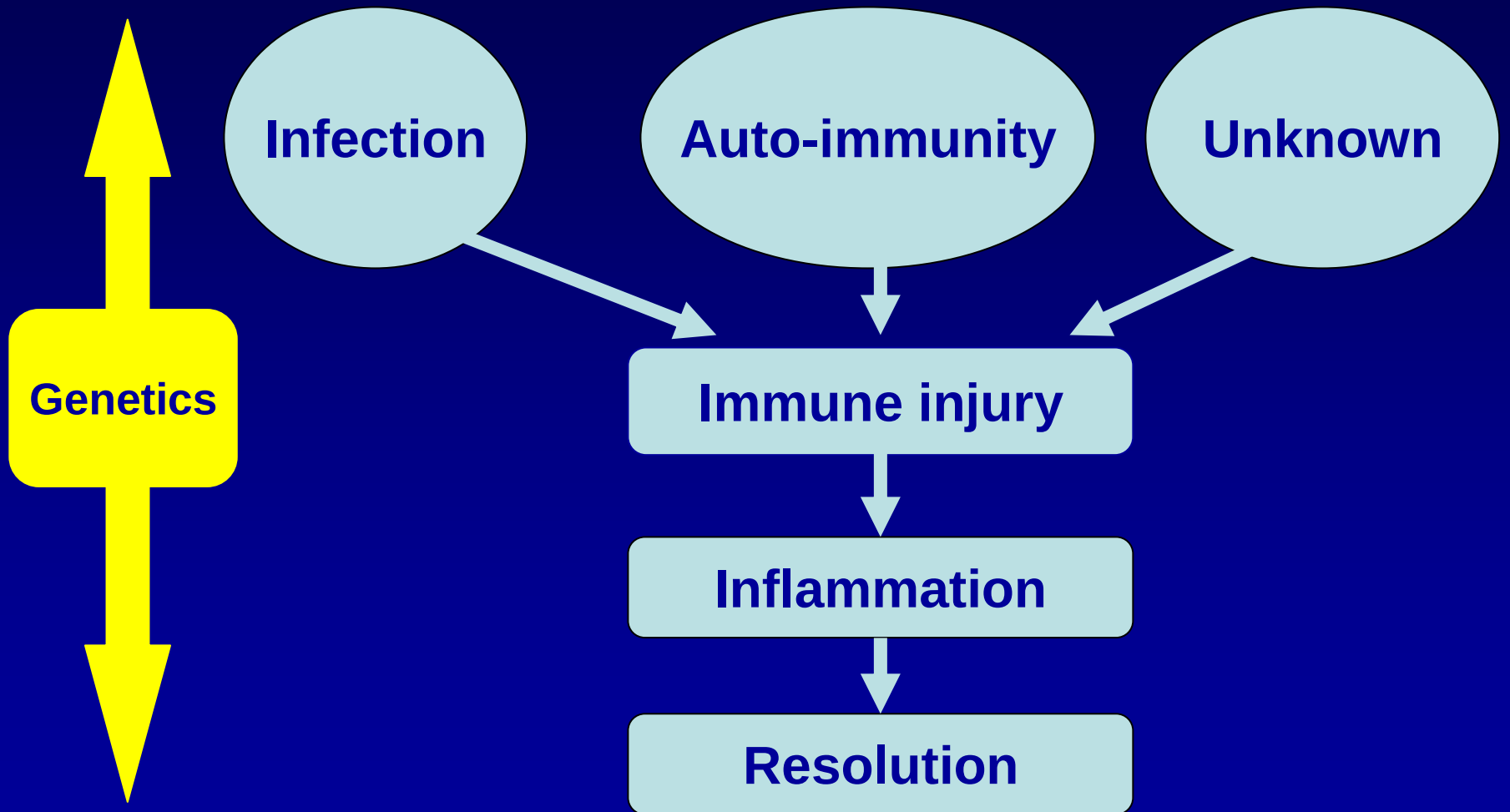
Other identifiable environmental antigens

Auto-immunity

Other

Genetics

DISEASE MECHANISMS IN GLOMERULONEPHRITIS



PATHOGENESIS OF GN

Evidence from renal transplantation

Some patterns of GN have always recurred despite innovative anti-rejection therapy

ISSUES IN GLOMERULONEPHRITIS

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INTERPRETING NATURAL HISTORY STUDIES & TREATMENT TRIALS IN GLOMERULONEPHRITIS

Patterns or diseases ?

Changing incidences ?

Worldwide variations ?

Inclusion criteria ?

Disease onset ?

Therapeutic effects ?

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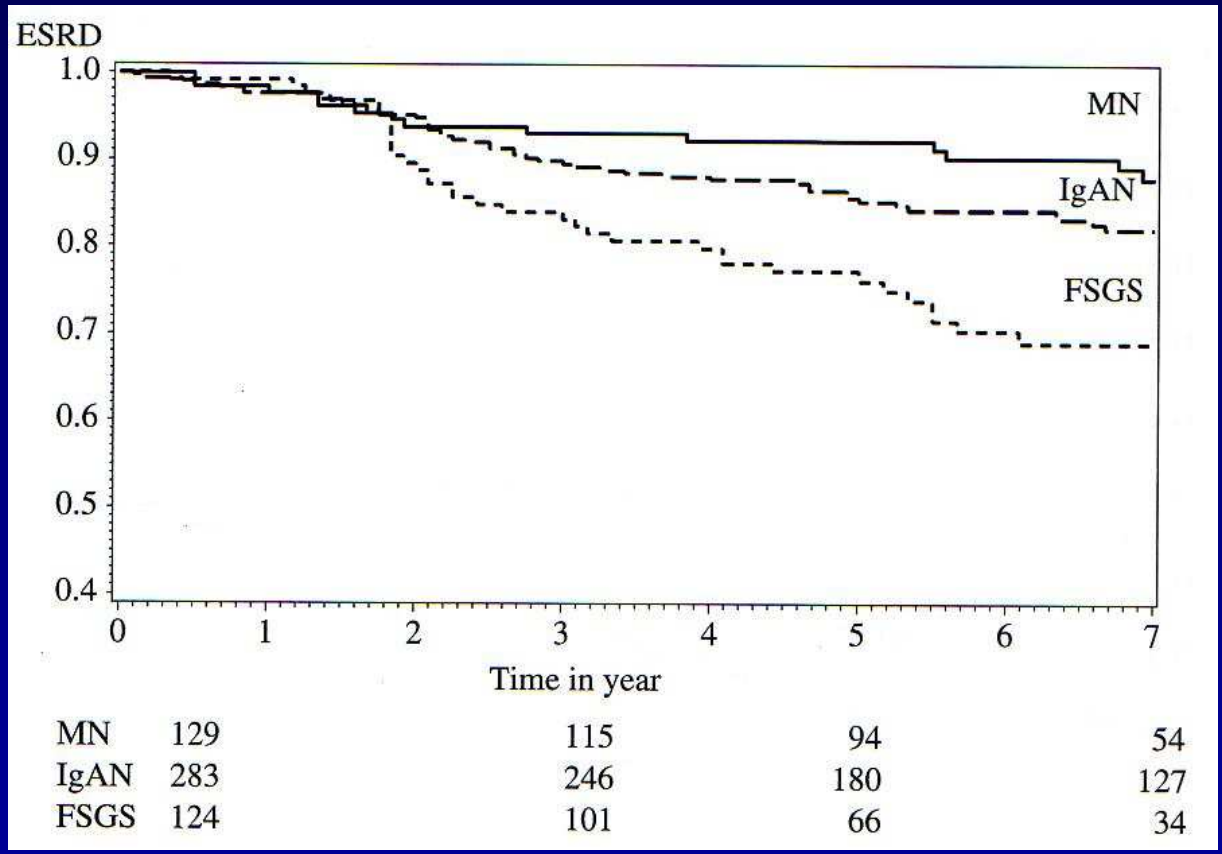
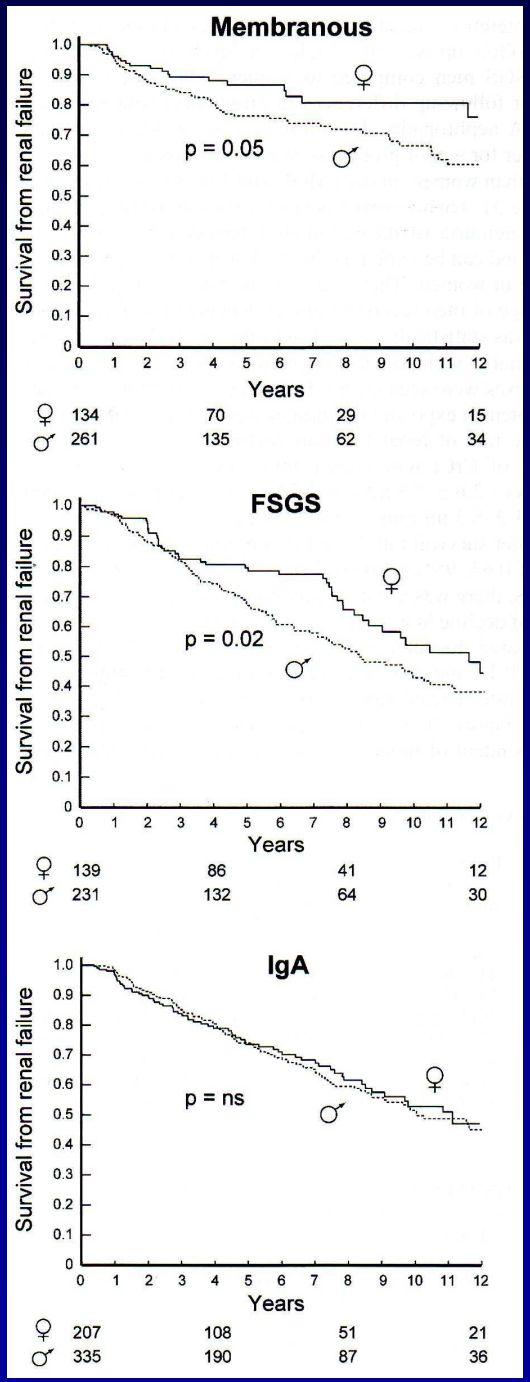


Moranne O *et al. Quart J Med* 2008; 101: 215



GENDER & OUTCOME IN PRIMARY GN

Benefit of female gender

…mostly explained by

lower proteinuria & BP

throughout follow up

Cattran D *et al.* NDT 2008; 23: 2247

ISSUES IN GLOMERULONEPHRITIS

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WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD ?

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The progress of immunology ?

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The progress of immunology ? X

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Antibiotics ?

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Antibiotics ? X

Public health ?

WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD ?

The progress of immunology ? X

Antibiotics ? X

Public health ? YES

WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD ?

The progress of immunology ? X

Antibiotics ? X

Public health ? YES

Spontaneous changes in streptococcal types ? ?

PREVENTION OF INFECTION-RELATED GN

Progress with infection control

Schistosomiasis

Malaria

HBV

PREVENTION OF INFECTION-RELATED GN

Progress with infection control

Schistosomiasis

Malaria

HBV

DURBAN, SOUTH AFRICA

HBV childhood immunisation from 1995 – incomplete coverage

Incidence of HBV-associated MN reduced by 80%
After 1998: no child age < 4 years

Bhimma R *et al.* 2003

TREATMENT OF GN

Why are we still treating these diseases with immunosuppressive drugs introduced into clinical practice..

..while I was still at school ?

TREATMENT OF GN

Why are we still treating these diseases with immunosuppressive drugs introduced into clinical practice..

..while I was still at school ?

… and which can be toxic ?

TREATMENT OF GN

Why are we still treating these diseases with immunosuppressive drugs introduced into clinical practice..

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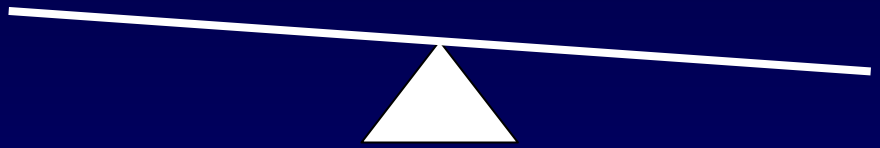
… and which can be toxic ?

CORTICOSTEROIDS

CYCLOPHOSPHAMIDE

AZATHIOPRINE

IMMUNE TREATMENT FOR GLOMERULONEPHRITIS



SIDE EFFECTS OF TREATMENT

- Cushingism
- Opportunistic infection
- Infertility
- Osteopenia
- Secondary neoplasia

IMPLICATIONS OF RENAL FAILURE

- Cardiovascular morbidity
- Infertility
- Transplant recurrence
- Quality of life

Lack of

PROGRESS IN TREATMENT OF GN

Transience of initiating events

Failure to learn lessons from recurrence after transplantation

Broad effects of existing immune therapy

Lack of

PROGRESS IN TREATMENT OF GN

Newer immunosuppressives have been developed for transplantation

Focus on suppressing T cell driven alloimmunity

Lack of

PROGRESS IN TREATMENT OF GN

Complexity and redundancy of inflammatory and anti-inflammatory pathways

NEW TREATMENTS OF GLOMERULONEPHRITIS

POTENTIAL TARGETS

T cells

Macrophages

Cytokines

Adhesion molecules

Chemokines

Profibrotic growth factors

NEW TREATMENTS OF GLOMERULONEPHRITIS

POTENTIAL TARGETS

T cells

Macrophages

Cytokines

Adhesion molecules

Chemokines

Profibrotic growth factors

PROBLEMS

Development costs

Timing

Kidney-specific delivery

Need multiple interventions

Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT's in this field ?

Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT's in this field ?

Uncommon

Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT's in this field ?

Uncommon

Slowly progressive

Lack of

PROGRESS IN TREATMENT OF GN

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Slowly progressive

Opinion

Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT's in this field ?

Uncommon

Slowly progressive

Opinion

'Precious patients'

TREATMENT OF GLOMERULONEPHRITIS

Active treatment
does not *only* mean immunosuppression

Symptoms can be relieved

and

renal failure may be delayed

TREATMENT OF GLOMERULONEPHRITIS

No steroids or immunosuppressives does not = no treatment

Blood pressure

Oedema

Proteinuria

Cholesterol

Smoking

GLOMERULAR DISEASE

GLOMERULAR DISEASE

Minimal change/FSGS

Membranous

MCGN

IgA nephropathy

Post-infectious GN

GLOMERULAR DISEASE

Minimal change/FSGS

Membranous

MCGN

IgA nephropathy

Post-infectious GN

Lupus

Vasculitis

Henoch-Schönlein nephritis

Cryoglobulinaemia

Anti-GBM nephritis

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Thrombotic microangiopathy

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Thrombotic microangiopathy

Amyloid, MIDD & fibrillary GN

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Amyloid, MIDD & fibrillary GN

Diabetic nephropathy

HEREDITARY

Alport
Fabry
Nail-patella
LCAT deficiency

etc ..

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MINIMALCHANGE DISEASE IN ADULTS

- 10-20% of adults with nephrotic syndrome (*cf* children 90%)
- Spontaneous remission occurs in 5-10% of cases within 2 months
- Non-nephrotic proteinuria does not respond well to immunosuppression

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- Spontaneous remission occurs in 5-10% of cases within 2 months
- Non-nephrotic proteinuria does not respond well to immunosuppression

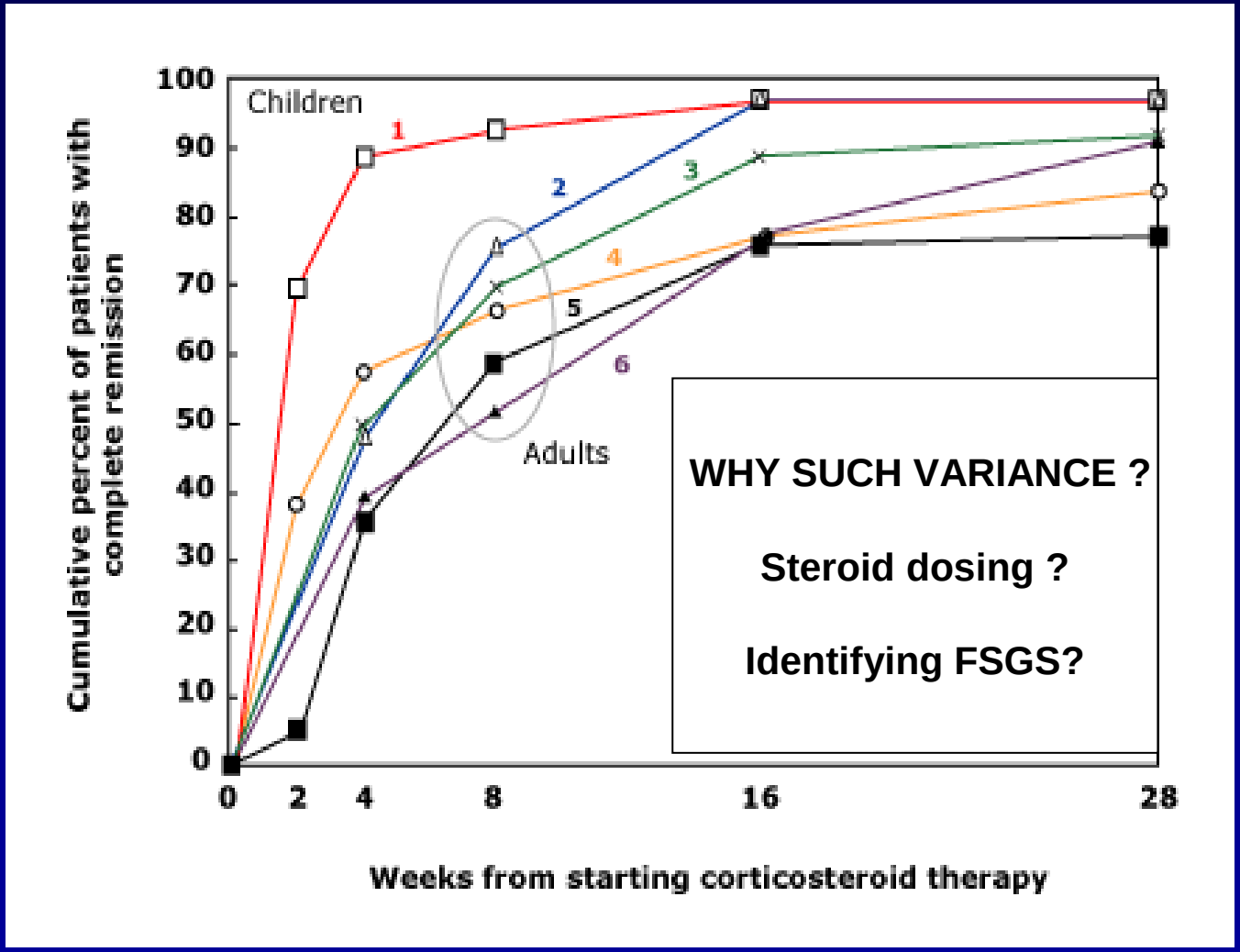
Is this the same disease ?

TREATMENT OF MINIMAL CHANGE DISEASE IN ADULTS

SPECIFIC THERAPY

- Few controlled trial in adults
- Guidelines extrapolated from studies in children and cohort studies
- Controversies in corticosteroid therapy
  - Time to response
  - Dosage & duration of corticosteroids

CORTICOSTEROIDS for MINIMAL CHANGE DISEASE
TIME TO REMISSION IN ADULTS AND CHILDREN



MINIMALCHANGE DISEASE IN ADULTS
Course after steroid treatment

- ~50% will have at least one relapse
- 10-25% frequently relapse
- 25-30% are steroid dependent

MINIMALCHANGE DISEASE IN ADULTS
Second line therapy for frequent relapsing/ steroid dependence

Corticosteroids

- Low dose alternate day regimens

Cyclophosphamide

- 12weeks - 2mg/kg/day(cumulative ‘safe’ dose of 150-250mg/kg)
- Ideally commence following induction of remission

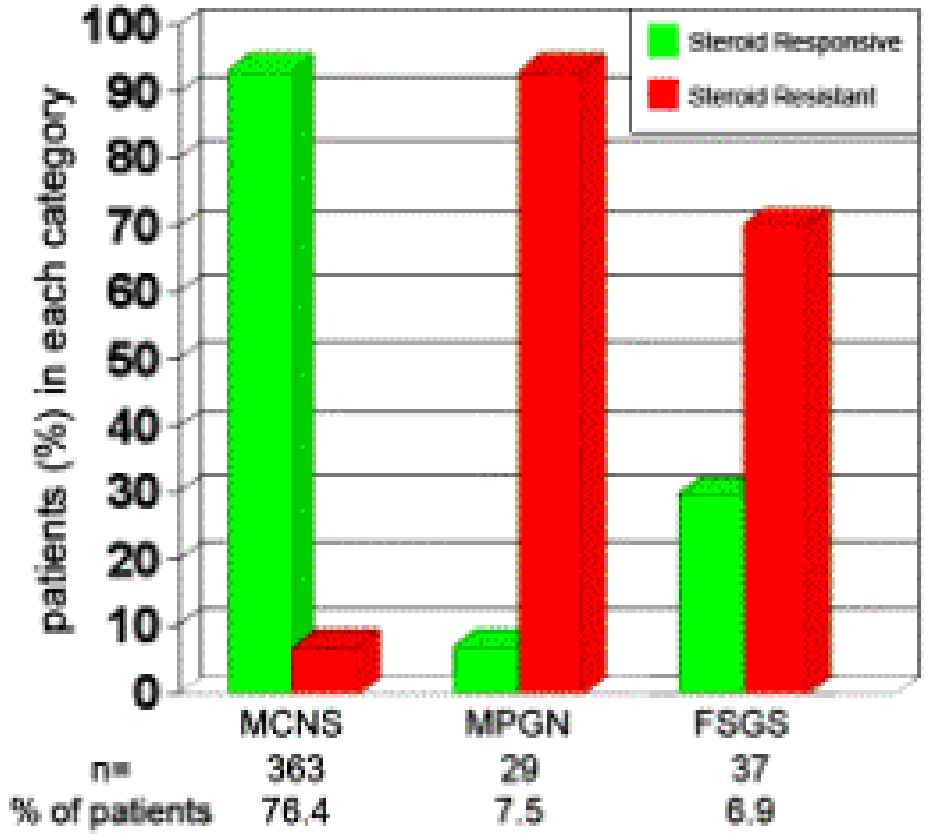
Cyclosporin

- 3-5mg/kg/day (trough level 50-150ng/ml)
- May be first choice in younger patients
- Response within 3 months
- If effective try to withdraw after 1 year

International Study of Kidney Disease in Children

FSGS first described by Habib and others

…correlating histology findings with response to corticosteroids



CAUSES OF ADULT NEPHROTIC SYNDROME

CHICAGO	1976-9		1995-7	
	White	Black	White	Black
Membranous	38%	34%	38%	18%
Minimal change	22%	19%	16%	12%
FSGS	**9%**	**30%**	**25%**	**56%**
IgAN	4%	0%	14%	1%
MCGN	8%	0%	2%	1%

Haas AJKD 1997; 30: 621

FSGS IN WEST AFRICA

SENEGAL
115 biopsies 1993-98

Two thirds - nephrotic syndrome

Primary GN

47% **FSGS**

12.5% **Membranous**

Abdou N et al. Saudi J Kidney Dis Transpl 2003; 14: 212

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

An histological pattern ……. *not* a diagnosis

PATHOLOGICAL CLASSIFICATION OF FSGS

Classic FSGS

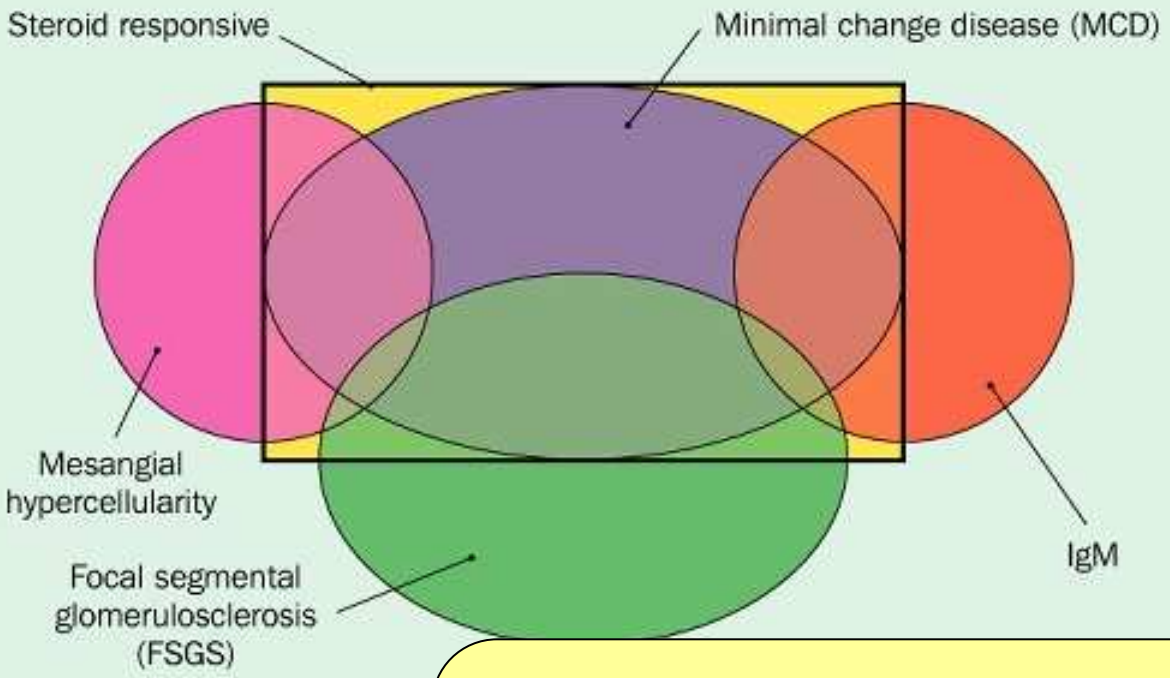
Perihilar variant

Cellular variant

Collapsing variant

Tip variant

Histologic patterns and steroid responsiveness in diseases causing nephrotic syndrome



Does steroid responsiveness define a ‘disease’ ?

Is it more important than presence of FSGS ?

Can minimal change ‘evolve’ into FSGS ?

CLINICAL PRESENTATIONS OF FSGS

PRIMARY FSGS

Typically ‘like minimal change’:

Sudden onset of nephrotic syndrome

Any age –
but commonest in children
and young adults

CLINICAL PRESENTATIONS OF FSGS

PRIMARY FSGS

Typically ‘like minimal change’:

Sudden onset of nephrotic syndrome

Any age –
but commonest in children
and young adults

SECONDARY FSGS

More often:

Asymptomatic proteinuria

Normal serum albumin

Any age

Secondary FSGS

Drugs

Intravenous heroin
Pamidronate
Interferon-α

Secondary FSGS

Drugs

Intravenous heroin
Pamidronate
Interferon-α

Viruses

HIV
Parvovirus B19

Secondary FSGS

Drugs

Intravenous heroin
Pamidronate
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Viruses

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Parvovirus B19

Secondary FSGS

Adaptive response
to
reduced renal mass

Renal agenesis/dysplasia
Oligomeganephronia
Surgical renal ablation
Reflux nephropathy
Cortical necrosis
Chronic allograft nephropathy
Any advanced renal disease
with reduction in functioning nephrons

Drugs

Intravenous heroin
Pamidronate
Interferon-α

Viruses

HIV
Parvovirus B19

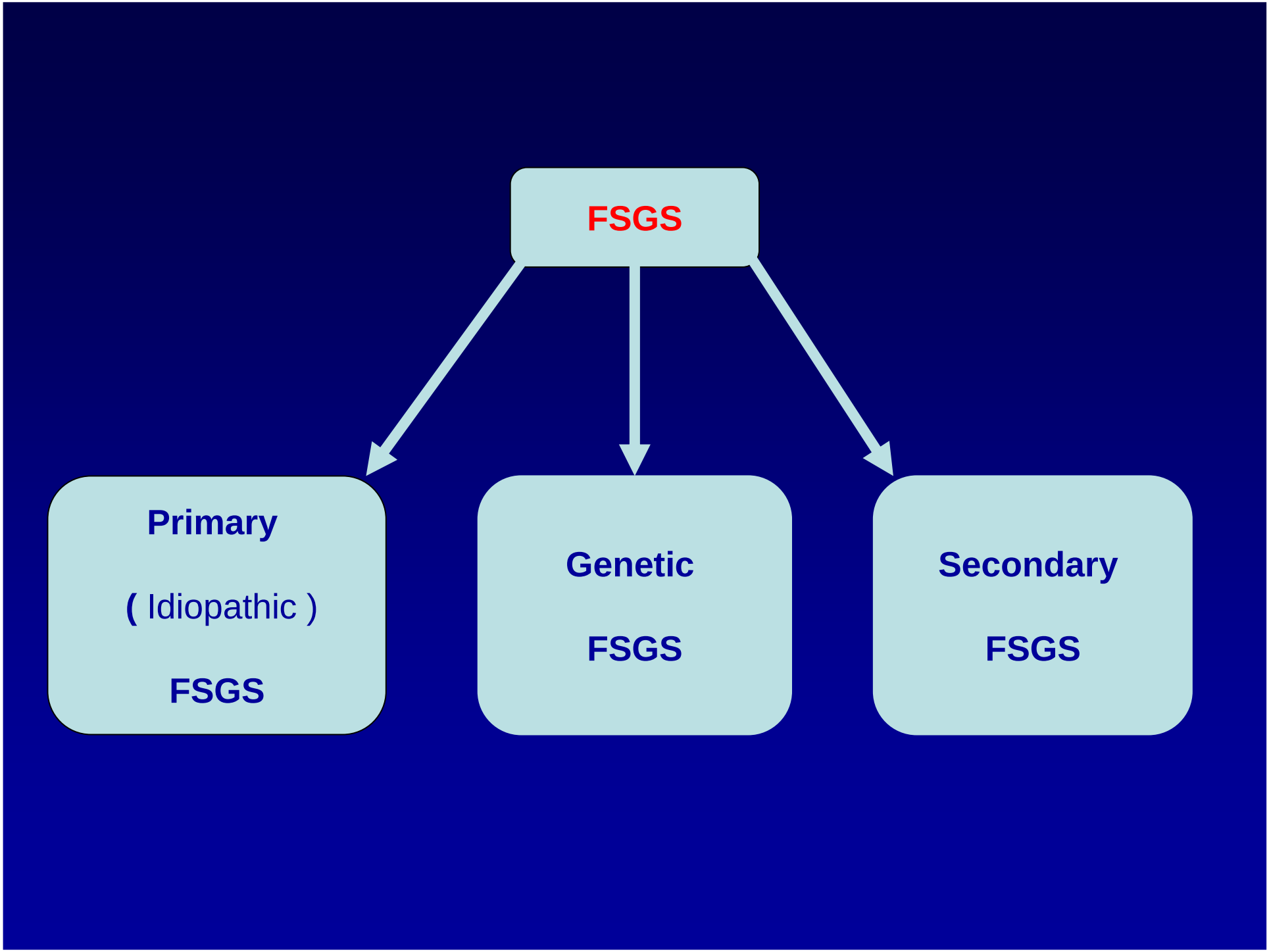
Secondary FSGS

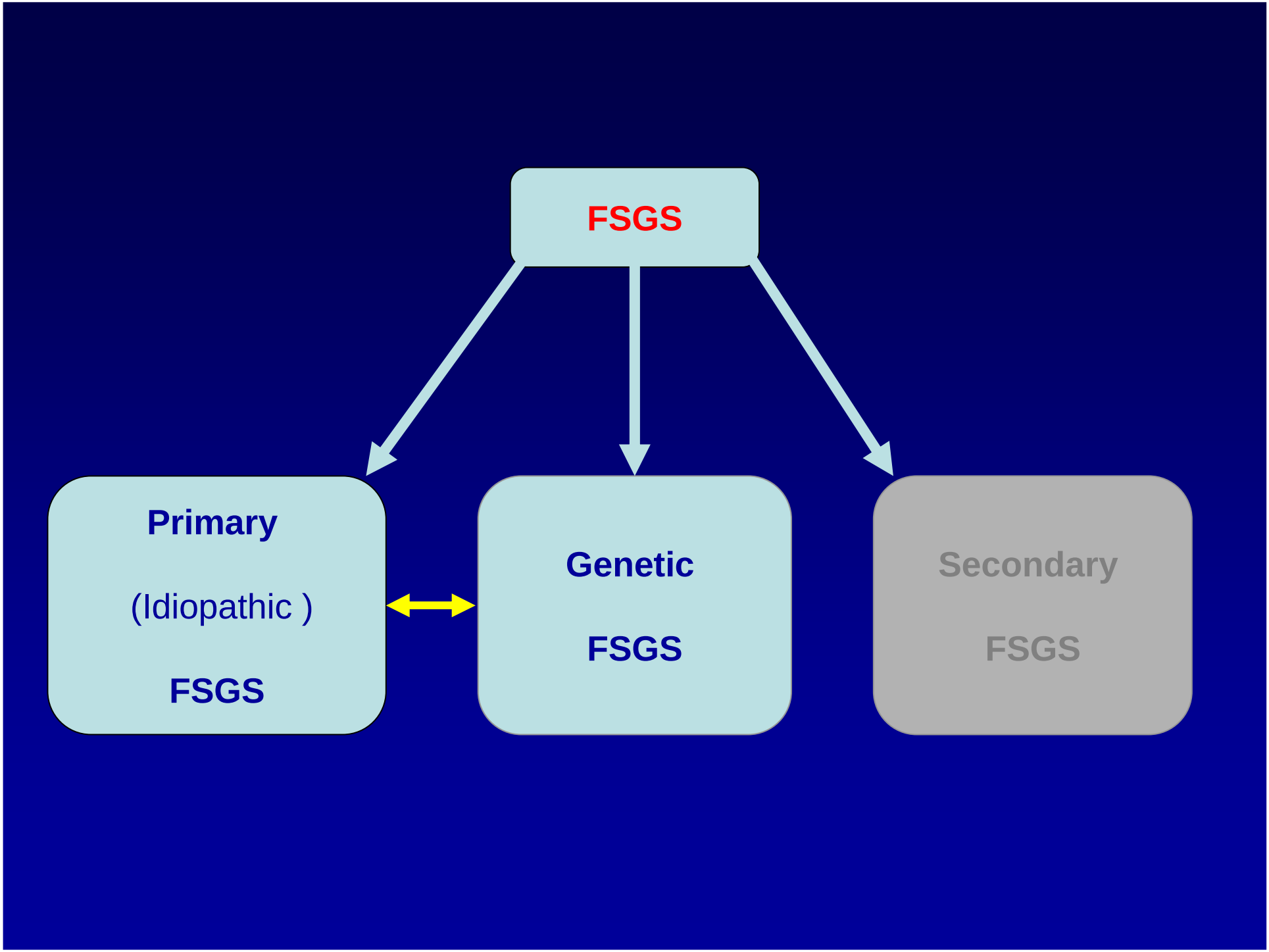
Adaptive response to reduced renal mass

Renal agenesis/dysplasia
Oligomeganephronia
Surgical renal ablation
Reflux nephropathy
Cortical necrosis
Chronic allograft nephropathy
Any advanced renal disease with reduction in functioning nephrons

Adaptive response with initially normal renal mass

Obesity
Sickle cell nephropathy
Congenital cyanotic heart disease


FSGS
Primary
(Idiopathic)
FSGS
Genetic
FSGS
Secondary
FSGS


FSGS
Primary
(Idiopathic)
FSGS
Genetic
FSGS
Secondary
FSGS

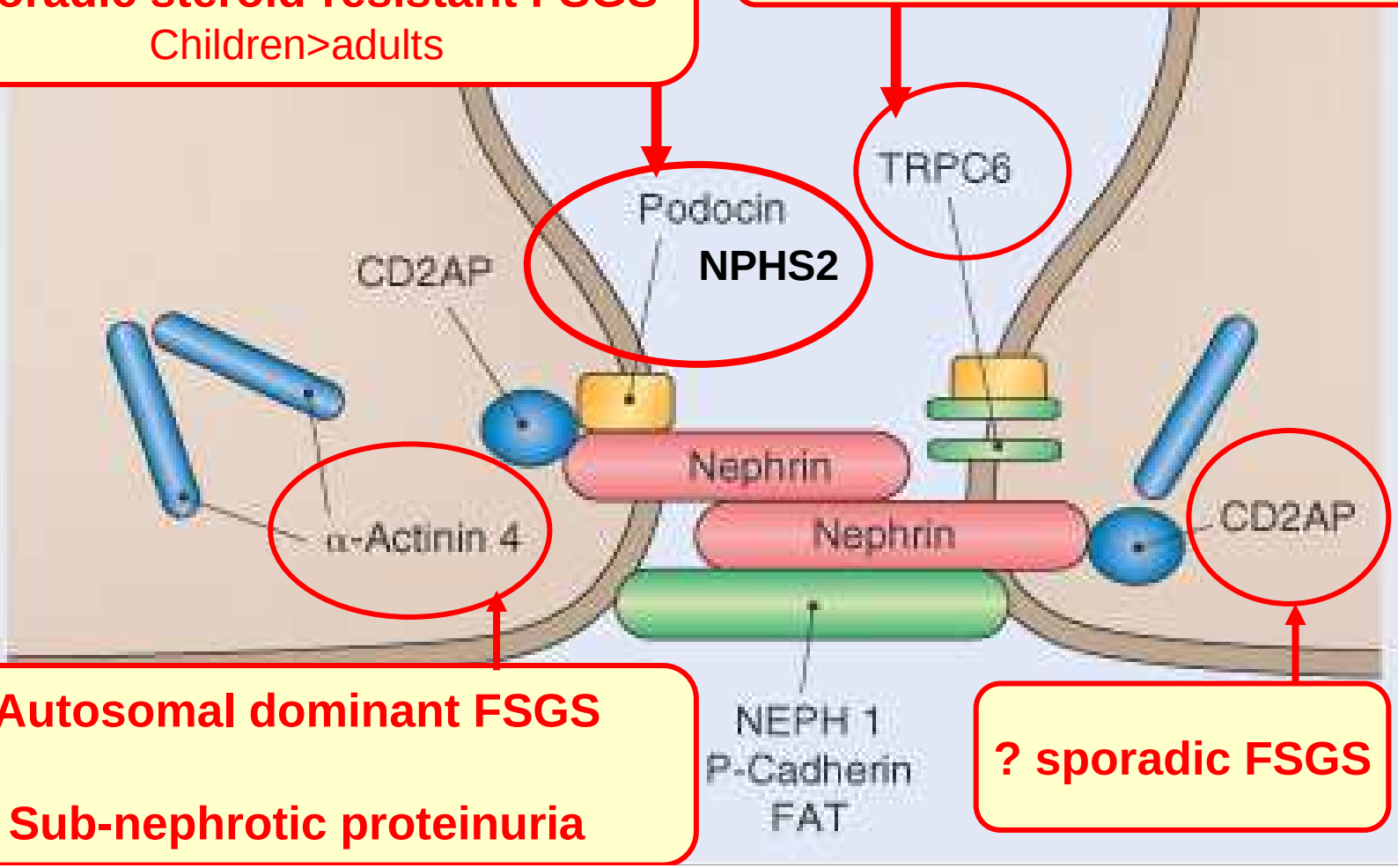
Proteins of the podocyte slit diaphragm involved in proteinuria

Autosomal recessive FSGS

Sporadic steroid-resistant FSGS

Children>adults

Autosomal dominant FSGS



Autosomal dominant FSGS

Sub-nephrotic proteinuria

? sporadic FSGS

PREDICTIONS

FSGS associated with podocyte protein mutations

PREDICTIONS

FSGS associated with podocyte protein mutations

… will be steroid resistant

PREDICTIONS

FSGS associated with podocyte protein mutations

… will be steroid resistant

… will not recur in transplants

PATHOGENESIS OF FSGS

Lessons from transplant recurrence

PATHOGENESIS OF FSGS

Lessons from transplant recurrence

RECURRENCE
is not inevitable

PATHOGENESIS OF FSGS

Lessons from transplant recurrence

RECURRENCE
is not inevitable

CLINICAL
recurrent proteinuria may be immediate
……implies ‘circulating factor’

PATHOGENESIS OF FSGS

Lessons from transplant recurrence

RECURRENCE
is not inevitable

CLINICAL
recurrent proteinuria may be immediate
……implies ‘circulating factor’

PATHOLOGICAL
After one month of recurrence
there may be foot process effacement
***…….but* no segmental lesions**

PATHOGENESIS OF PRIMARY FSGS

Genetics

Circulating factor[s]

Second [or third] 'hit'

PRIMARY FSGS

Can we predict outcome at presentation ?

Does spontaneous remission occur ?

Can we select which patients should receive corticosteroids ?

PRIMARY FSGS

Can we predict outcome at presentation ?

Histology

Genetics

Clinical

PRIMARY FSGS

Can we predict outcome at presentation ?

HISTOLOGY

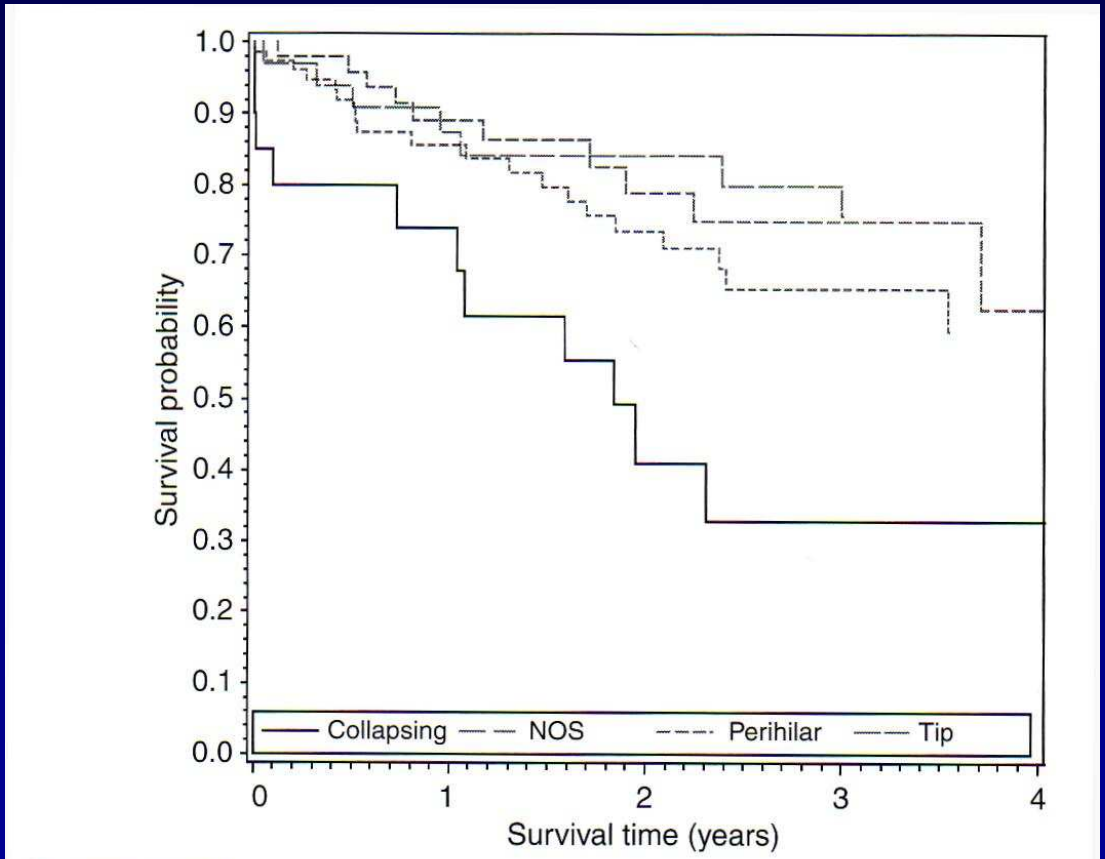
Tip lesion

Collapsing variant

Number of glomeruli with segmental / global sclerosis ?

Tubular atrophy & interstitial fibrosis

FSGS – HISTOLOGICAL VARIANTS & OUTCOME



Patients at risk					
Collapsing	20	12	5	3	3
NOS	78	47	33	17	6
Perihilar	50	35	21	12	4
Tip	34	26	22	19	11

Thomas DB *et al*. KI 2006; 69: 920

PRIMARY FSGS

Can we predict outcome at presentation ?

GENETICS

Not yet ……

PRIMARY FSGS

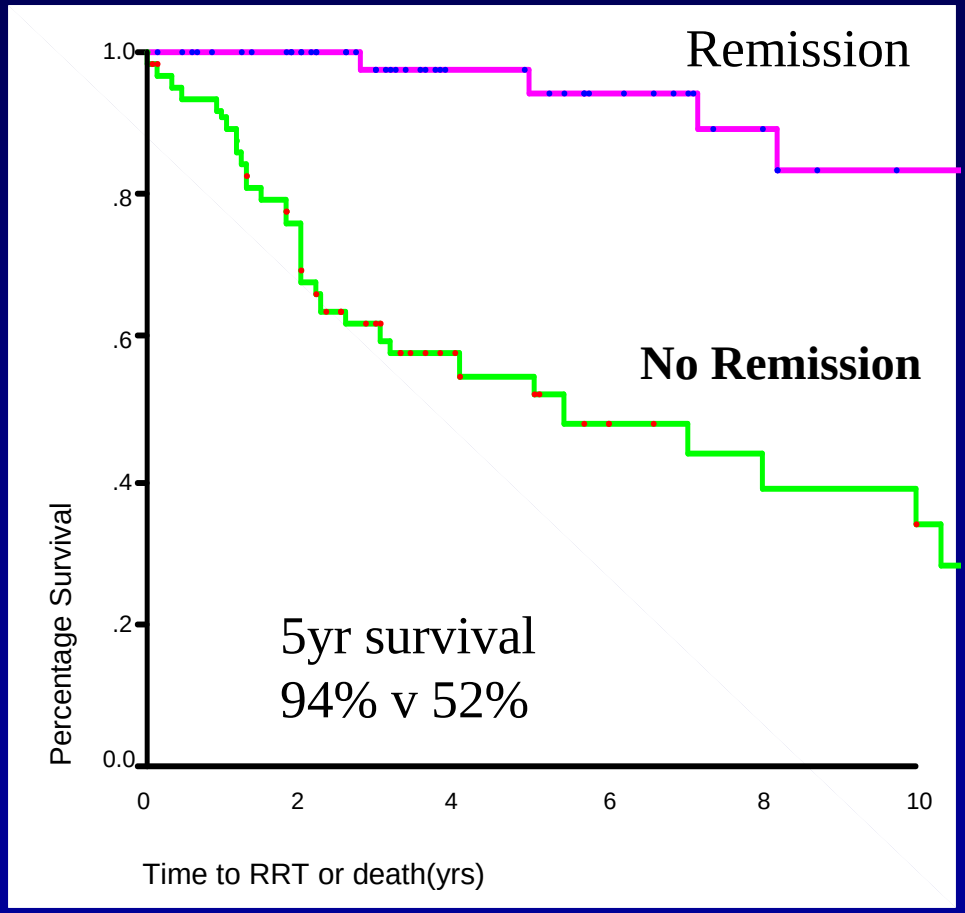
Can we predict outcome at presentation ?

IMPORTANCE OF PROTEINURIA

Non-nephrotic	**20% ESRD at 10 years**
Nephrotic	**>50% ESRD at 5-10 years**
Nephrotic >10g/day	**~100% ESRD at 5-10 years**

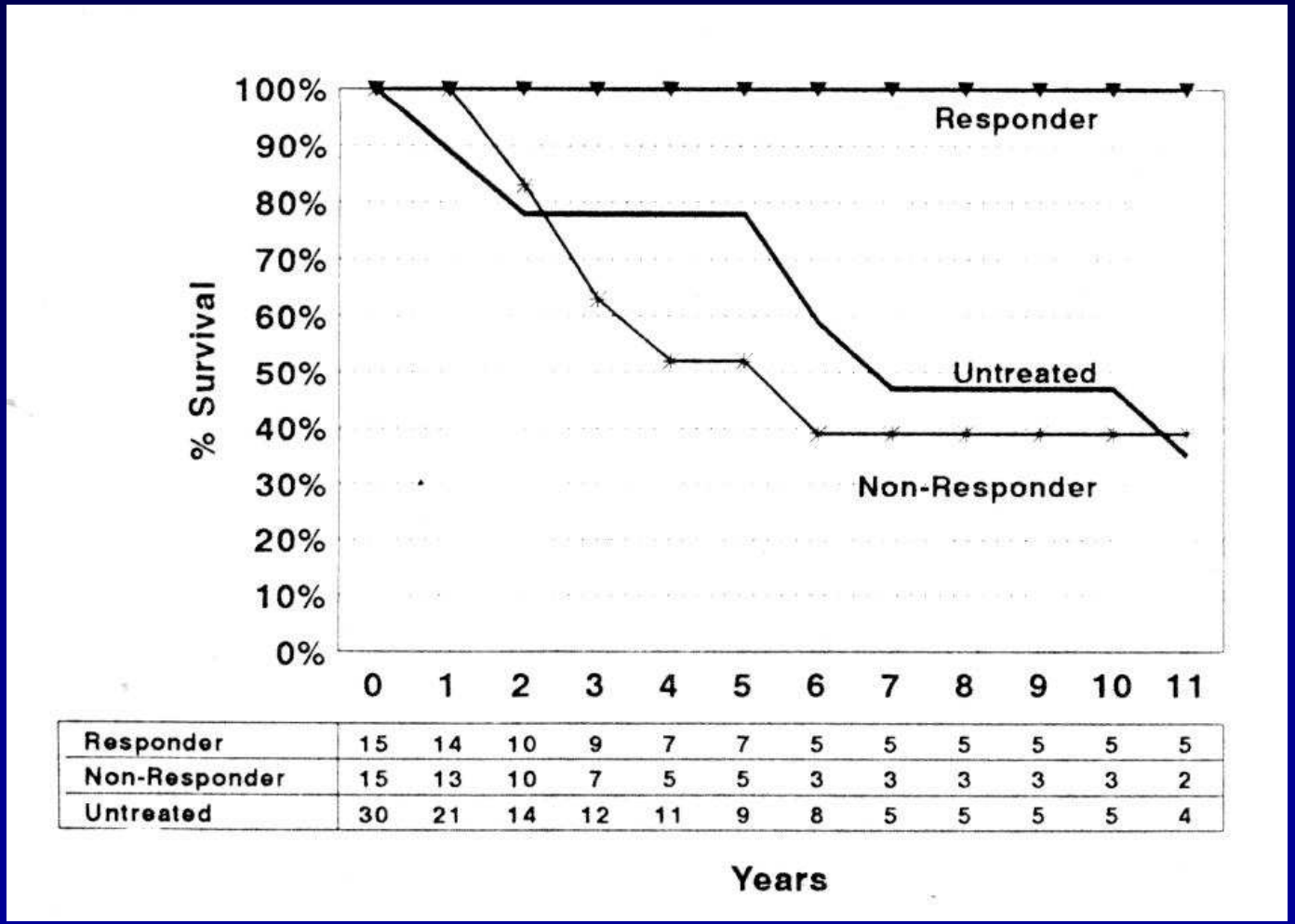
Malignant FSGS

PRIMARY FSGS
Survival according to remission



Stirling C *et al*– QJM 2005; 98: 443

PROGNOSIS IN NEPHROTIC PRIMARY FSGS



Responder	15	14	10	9	7	7	5	5	5	5	5	5
Non-Responder	15	13	10	7	5	5	3	3	3	3	3	2
Untreated	30	21	14	12	11	9	8	5	5	5	5	4

Rydel et al AJKD 1995; 25: 534

TREATMENT OF

NEPHROTIC PRIMARY FSGS

TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
Statins

TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
Statins

IMMUNOSUPPRESSION

Corticosteroids
Cyclophosphamide
Cyclosporine

TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
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Corticosteroids
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NEWER IMMUNOSUPPRESSIVES

Tacrolimus
Mycophenolate

TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
Statins

IMMUNOSUPPRESSION

Corticosteroids
Cyclophosphamide
Cyclosporine

NEWER IMMUNOSUPPRESSIVES

Tacrolimus
Mycophenolate

Plasma exchange

Plasma adsorption

CORTICOSTEROIDS IN FSGS

Evidence from randomised controlled trials…

CORTICOSTEROIDS IN FSGS

No RCTs - retrospective cohort studies

1980's

8 weeks oral prednisolone ~ 1mg/kg/day [based on MCNS in children]

Complete remission ~ 20-30%

CORTICOSTEROIDS IN FSGS

No RCTs - retrospective cohort studies

1980's

8 weeks oral prednisolone ~ 1mg/kg/day [based on MCNS in children]

Complete remission ~ 20-30%

1990's

At least 4 months - prednisolone starting 1-2 mg/kg/day

- **4 months treatment - complete remission – 50-60%**

INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response

INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response

Are the demographics typical ?

INERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response

Are the demographics typical ?

Is the histology defined ?

INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response

Are the demographics typical ?

Is the histology defined ?

Were causes of secondary FSGS excluded ?

INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Who got the treatment?

The worst nephrotics

Those considered fit enough to have steroids ?

Physician choice/prejudice ?

INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Any immunosuppressive therapy must add benefit to 'best supportive therapy'…

BP 125/75

ACE inhibitor ± ARB

Statin

Were these achieved in retrospective studies ?

PRIMARY FSGS WITH NEPHROTIC SYNDROME

Does spontaneous remission occur ?

PRIMARY FSGS WITH NEPHROTIC SYNDROME

Does spontaneous remission occur ?

United States	**4-6%**
European study	**16%**
UK 5 centre study	**23%**

PRIMARY FSGS

Remission rates

	Spontaneous remission	Treatment remission	Benefit
Conventional view	5%	20-50%	4 – 10 fold
UK 5 centre study	23%	65%	< 3 fold

CORTICOSTEROIDS IN FSGS

There are no RCTs ..we rely on retrospective cohort studies

Is a 'response' to 6 months of corticosteroids just a spontaneous remission?

Half of all patients with FSGS will receive 6 months of futile corticosteroids

What is acceptable toxicity ?

PREDICTING RESPONSE TO CORTICOSTEROIDS IN FSGS

Genetics

- **More steroid resistance in Blacks**
- **Familial FSGS – usually steroid resistant**

PREDICTING RESPONSE TO CORTICOSTEROIDS IN FSGS

Histology

Tip lesion – steroid responsive

Collapsing variant – steroid resistant

Number of glomeruli with segmental / global sclerosis

Tubulo-interstitial fibrosis

CYCLOPHOSPHAMIDE IN FSGS

Evidence from randomised controlled trials…

CYCLOSPORINE IN FSGS

ONE

randomised controlled trial

IMMUNOSUPPRESSION IN PRIMARY FSGS

Initial response to steroids	*N*	Complete remission	Partial remission	No response
Cytotoxic therapy				
Steroid-responsive	43	22 (51%)	10 (23%)	11 (26%)
Steroid-resistant	185	31 (17%)	27 (15%)	127 (69%)
Cyclosporine A therapy				
Steroid-responsive	15	11 (73%)	1 (7%)	3 (20%)
Steroid-resistant	281	82 (29%)	61 (22%)	138 (49%)

Korbet S *et al.* KI 2002; 62: 2301

IMMUNOSUPPRESSION IN PRIMARY FSGS

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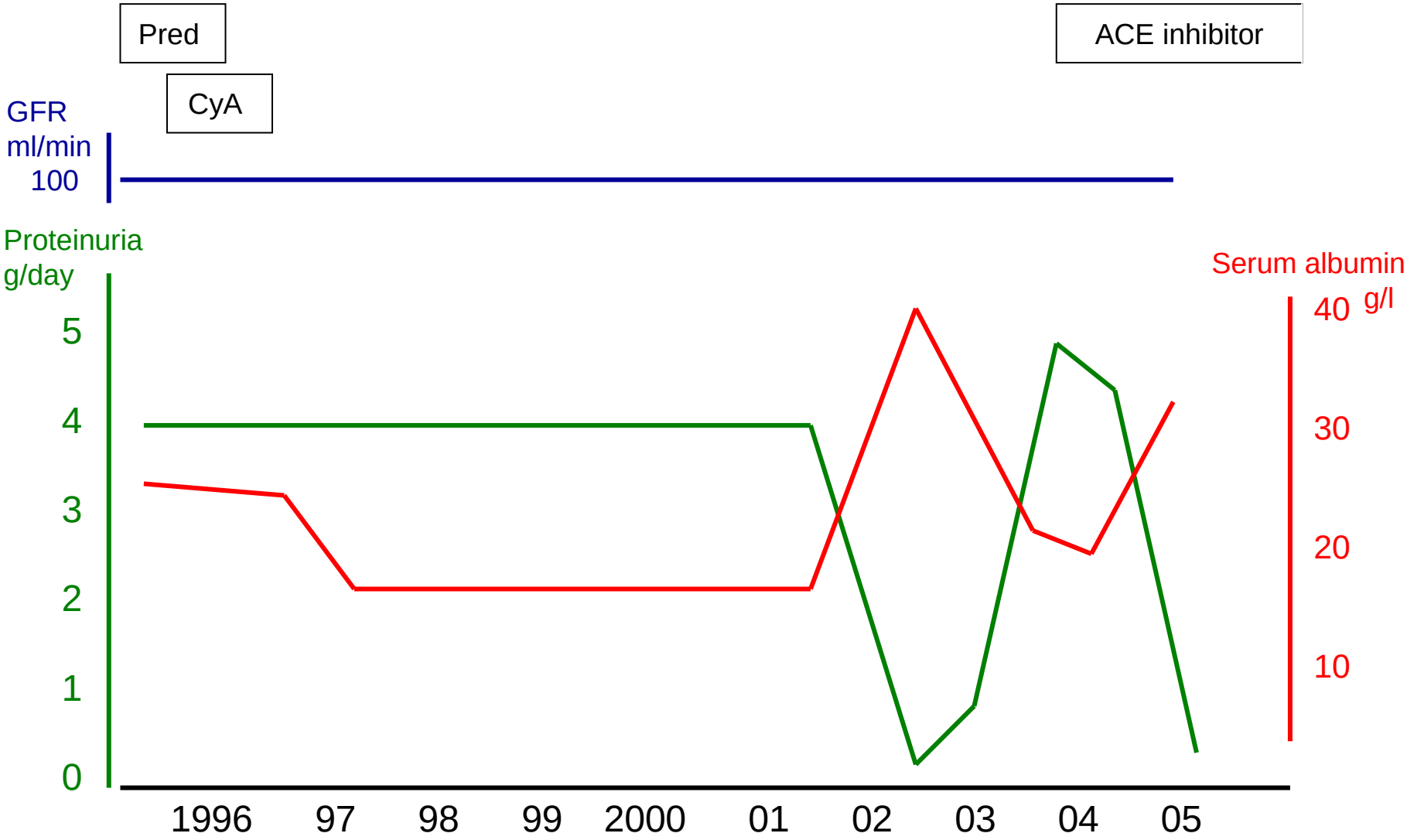


Female, born 1955 – Primary FSGS

TACROLIMUS IN PRIMARY FSGS

Anecdotal evidence only

MYCOPHENOLATE IN PRIMARY FSGS

Anecdotal evidence only

SIROLIMUS IN PRIMARY FSGS

Anecdotal evidence only

PLASMA EXCHANGE IN FSGS

PRIMARY FSGS

Evidence base is small

~ 20 patients - < 50% have some response

PLASMA EXCHANGE IN FSGS

PRIMARY FSGS

Evidence base is small

~ 20 patients - < 50% have some response

TRANSPLANT RECURRENCE OF PRIMARY FSGS

~ 50% respond. Often completely

TREATMENT OF MEMBRANOUS NEPHROPATHY

Idiopathic

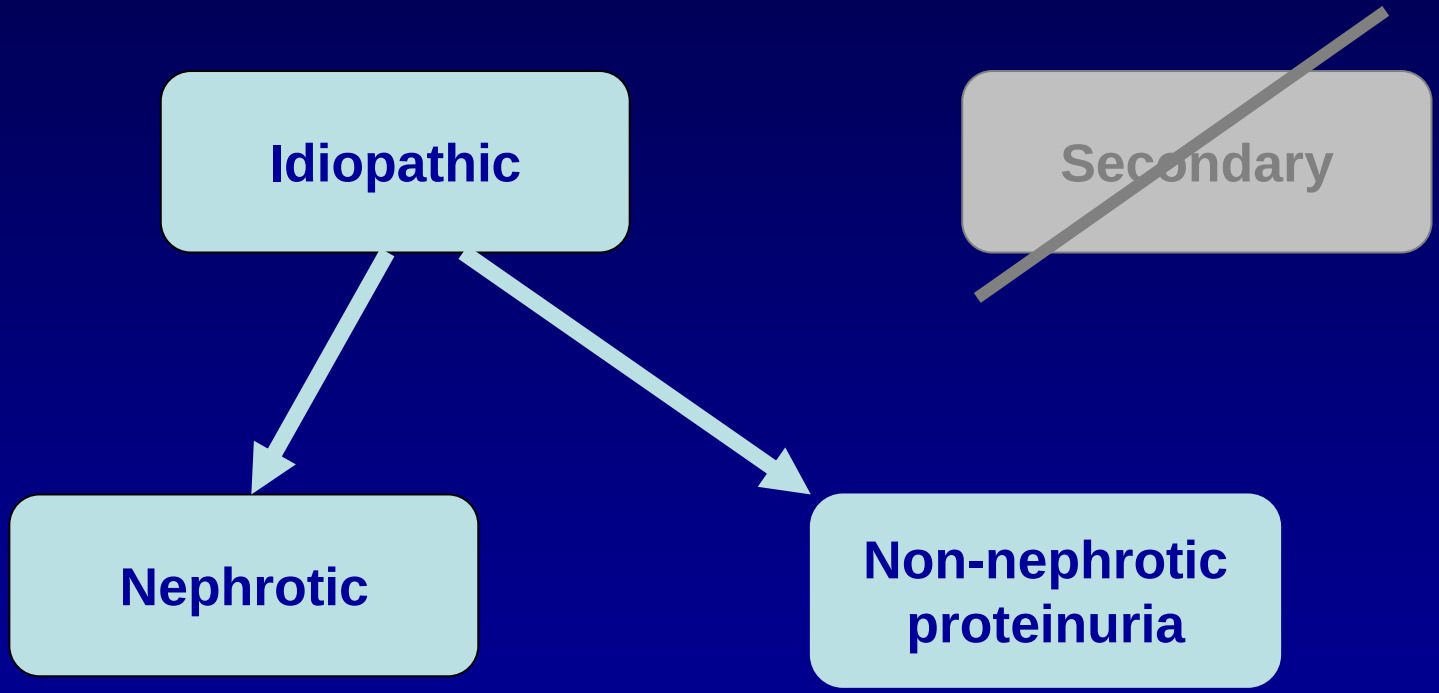
Secondary

TREATMENT OF MEMBRANOUS NEPHROPATHY

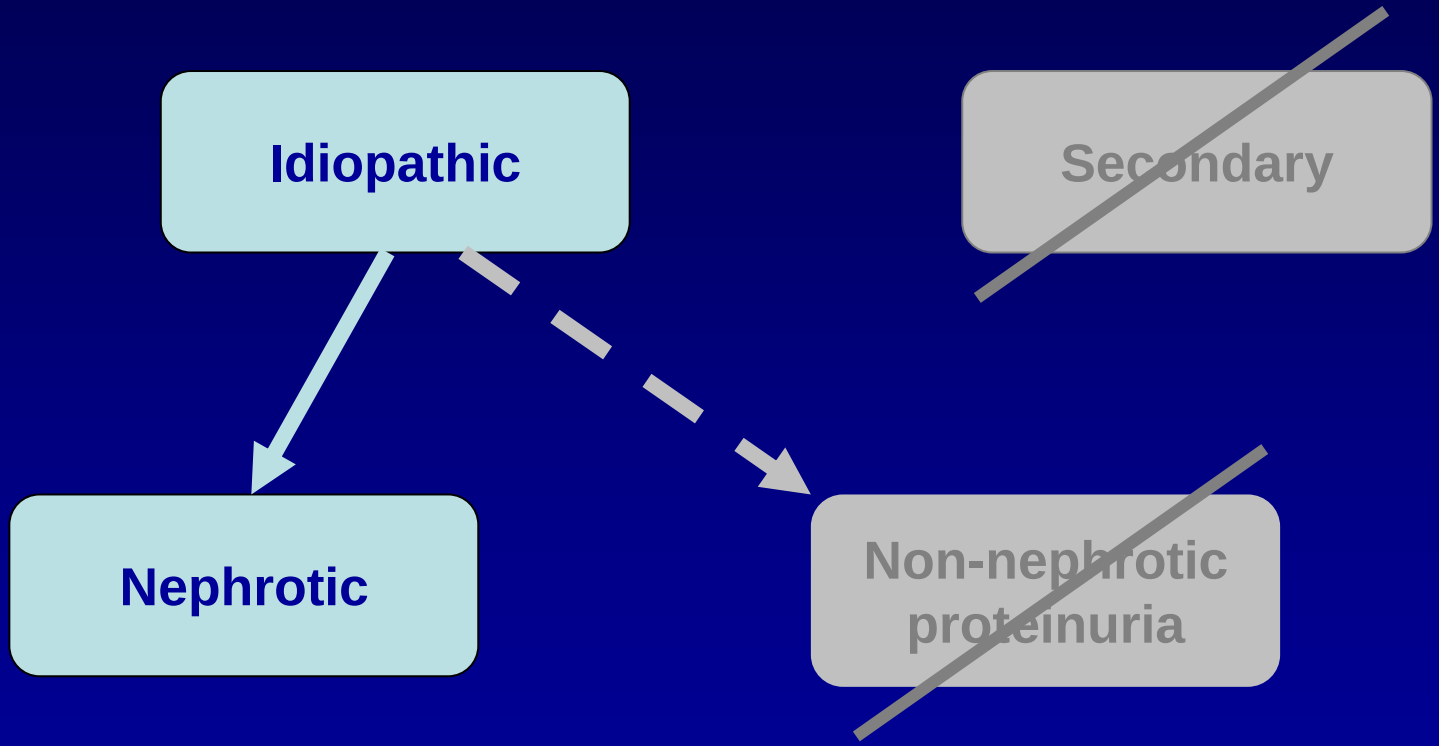
Idiopathic

~~Secondary~~

TREATMENT OF MEMBRANOUS NEPHROPATHY



TREATMENT OF MEMBRANOUS NEPHROPATHY



TREATMENT GOALS
IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

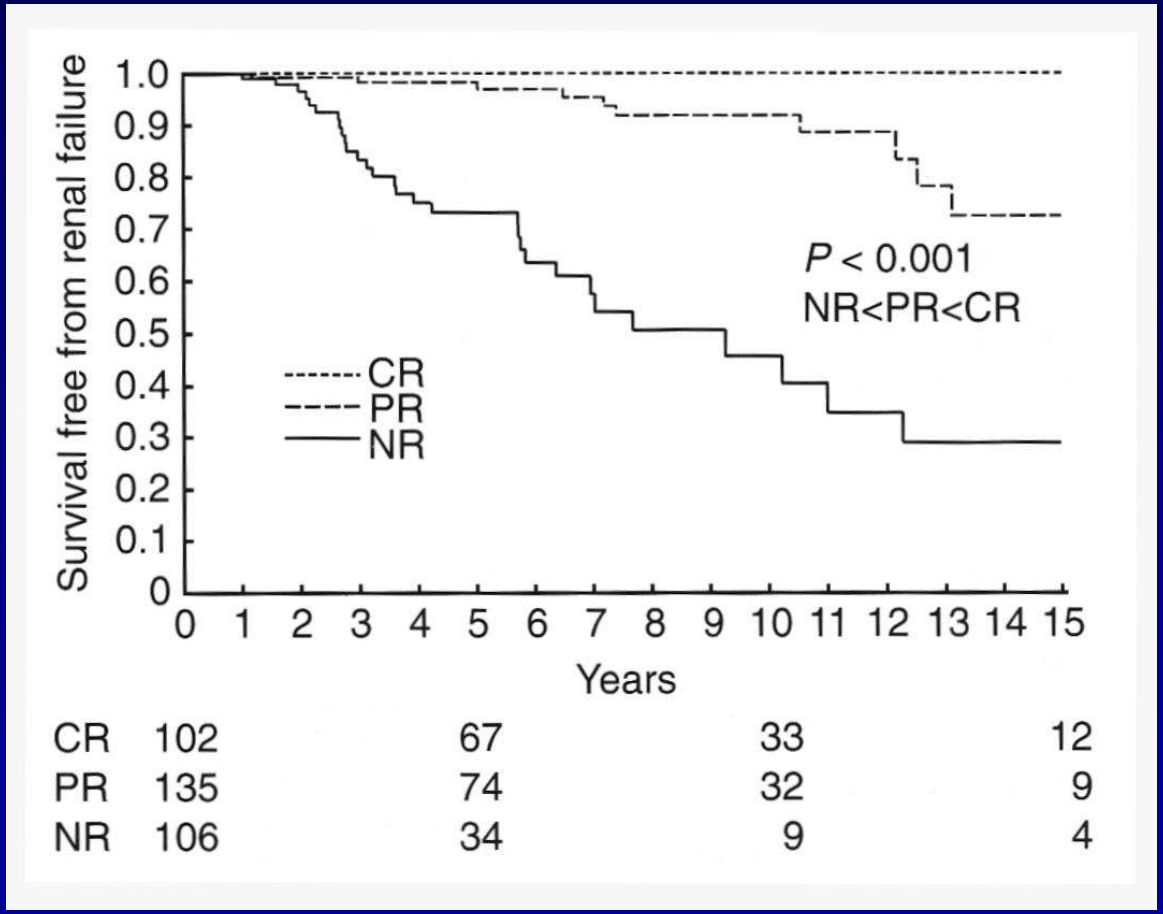
Complete or partial remission of proteinuria

Avoid ESRD

Avoid death

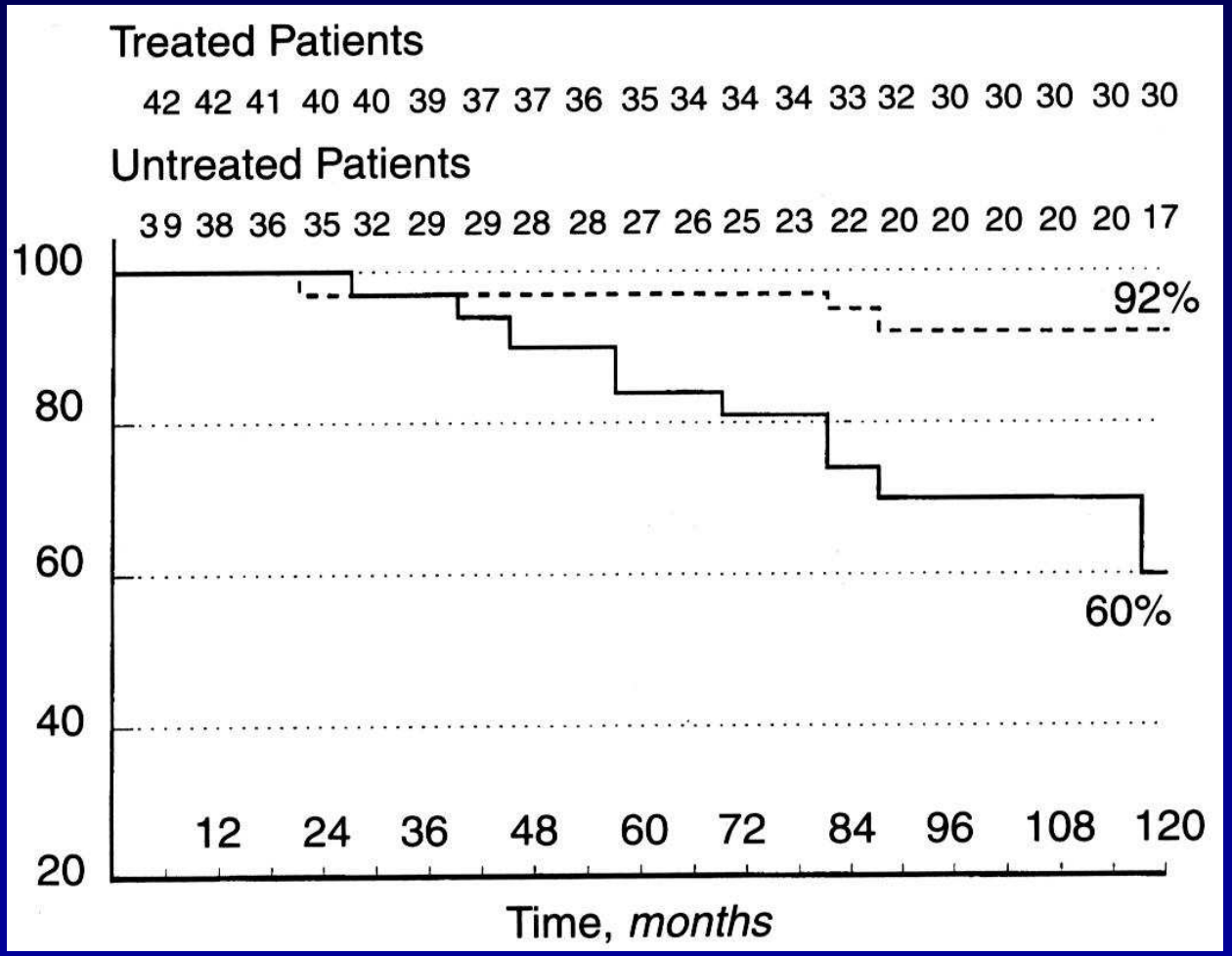
VALUE OF PARTIAL REMISSION IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

TORONTO GN REGISTRY - 343 patients



Troyanov S et al. KI 2004; 66: 1199

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



Ponticelli C *et al*. KI 1995; 48: 1600

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

In 6 months the patient receives:

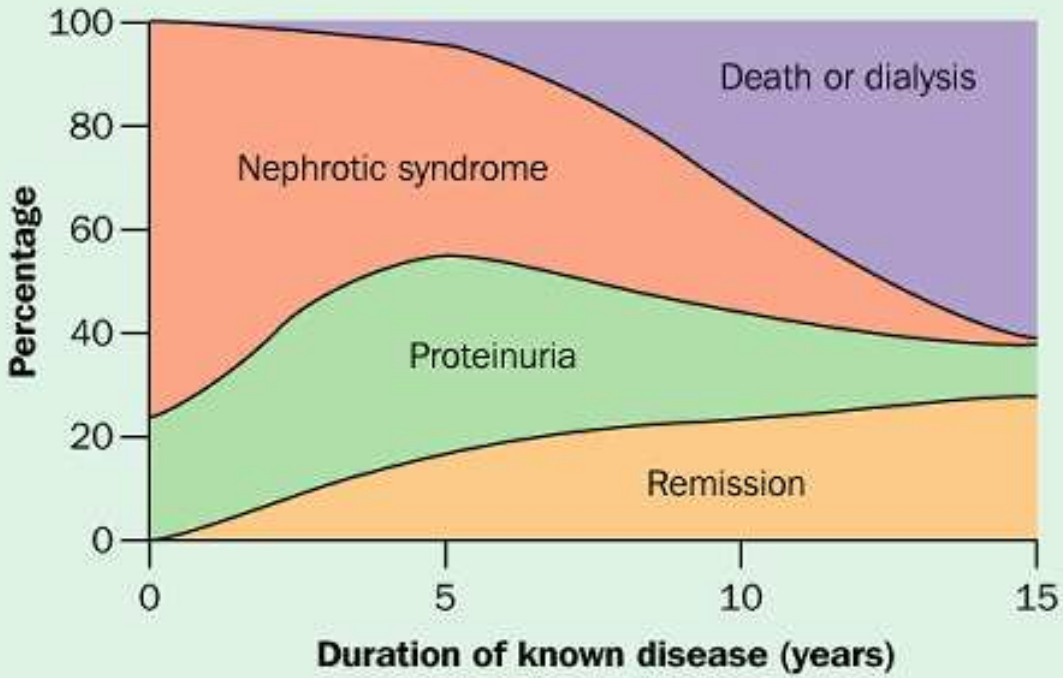
9 grams Methylprednisolone
***And* oral Prednisolone 0.4mg/kg/alt day for 3 months**

plus

Chlorambucil 0.2 mg/kg/day for 3 months
or
Cyclosphosphamide 2.5 mg/kg/day

Ponticelli C *et al*. KI 1995; 48: 1600

Outcomes in untreated membranous nephropathy



RESTRICTED USE OF IMMUNOSUPPRESSIVE TREATMENT IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

The Nijmegen strategy

Immunosuppression only for deteriorating renal function or intractable nephrotic syndrome

74% 7 year renal survival [32% in historical controls]

Complete or partial remission 86%

Wetzels J *et al*: QJM 2004; 97: 353 – NDT 2004; 19: 1142 - NDT 2004; 19: 2036

IMPACT OF IMMUNOSUPPRESSIVE TREATMENT ON ESRD IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

The Nijmegen strategy

Prednisolone & cyclophosphamide only for declining GFR or intractable nephrotic syndrome

Incidence of ESRD due to IMN: 1991 – 2005

70% reduction in Nijmegen

compared to remainder of Netherlands

Hofstra J, Wetzels J *et al*. NDT 2008 epub 17 July

IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

CORTICOSTEROIDS

No beneficial effect on any end point

Schieppati A *et al.* www.thecochranelibrary.com

IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

CYCLOSPORIN

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Schieppati A *et al.* www.thecochranelibrary.com

IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

ALKYLATING AGENTS

Beneficial effect on complete remission only

Cyclophosphamide – fewer discontinuations for adverse effects than Chlorambucil

Schieppati A *et al.* www.thecochranelibrary.com

PROGNOSIS OF UNTREATED PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY

100 ‘consecutive’ patients

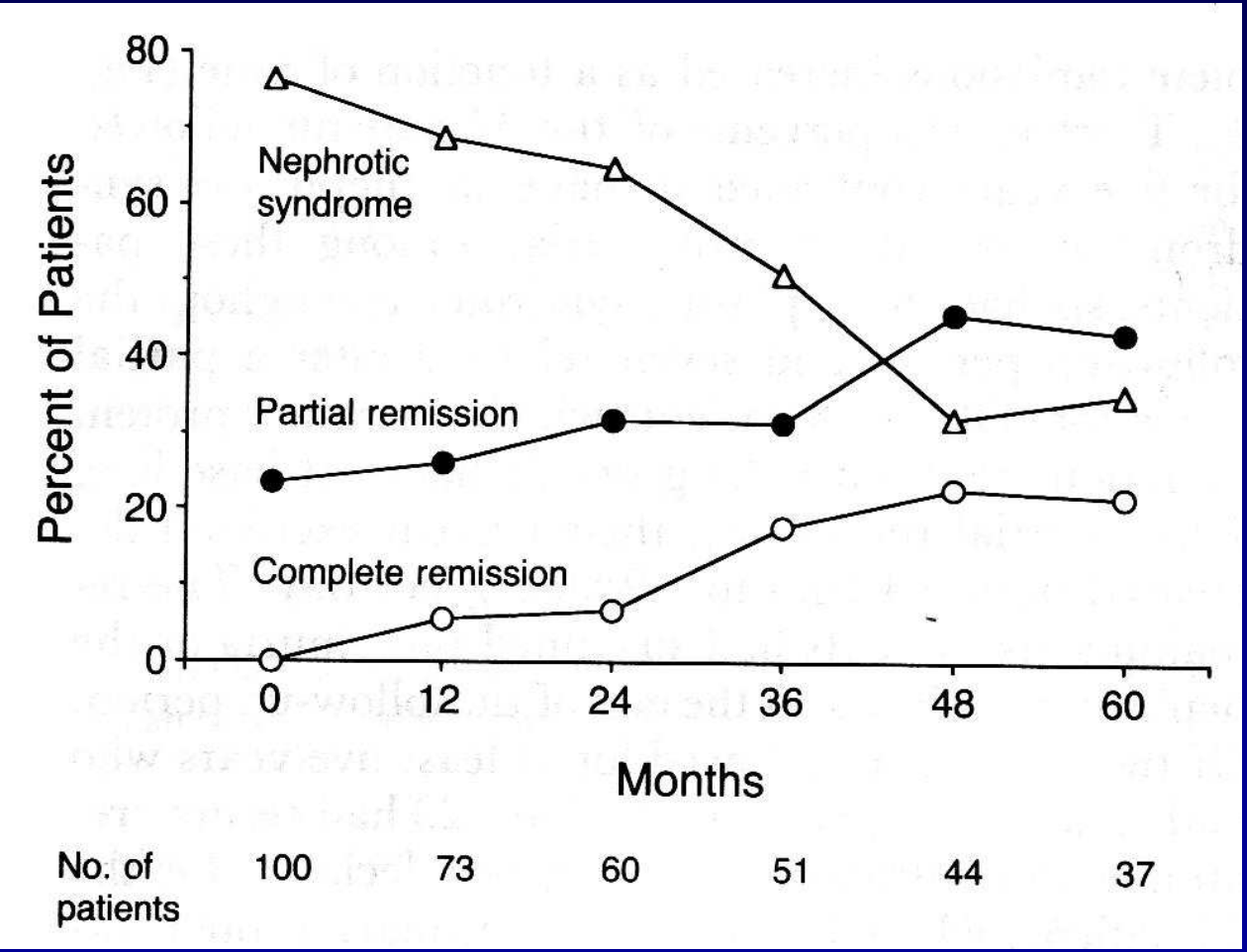
BP Rx / diuretics as indicated

Some ACE inhibitors

BP defined >160/95

Schieppati A et al. NEJM 1993; 329: 85

PROGNOSIS OF UNTREATED PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY

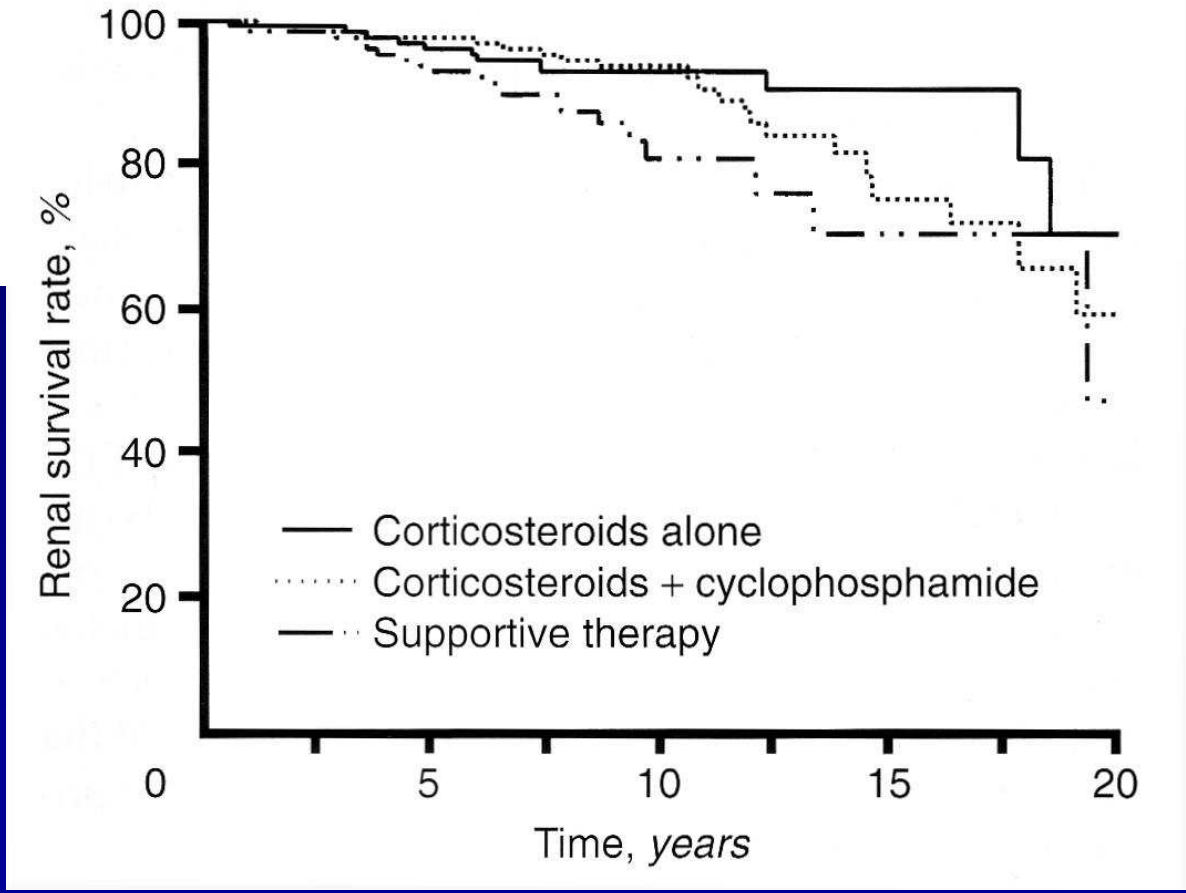


Schieppati A *et al*. NEJM 1993; 329: 85

PROGNOSIS OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN JAPAN

949 patients followed for 20 years
No RCTs

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



Shiiki H et al. Kidney Int 2004; 5: 1400

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

Blood pressure defined as > 160/90

Renin-angiotensin blockade ?

Ponticelli C *et al*. KI 1995; 48: 1600

IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

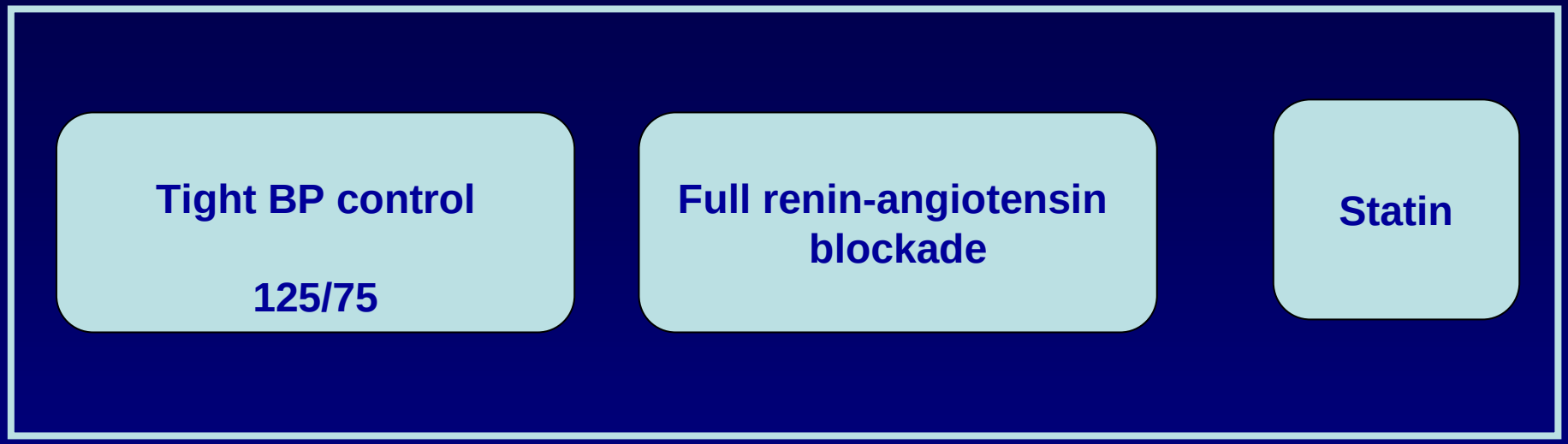
Cochrane Review: 18 trials – 1025 patients

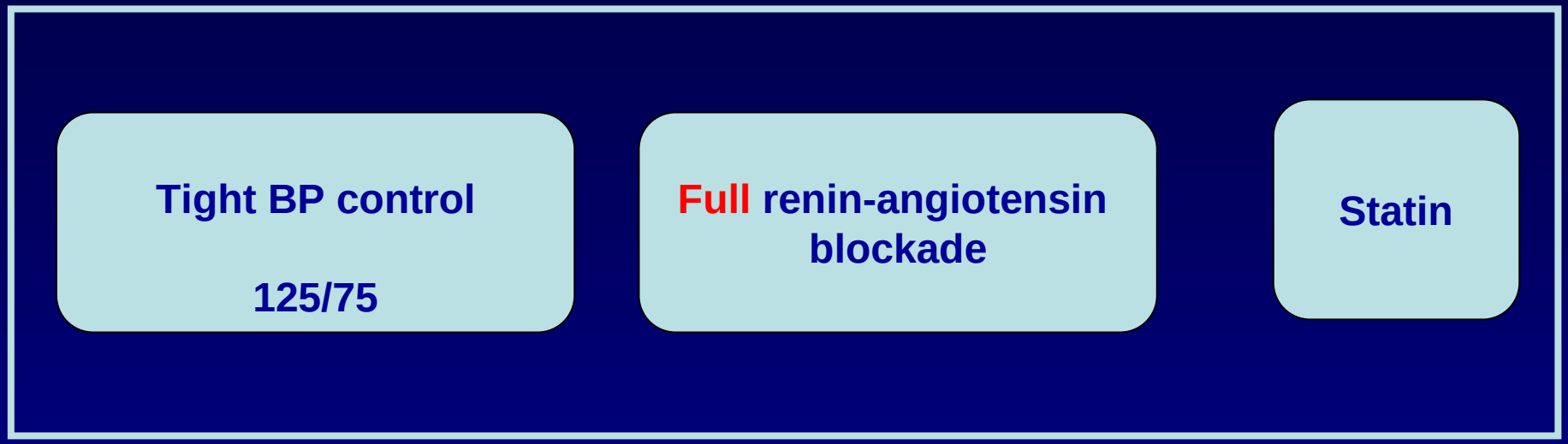
POSSIBLE CONFOUNDING FACTORS

Use of ACE inhibitors/ARB - *? no effect*

BP control – *no data*

Schieppati A *et al.* www.thecochranelibrary.com


Tight BP control
125/75
Full renin-angiotensin blockade
Statin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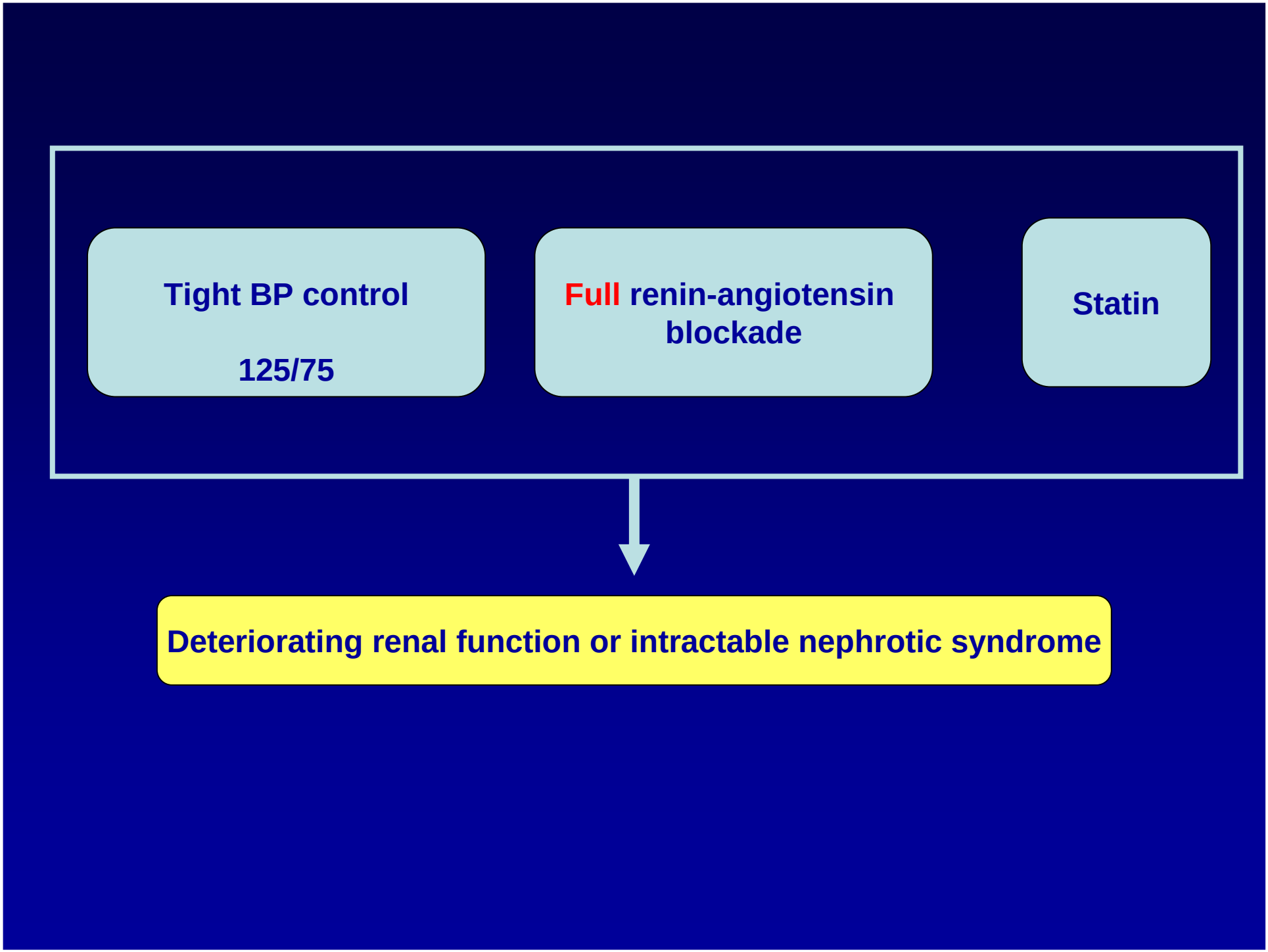
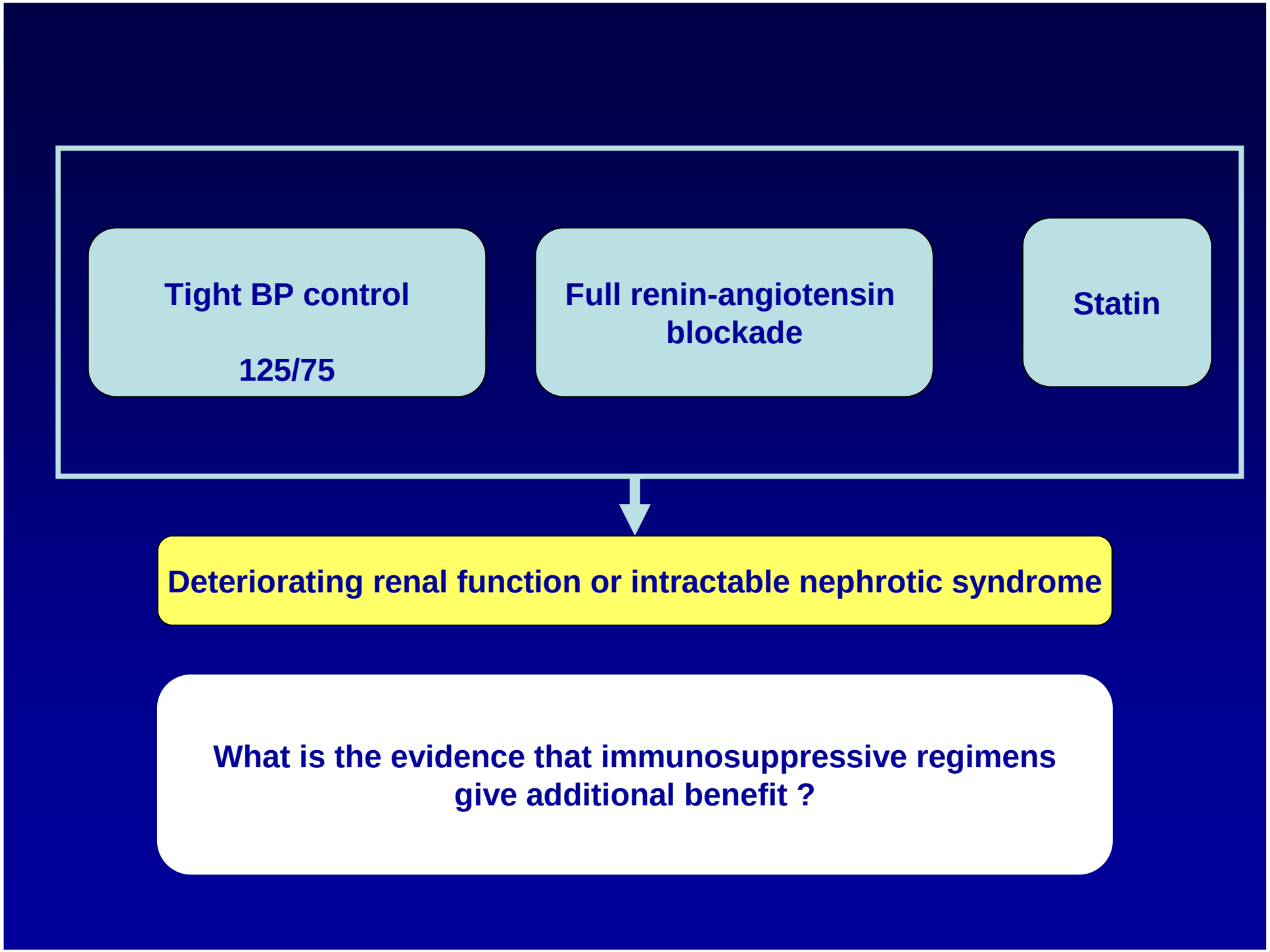

Tight BP control
125/75
Full renin-angiotensin blockade
Statin
Deteriorating renal function or intractable nephrotic syndrome


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 ?

MYCOPHENOLATE IN RESISTANT MEMBRANOUS NEPHROPATHY

4 SMALL 'PILOT' STUDIES – total 80 patients

MMF 2g/day for 6-16 months

Proteinuria reduced in 3 of 4 studies

No effect on renal function

Miller G *et al*. AJKD 2000; 36: 250
Polenakovic M et al. NDT 2003; 18: 1235
Chan TM *et al.* Nephrology 2007; 12: 576
Dussol B *et al.* AJKD 2008 epub 26 June

RITUXIMAB

Anti-CD20 monoclonal antibody

Two doses typically depletes peripheral B cells for 4-6 months

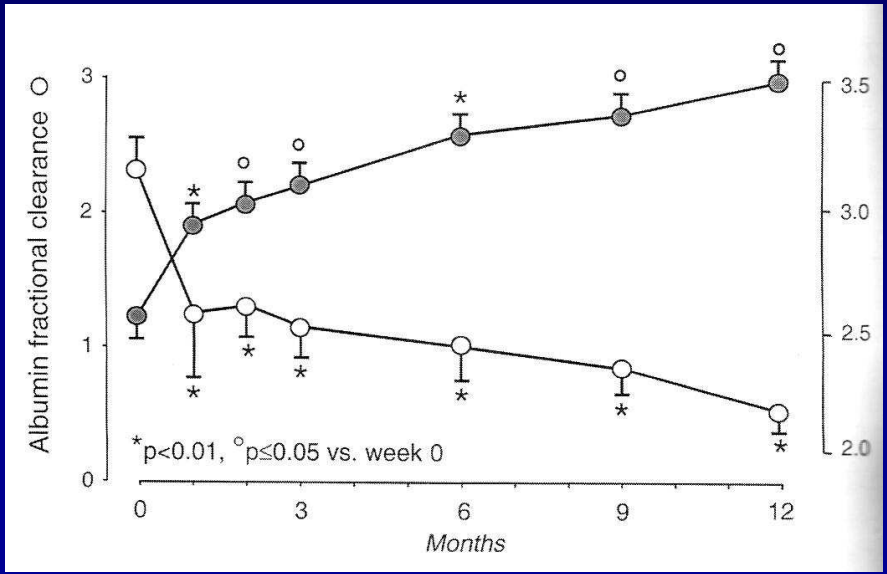
? FcγRIII polymorphisms modify B cell response

Safety profile encouraging

RITUXIMAB
IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

8 patients
Proteinuria > 3.5g/day for 6 months before Rx

Rituximab – 4 weekly infusions



BP 'controlled'

Full dose ACE inhibitor

Ruggenenti P et al. JASN 2003; 14: 1851

RITUXIMAB
IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

8 patients
Proteinuria > 3.5g/day for 6 months before Rx

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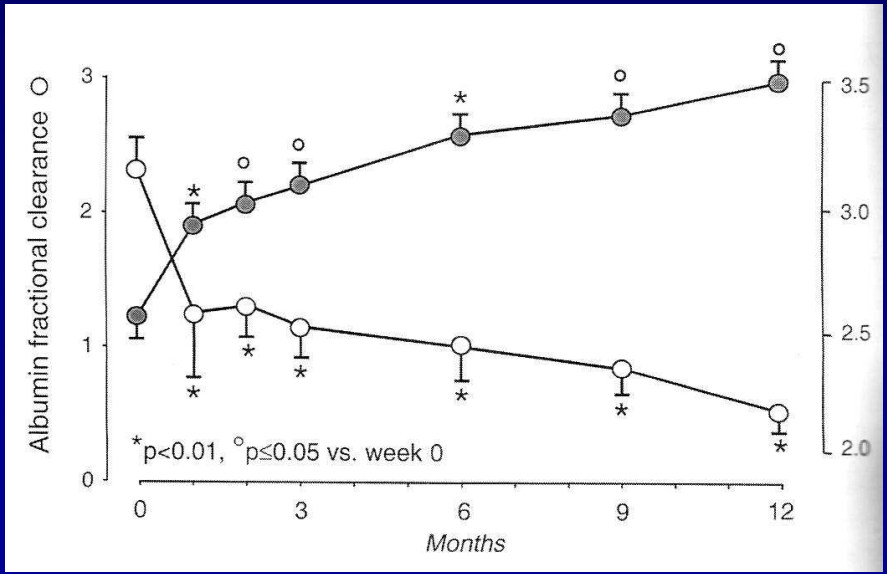


Repeat biopsy in 7 patients

Partial reabsorption of subepithelial deposits

Increase in slit diaphragms

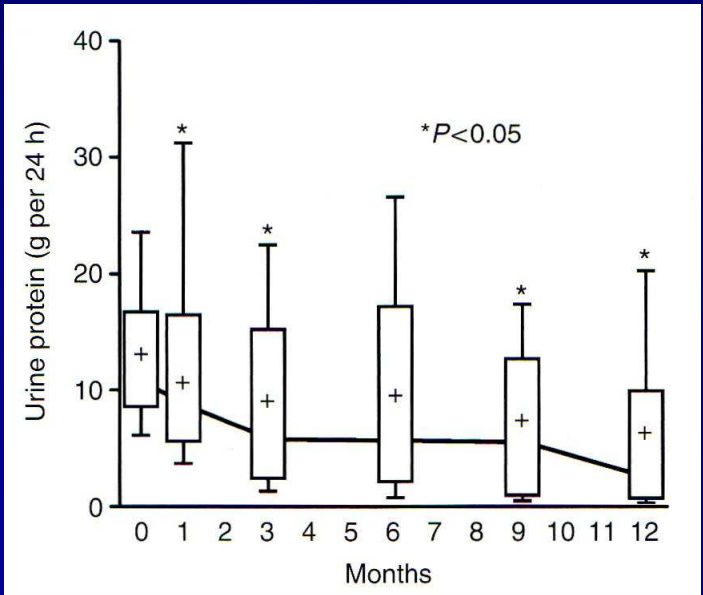
Reduced IgG4 staining

Ruggenenti P et al. JASN 2003; 14: 1851

RITUXIMAB
IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

N = 14 - mean proteinuria 10.8 g/day despite BP control & RAS blockade

Rituximab – 1g x 3 over 6 months



2 complete remissions
6 partial remissions

Responsiveness *not* predictable

Fervenza FC *et al.* Kidney Int 2008; 73: 117

ECULIZAMAB [C5 COMPLEMENT INHIBITOR] IN MEMBRANOUS NEPHROPATHY

RCT

No effect on proteinuria or renal function

Incomplete complement inhibition

Appel G et al. JASN 2002; 13: 668A

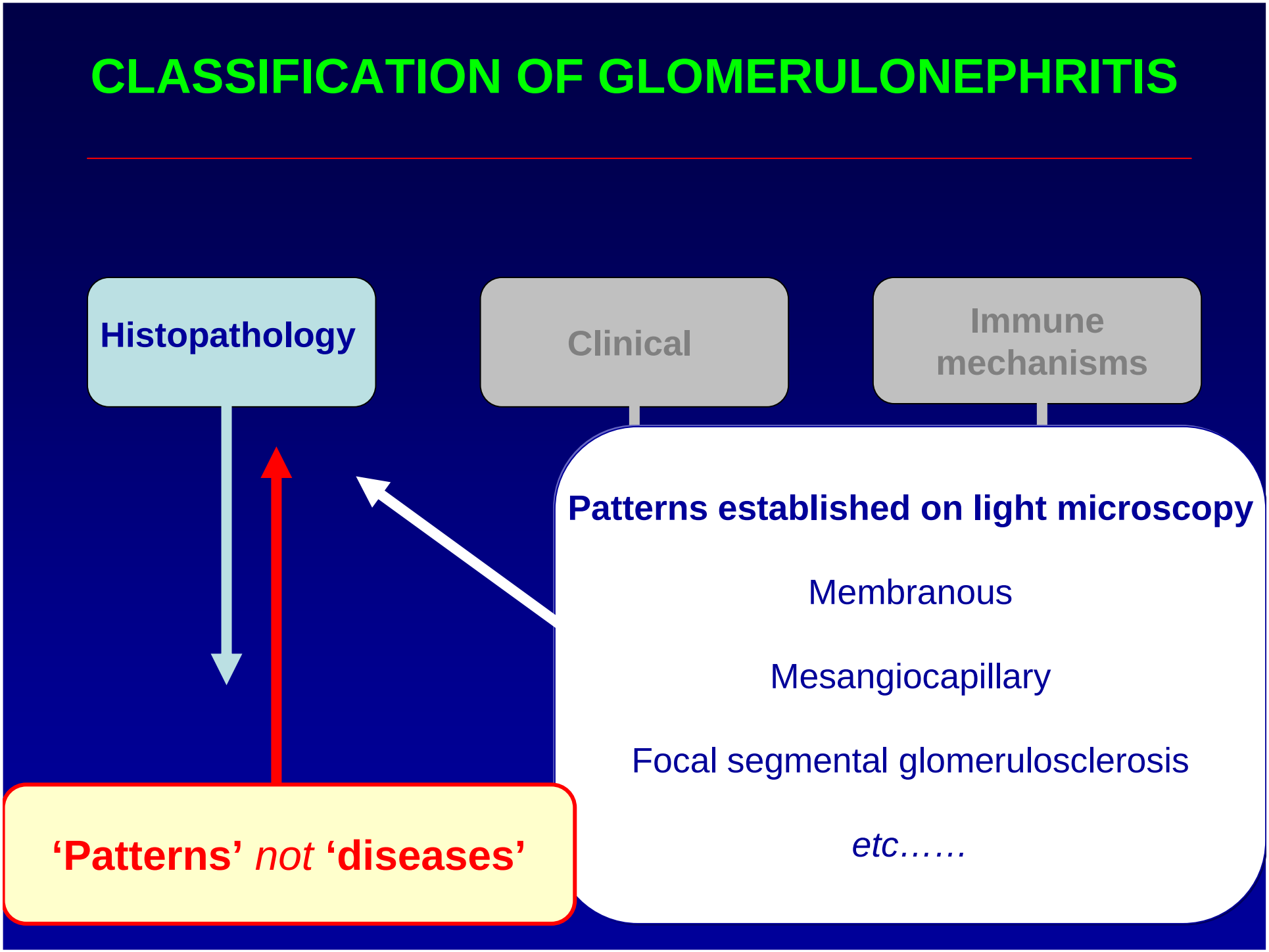
MEMBRANOPROLIFERATIVE / MESANGIOCAPILLARY GLOMERULONEPHRITIS

MEMBRANOPROLIFERATIVE /

MESANGIOCAPILLARY

GLOMERULONEPHRITIS

CLASSIFICATION OF GLOMERULONEPHRITIS



AETIOLOGY OF MESANGIOCAPILLARY GN

Infection

- Hepatitis B & C
- Bacterial endocarditis
- Infected shunt/abscess
- HIV
- Hantavirus

Auto-immune disease

- Lupus
- Sjogren syndrome
- Cryoglobulinaemia (HCV)

Malignancy

- CLL
- Lymphoma

Inherited or acquired complement deficiency

AETIOLOGY OF MESANGIOCAPILLARY GN

Infection

- Hepatitis B & C
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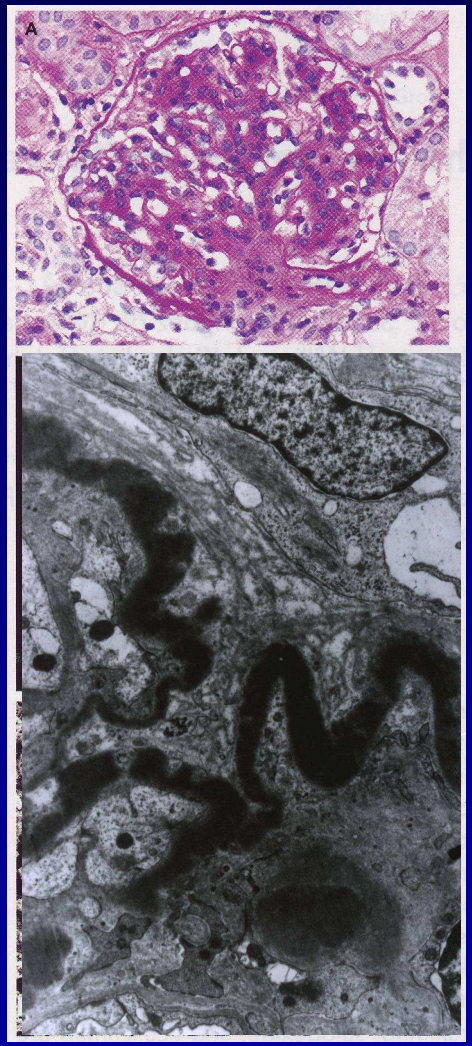
- Lymphoma

Inherited or acquired complement deficiency

“ IDIOPATHIC “

MESANGIOCAPILLARY GN TYPE II



Only identified

as a separate entity

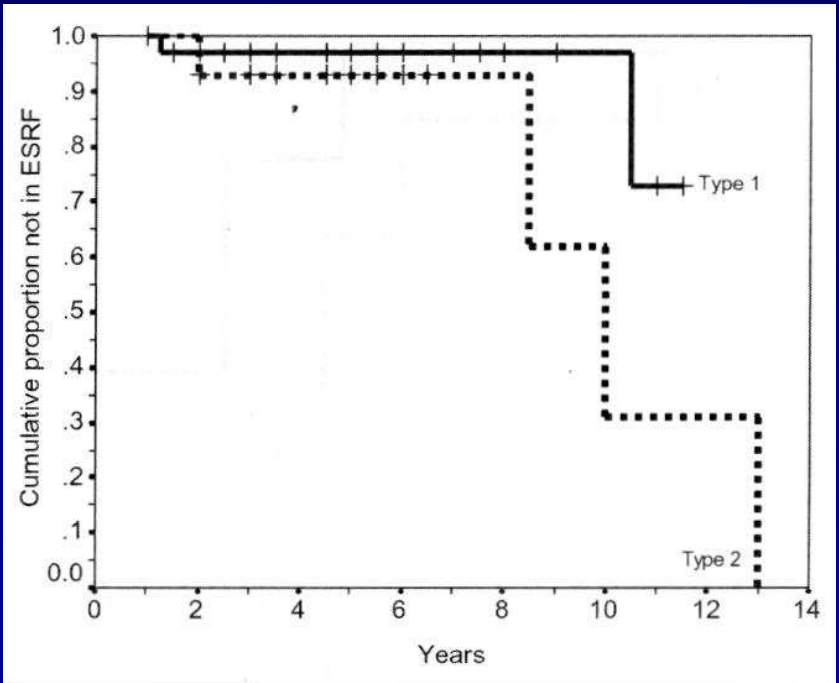
when EM became available

‘Dense deposit disease’

MESANGIOCAPILLARY GN

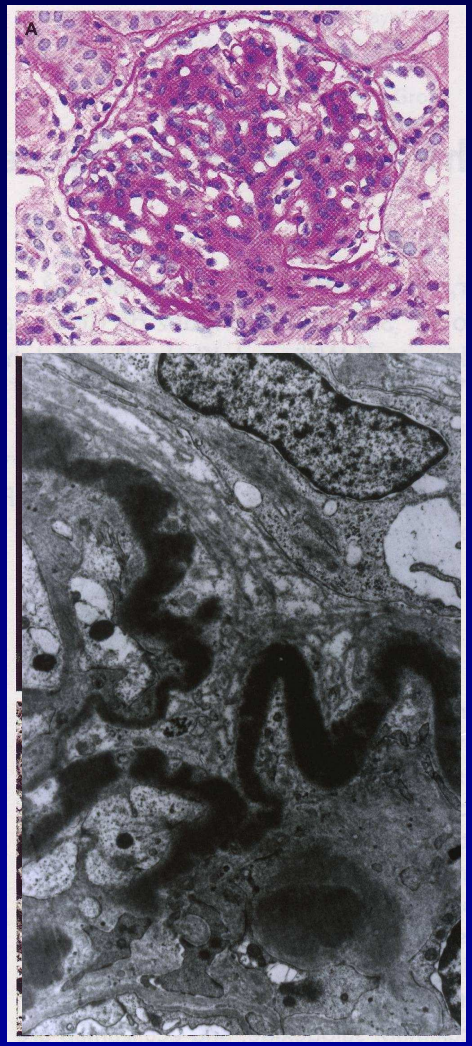
53 children presenting 1980 - 2000 Birmingham & Bristol, UK

31 Type 1
14 Type 2
2 Type 3



Cansick JC *et al*. NDT 2004; 19: 2769

DENSE DEPOSIT DISEASE



LIGHT MICROSCOPY

Mesangiocapillary 25%

Mesangial proliferative 45%

Crescentic 18%

Walker P et al. 2007

Transplant recurrence 100%

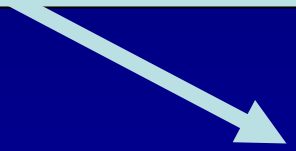
Characteristic alternative pathway complement activation

COMPLEMENT ACTIVATION IN DENSE DEPOSIT DISEASE

C3 NEPHRITIC FACTOR

A stabilising autoantibody

against C3 convertase



PERSISTENT C3 ACTIVATION

COMPLEMENT ACTIVATION IN DENSE DEPOSIT DISEASE

C3 NEPHRITIC FACTOR

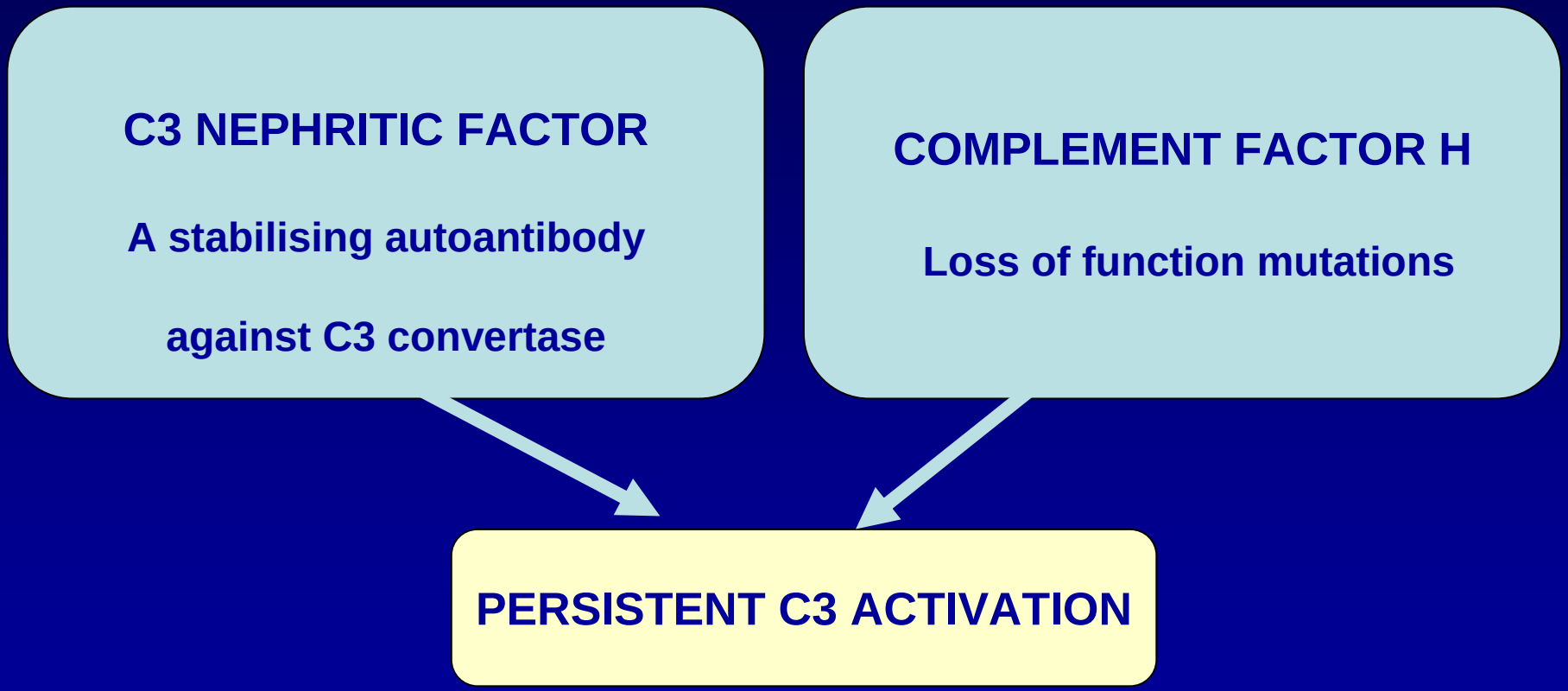
A stabilising autoantibody

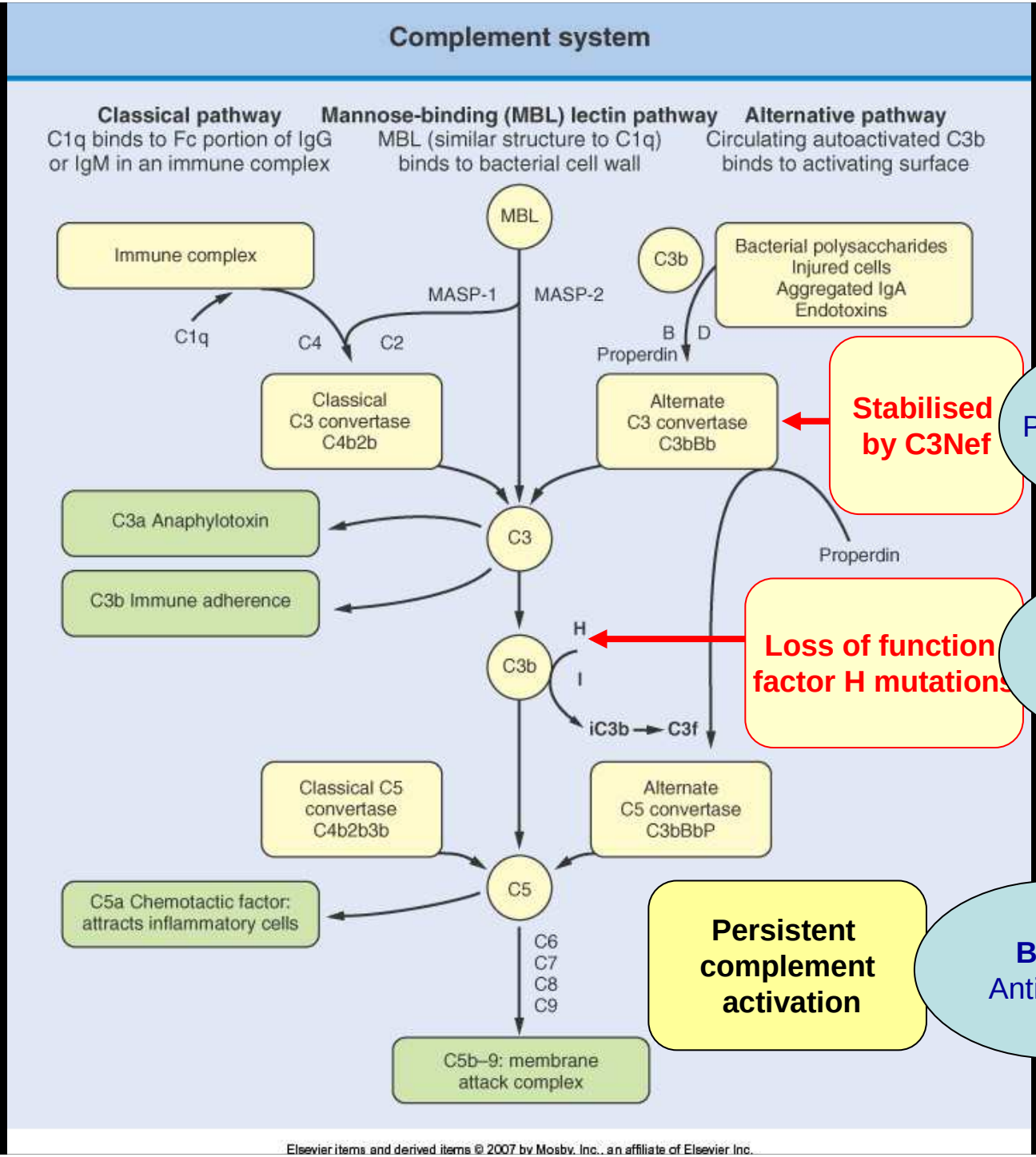
against C3 convertase

Associated with partial lipodystrophy

PERSISTENT C3 ACTIVATION

COMPLEMENT ACTIVATION IN DENSE DEPOSIT DISEASE





Stabilised by C3Nef

Deplete
Plasma exchange
Rituximab

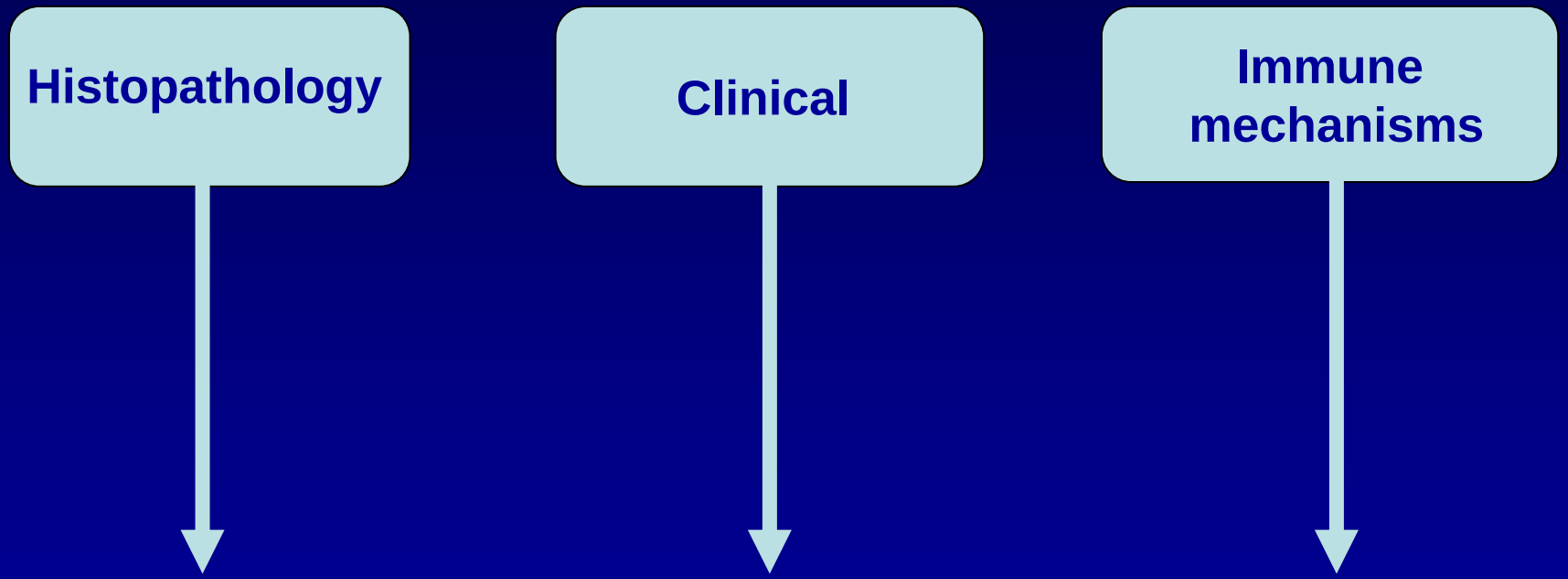
Loss of function factor H mutations

Replace
Plasma infusion

Persistent complement activation

Block
Anti-C5Ab

CLASSIFICATION OF GLOMERULONEPHRITIS



TREATMENT OF MESANGIOCAPILLARY GN

Very few RCTs

Most are > 20 years old

Cohorts include MCGN I of many aetiologies

And may include dense deposit disease

TREATMENT OF GLOMERULAR DISEASE PATTERNS

Do the simple things properly

Minimise adverse effects of treatment

Wait for evidence

Help create the evidence

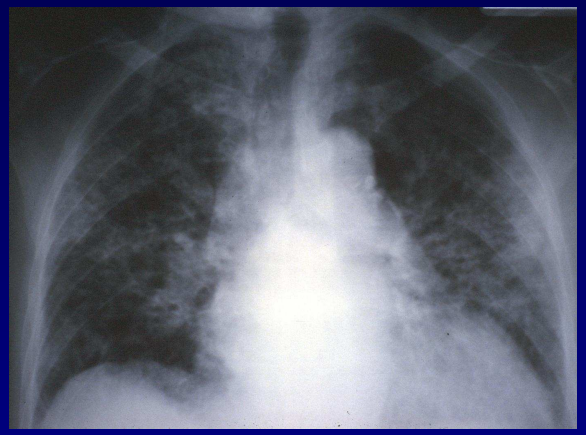
TREATMENT OF GN ASSOCIATED WITH EXTRARENAL IMMUNE DISEASE

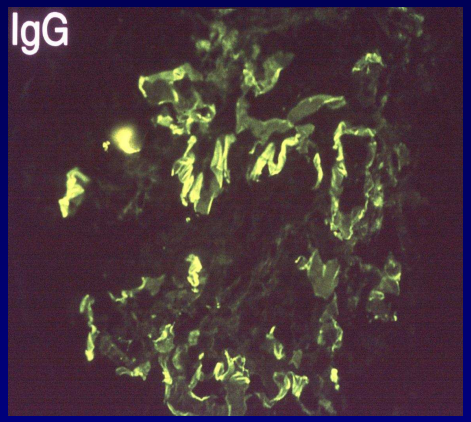
Goodpasture's disease

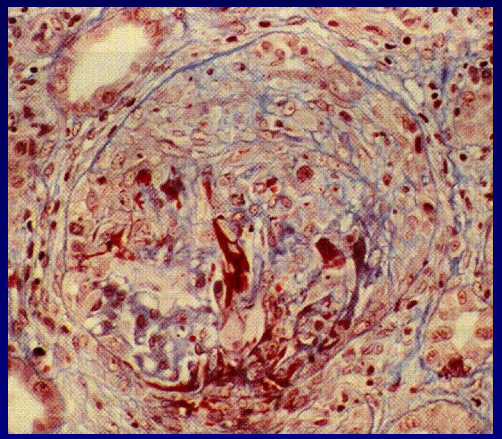
Lupus

Systemic vasculitis

GOODPASTURE'S DISEASE – ANTI-GBM DISEASE







A *rare* condition studied in great detail…

Expecting that general principles will emerge

about auto-immunity and self-tolerance

which will improve treatment of all types of GN

TREATMENT OF GOODPASTURE'S DISEASE

1980

Prednisolone

Cyclophosphamide

Plasma exchange

TREATMENT OF GOODPASTURE'S DISEASE

2008

Prednisolone

Cyclophosphamide

Plasma exchange

PROBLEMS IN THE TREATMENT OF

LUPUS NEPHRITIS

QUESTION:

How do you get ten different opinions

about the treatment of lupus nephritis?

QUESTION:

How do you get ten different opinions

about the treatment of lupus nephritis?

ANSWER:

Ask nine different nephrologists

LUPUS NEPHRITIS

The archetypal ‘immune complex’ disease

Glomerular immune deposits

…. although the antigens involved in the complexes remain incompletely defined

Highly variable expression of renal disease

PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

The evidence base is small

PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

There are few Randomised Controlled Trials

Nearly all are trials in ‘Proliferative’ (III & IV) lupus nephritis

Most studies use histological entry criteria

Most studies include only previously untreated patients

Most studies exclude severely ill patients

PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

Little evidence about….

Mild disease

Very severe disease

Prolonged relapsing disease

PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

The ‘precious’ patient

Seeing beyond the kidneys

THE EVIDENCE BASE FOR TREATMENT OF LUPUS NEPHRITIS

WHO Class I & II	**No trials**
WHO Class III & IV	**Many reports**
	but
	Fewer RCTs than most people think
	… and some are from a different era
WHO Class V	**One small RCT**

Lupus causes premature mortality

…. even without renal failure

Infection

Cardiovascular disease

including premature atherosclerosis

TREATMENT DECISIONS IN LUPUS NEPHRITIS

Base a treatment decision on *all* of the following

Renal histology

Extent of clinical renal disease

Extrarenal lupus

Serology

Previous treatment

TREATMENT FOR WHO III & IV 'PROLIFERATIVE' LUPUS NEPHRITIS

Induction treatment

Maintenance treatment

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

META-ANALYSIS

There is very strong evidence that

corticosteroids plus a cytotoxic agent

gives superior outcome to corticosteroids alone

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

META-ANALYSIS

There is very strong evidence that corticosteroids plus a cytotoxic agent gives superior outcome to corticosteroids alone

…… but which cytotoxic agent ?

TREATMENT FOR WHO III & IV LUPUS NEPHRITIS

Induction treatment

Most physicians accept that ….

Cyclophosphamide is more potent and allows more rapid control of severe disease

TREATMENT FOR WHO III & IV LUPUS NEPHRITIS

Induction treatment

Most physicians accept that ….

Cyclophosphamide is more potent and allows more rapid control of severe disease

But does that mean all patients require cyclophosphamide ?

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine ?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required ?

Is mycophenolate good enough ?

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine ?

Is IV cyclophosphamide better than oral?

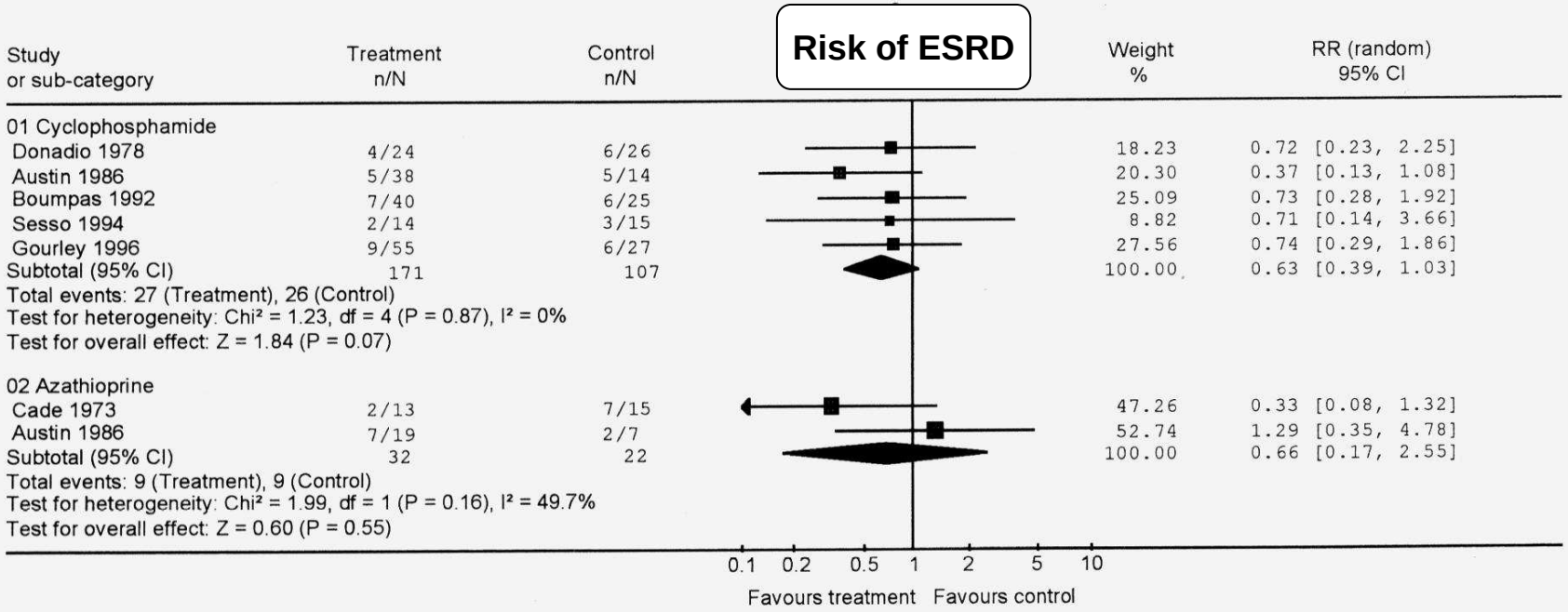
How much cyclophosphamide is required ?

Is mycophenolate good enough ?

TREATMENT OF DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS

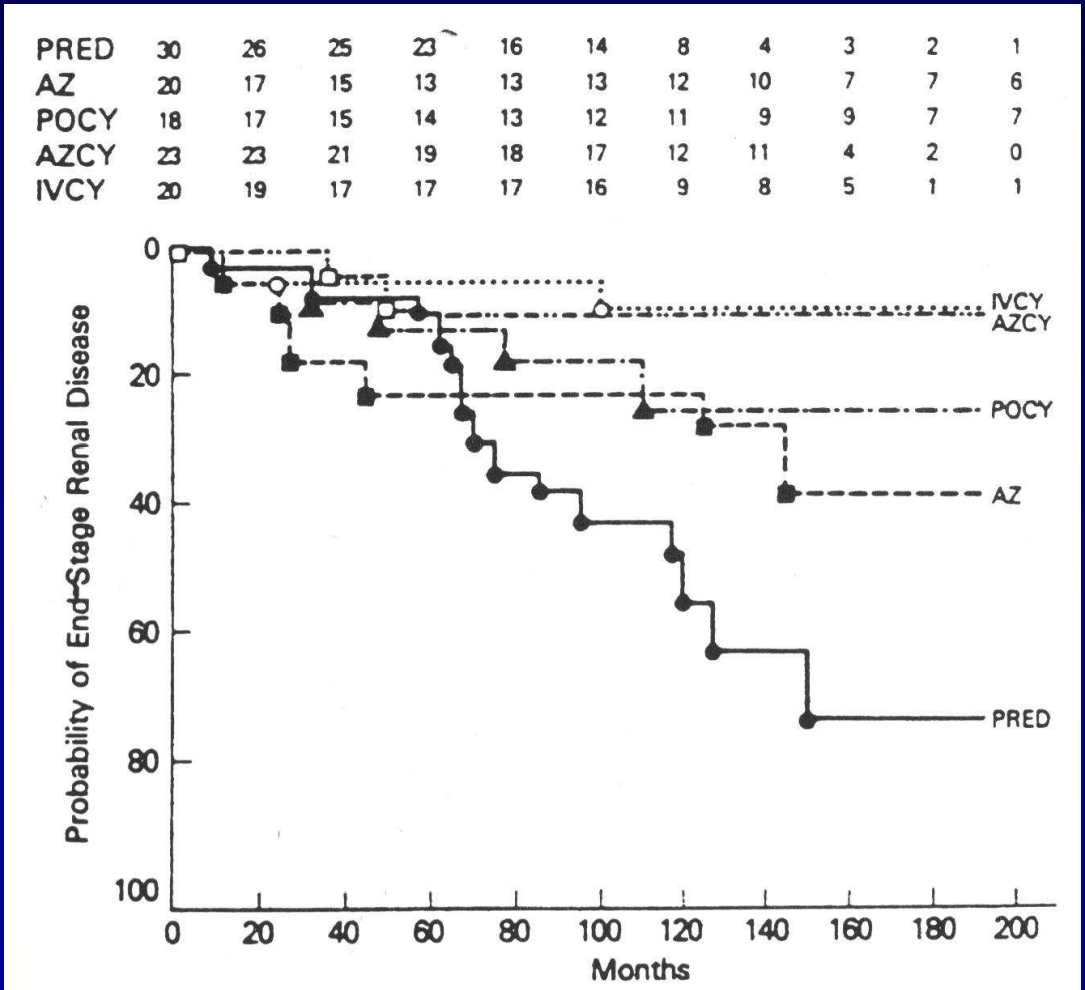
Meta-analysis – Cochrane methodology

Cyclophosphamide or azathioprine + steroids *vs* steroids alone



AJKD 2004; 43:197

NIH DATA ON CYTOTOXIC AGENTS IN PROLIFERATIVE LUPUS NEPHRITIS



Steinberg A *et al* Arth Rheum 1991; 34: 945

There has never been

a head-to-head comparison of

Cyclophosphamide and azathioprine

in an RCT

There has ~~never~~ been

a head-to-head comparison of

Cyclophosphamide and azathioprine

in an RCT

INDUCTION *and* MAINTENANCE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

CYCLOPHOSPHAMIDE *vs* AZATHIOPRINE

RCT n = 87 WHO III & IV

IV cyclophosphamide for 3 years
+ oral prednisolone

Vs

Oral azathioprine for 3 years
+ oral prednisolone + initial IV methylprednisolone

Ligtenberg G *et al* ASN abstract 2002

INDUCTION *and* MAINTENANCE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

CYCLOPHOSPHAMIDE *vs* AZATHIOPRINE

RCT n = 87

Interim analysis at 32 months

No difference in renal outcome

Herpes zoster increased with cyclophosphamide

No other differences in adverse events

Ligtenberg G *et al* ASN abstract 2002

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine ?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required ?

Is mycophenolate good enough ?

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine ?

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How much cyclophosphamide is required ?

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TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is IV cyclophosphamide better than oral?

High intermittent dosing may improve therapeutic index

May reduce cytopenias and infections

May assist compliance

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is IV cyclophosphamide better than oral?

There are no RCTs

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine ?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required ?

Is mycophenolate good enough ?

CYCLOPHOSPHAMIDE IN PROLIFERATIVE LUPUS NEPHRITIS

NIH Study

Maintenance quarterly IV cyclophosphamide

is superior to short induction treatment

… but this was compared to steroid only maintenance treatment

Boumpas DT et al. Lancet 1992; 340:741

LOW DOSE VERSUS HIGH DOSE CYCLOPHOSPHAMIDE IN PROLIFERATIVE LUPUS NEPHRITIS

'Eurolupus Nephritis Trial'- RCT

90 patients – median follow up 41 months

HIGH DOSE CYCLOPHOSPHAMIDE

6 monthly + 2 quarterly pulses

Initial dose 500mg/m2
Dose increased according to WCC nadir

Mean total dose 8.5 gm

LOW DOSE CYCLOPHOSPHAMIDE

6 monthly pulses of 500mg

Total dose 3 gm

Followed by
AZATHIOPRINE 2mg/kg/day for 30 months

Houssiau *et al* Arth Rheum 2002; 46: 2121

LOW DOSE VERSUS HIGH DOSE CYCLOPHOSPHAMIDE IN PROLIFERATIVE LUPUS NEPHRITIS

'Eurolupus Nephritis Trial'- RCT

No difference
between high and low dose cyclophosphamide in:

Achieved renal remission [~80%]

Renal flares during follow up [28%]

Severe infection [2-fold increase with high dose-NS]

Houssiau et al. Arth Rheum 2002; 46: 2121

ETHNICITY & LUPUS NEPHRITIS

Lupus nephritis
is more common and more severe
in some racial groups including -

African Americans
Hispanics
South Asians
South East Asians

NIH studies: ~40% African Americans

European studies: White Caucasians

TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine ?

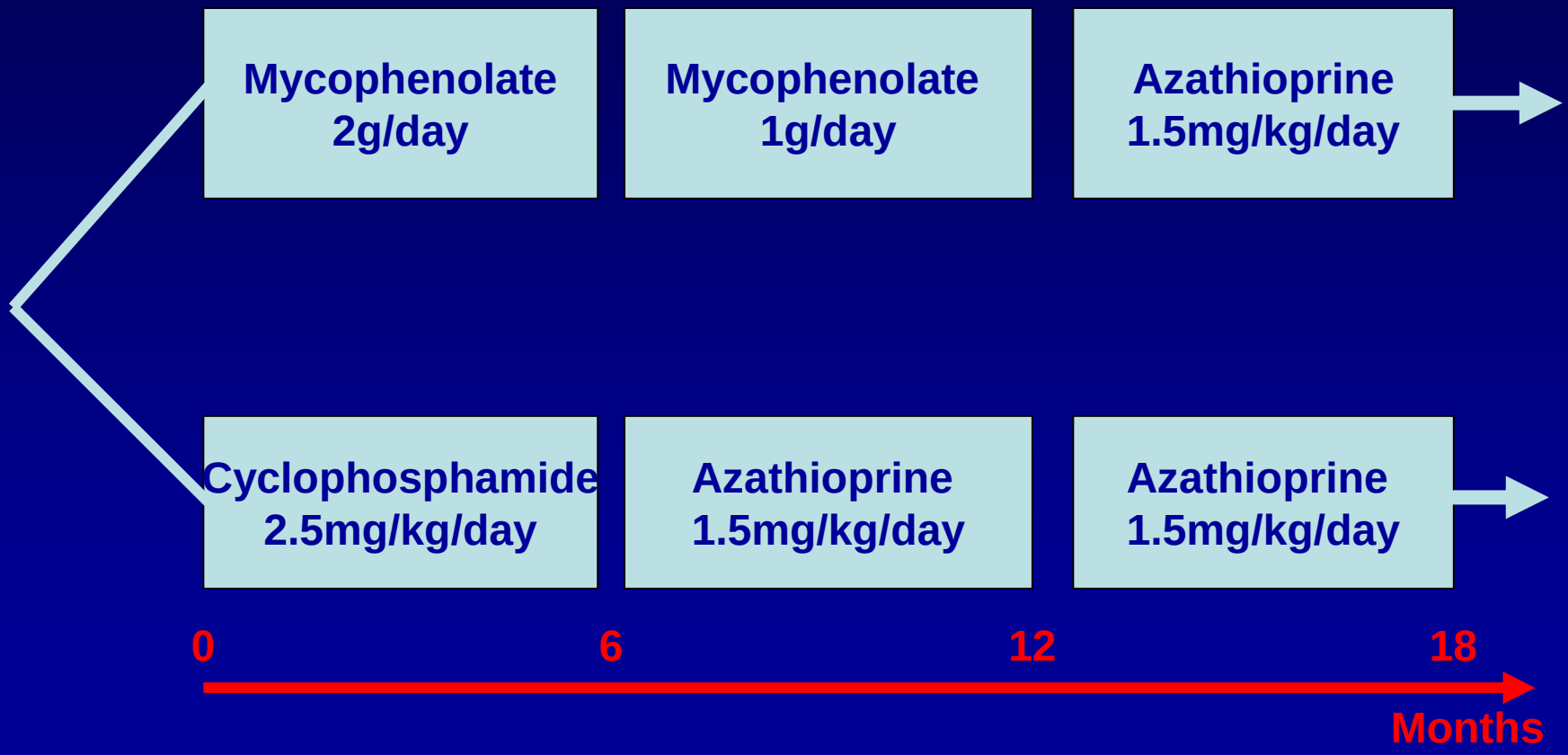
Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required ?

Is mycophenolate good enough ?

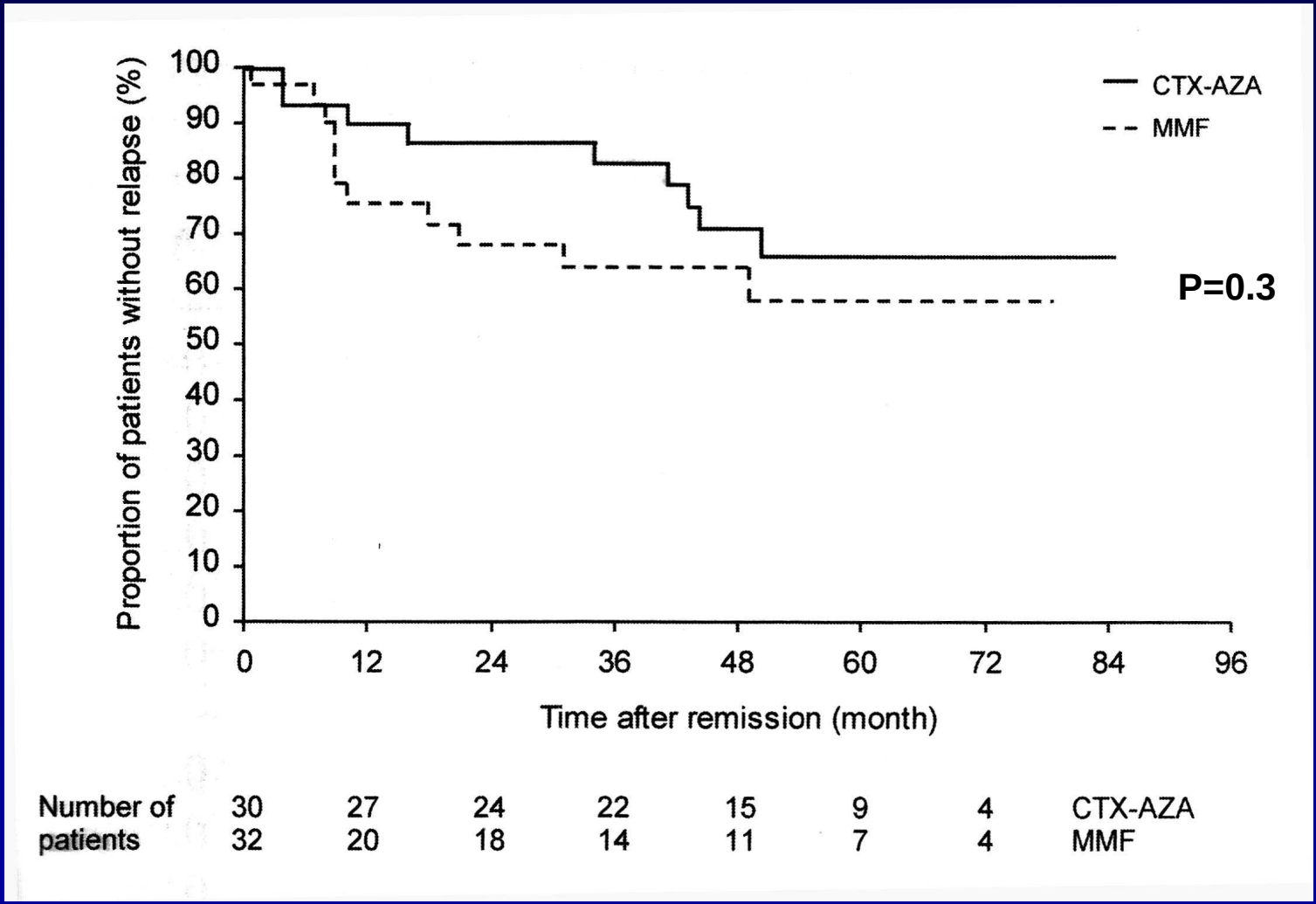
MYCOPHENOLATE IN PROLIFERATIVE LUPUS NEPHRITIS

Diffuse proliferative lupus nephritis
RCT – within 48 hours of biopsy



Chan; NEJM 2000; 343: 1156

MYCOPHENOLATE IN PROLIFERATIVE LUPUS NEPHRITIS



Chan TM *et al* JASN 2005; 16: 1076

MYCOPHENOLATE IN PROLIFERATIVE LUPUS NEPHRITIS

N = 46 - 6 months – open label prospective trial

Mycophenolate *vs* 'pulse' cyclophosphamide

At 6 months

MYCOPHENOLATE

Greater reduction in proteinuria and haematuria

Greater reduction in anti-dsDNA antibodies

More improvement in glomerular inflammation
[repeat biopsies in 30]

Li L *et al* – Chinese Med J 2002; 115: 705

MYCOPHENOLATE IN PROLIFERATIVE LUPUS NEPHRITIS

n = 130 United States

Mycophenolate [up to 3g/day] ***vs*** **'pulse' cyclophosphamide**

At 6 months

MYCOPHENOLATE

Superior response rate 67 vs 47% p=0.007

Cross over to other regimen less common

Fewer serious infections

Ginzler EM *et al* – Arth Rheum 2003; 48: S647

MYCOPHENOLATE IN PROLIFERATIVE LUPUS NEPHRITIS

Mycophenolate has mostly been studied as an induction agent

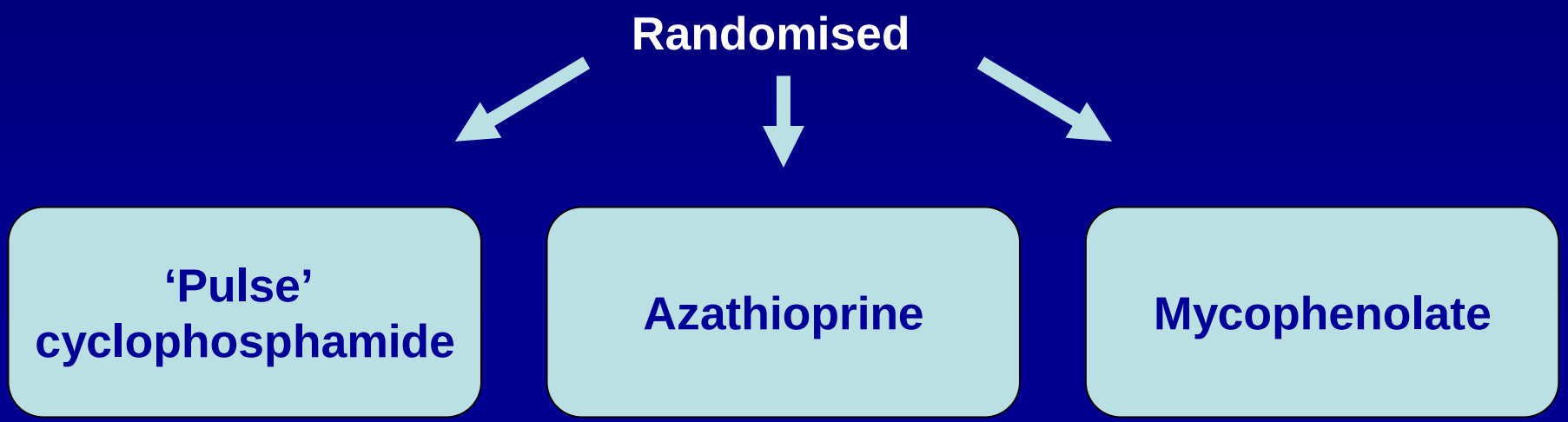
There is some evidence about its use and acceptability as a maintenance agent

MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

RCT n = 59 Miami

All received induction therapy with cyclophosphamide

THEN for maintenance therapy..



Contreras G *et al* NEJM 2004; 350:971

MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

Patient survival not different

ADVERSE EFFECTS

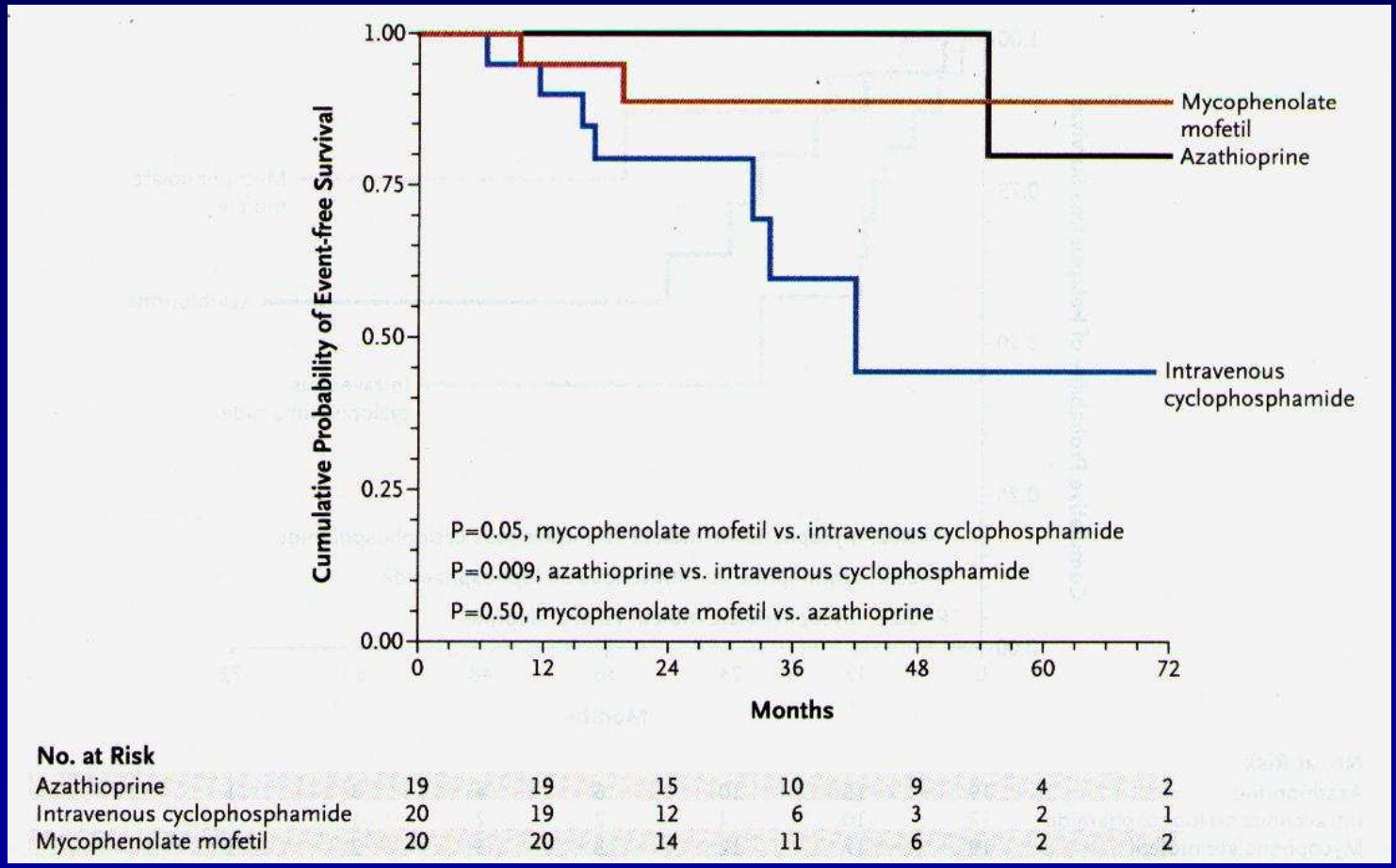
Cyclophosphamide > Azathioprine or mycophenolate

Hospitalisations
Amenorrhoea
Infections

Contreras G *et al* NEJM 2004; 350:971

MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

EVENT FREE SURVIVAL – death or double serum creatinine

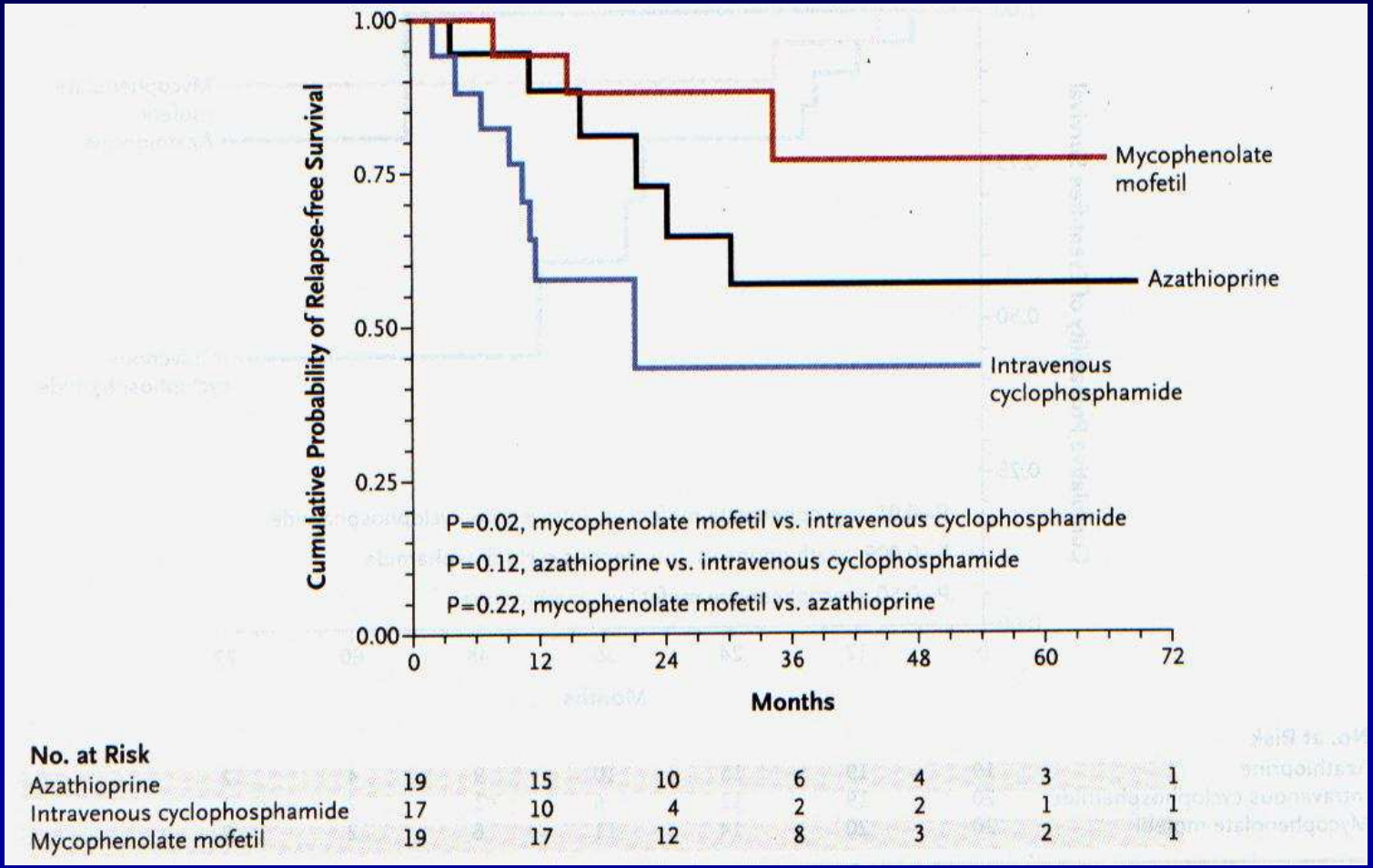


No. at Risk							
Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2

Contreras G *et al* NEJM 2004; 350:971

MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

RELAPSE FREE SURVIVAL



No. at Risk							
Azathioprine	19	15	10	6	4	3	1
Intravenous cyclophosphamide	17	10	4	2	2	1	1
Mycophenolate mofetil	19	17	12	8	3	2	1

Contreras G *et al* NEJM 2004; 350:971

MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

Because of the relative toxicity of cyclophosphamide

It is only necessary to prove equivalence

for azathioprine or mycophenolate

Given the cost

it is only necessary to prove equivalence

between azathioprine and mycophenolate

OTHER TREATMENTS FOR LUPUS NEPHRITIS

Calcineurin inhibitors

Sirolimus

Total lymphoid irradiation

Anti-CD40 ligand antibody

Rituximab

Abetimus

etc….

OTHER TREATMENTS FOR LUPUS NEPHRITIS

Calcineurin inhibitors

The evidence for all these is anecdotal

Anti-CD40 ligand antibody

Rituximab

Abetimus

etc….

OTHER TREATMENTS FOR LUPUS NEPHRITIS

Calcineurin inhibitors

Sirolimus

Total lymphoid irradiation

Anti-CD40 ligand antibody

→ **Rituximab**

Abetimus

etc….

RITUXIMAB IN LUPUS NEPHRITIS

6 studies

96 patients [64 nephritis]

Some response in all patients

Complete remission ~ 40%

Includes some patients resistant to cyclophosphamide

Walsh M, Jayne D. Kidney Int 2008; 72: 676

COURSE OF LUPUS NEPHRITIS AFER RESPONSE TO INDUCTION THERAPY

145 patients received induction treatment

with ‘pulse’ cyclophosphamide and methylprednisolone

Of those with complete or partial response…..

45% had at least one nephritic flare during 10 years follow up

9/11 who reached ESRD had severe nephritic flares

Illei *G et al* *Arth Rheum 2002; 46: 995*

COURSE OF LUPUS NEPHRITIS AFER RESPONSE TO INDUCTION THERAPY

Euro-Lupus Nephritis Trial

Remission at 6 months

is the best predictor of long term outcome

Houssiau F *et al* Arth Rheum 2004; 50: 3934

DIAGNOSIS OF RENAL FLARES IN LUPUS

Proteinuria persisting or increasing during treatment

Activity *or* chronicity ?

Increase immunosuppression
Or
Renin-angiotensin blockade

Or

Both ?

It is always a pleasure to take credit

for a therapeutic manoeuvre

in a patient with lupus…

It is always a pleasure to take credit

for a therapeutic manoeuvre

in a patient with lupus…

…when all you are doing

is observing spontaneous improvement

COMMON THERAPEUTIC ERRORS IN LUPUS NEPHRITIS

Toxicity because high dose induction treatment for too long

Flares because stop maintenance too early

Activity not distinguished from chronicity

TREATMENT FOR PROLIFERATIVE LUPUS NEPHRITIS

What do I do ?

INDUCTION

Prednisolone + azathioprine
unless fulminant disease

If no response
Mycophenolate [or cyclophosphamide]

TREATMENT FOR PROLIFERATIVE LUPUS NEPHRITIS

What do I do ?

MAINTENANCE

Low dose prednisolone + azathioprine

…. for a very long time

PERSONAL PRINCIPLES FOR THE MANAGEMENT OF LUPUS NEPHRITIS

‘Never kill the patient to save the kidneys’

People with lupus have the right not to look Cushingoid

Fertility must be respected

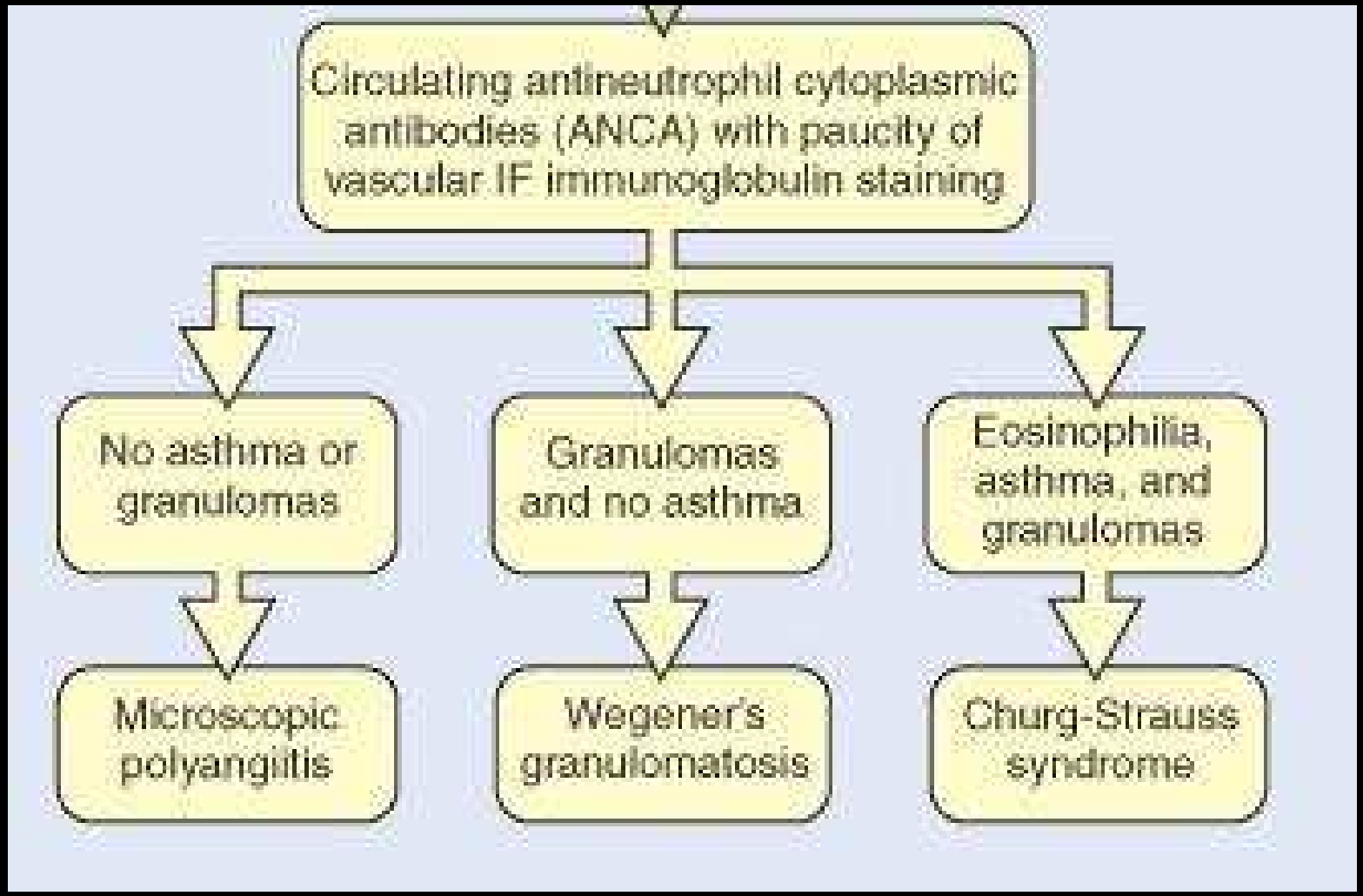
Maximise objective evidence about disease activity

Never forget lupus is an unpredictable disease

GLOMERULONEPHRITIS ASSOCIATED WITH SMALL VESSEL VASCULITIS

‘Pauci-immune’

Is ANCA directly pathogenic ?


Circulating antineutrophil cytoplasmic antibodies (ANCA) with paucity of vascular IF immunoglobulin staining
No asthma or granulomas
Granulomas and no asthma
Eosinophilia, asthma, and granulomas
Microscopic polyangiitis
Wegener's granulomatosis
Churg-Strauss syndrome

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

Treatment is effective

75% 5 year kidney survival

Better outcome if treat earlier

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

Treatment is effective

75% 5 year kidney survival

Better outcome if treat earlier

INDUCTION - Corticosteroids plus Cyclophosphamide

Effective *but* toxic

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

We have very little evidence about treatment of relapsing disease

Most evidence is about induction and maintenance of first remission

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

Specific therapeutic questions

‘Pulse’ or oral cyclophosphamide ?

Methylprednisolone or plasma exchange for severe disease ?

Azathioprine or cyclophosphamide for maintenance therapy ?

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

Specific therapeutic questions

‘Pulse’ or oral cyclophosphamide ?

Methylprednisolone or plasma exchange for severe disease ?

Azathioprine or cyclophosphamide for maintenance therapy ?

Before the mid-1990’s there were no available RCT’s

EUVAS

The European Vasculitis Study Group

Founded 1993

First trial started recruiting 1996

First trial published 2003

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

‘Pulse’ or oral cyclophosphamide ?

Azathioprine or cyclophosphamide for maintenance therapy ?

Methylprednisolone or plasma exchange for severe disease ?

CYCLOPHOSPHAMIDE IN ANCA-POSITIVE VASCULITIS
Oral or IV Pulse ?

Meta-analysis of 3 RCTs [154 patients] and 11 non-RCTs

Limited data……

Pulse therapy → More remissions

Less leucopenia

Fewer infections

More relapses

No difference in ESRD or death

de Groot NDT 2001; 17: 2018

CYCLOPS – a EUVAS TRIAL

Daily oral versus pulse cyclophosphamide for induction therapy in renal vasculitis

No difference in remission or relapse rates

Total dose halved using pulse regimen

Unpublished data

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

‘Pulse’ or oral cyclophosphamide ?

Azathioprine or cyclophosphamide for maintenance therapy ?

Methylprednisolone or plasma exchange for severe disease ?

CYCAZAREM

Randomised trial of cyclophosphamide versus azathioprine during remission in ANCA-associated systemic vasculitis

European Vasculitis Study Group (EUVAS)

143 patients randomised from 11 countries

CYCAZAREM

Remission therapy with azathioprine is equally effective to cyclophosphamide and probably safer

Adverse-effects are frequent and severe - 26%

TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

‘Pulse’ or oral cyclophosphamide ?

Azathioprine or cyclophosphamide for maintenance therapy ?

Methylprednisolone or plasma exchange for severe disease ?

MEPEX

Biopsy-proven ANCA-associated necrotizing GN with creatinine >500µmol/l

151 patients from 9 European countries

7 PE treatments (each of 60ml/kg) within the first two weeks
or
3 'pulses' of ivMeP (15mg/kg)

+ oral cyclophosphamide and prednisolone

European Vasculitis Study Group

MEPEX

Renal outcome at 3 months significantly better with Plasma Exchange

dialysis-free survival (p=0.017)

Difference most marked in patients requiring dialysis at presentation

RITUXIMAB IN RENAL VASCULITIS

7 published reports
62 patients [35 nephritis]

Mostly added to conventional therapy or ‘rescue’

73% complete remission

RITUXIMAB IN RENAL VASCULITIS

Unanswered questions ….

Dosing regimen ?

Long term adverse effects ?

Effective in induction ± conventional Rx ?

Impact on relapse rate ?

Two RCTs of induction therapy

are underway

Walsh M, Jayne D. Kidney Int 2008; 72: 676

EUVAS

European Vasculitis Study Group

A major success

conducting RCTs which where thought near impossible

Ongoing trials include -

EUVAS - ONGOING TRIALS

Long-term low dose immunosuppression versus treatment withdrawal for renal vasculitis

Mycophenolate or azathioprine for remission therapy in renal vasculitis

Rituximab as induction therapy