TREATMENT OF PROTIENURIA

- **MODERATOR –Dr.Raga Deepthi mam**
- **Presenter—Dr srinivas**

- *The treatment of proteinuria is mainly focused on* ***treating the specific underlying cause.***
- *Most treatment modalities focus on reducing the degree of proteinuria, particularly albuminuria.*
- *These include drugs acting on the renin-angiotensin-aldosterone system. The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guideline strongly recommends using ACE inhibitors or Angiotensin receptor antagonists (ARB) in adults with more than 300 mg/24 hours of persistent proteinuria.*
- *The Kidney Health Australia and the NICE guidelines in the UK do not recommend combination therapy for progression prevention in proteinuria.*

DIURETICS

- *Patients with moderate to severe proteinuria have fluid overload and require diuretic therapy and dietary salt restriction.*
- *Aldosterone antagonists have also shown an advantage in their efficacy for proteinuria.*
- *Combination therapy of ACE inhibitors with aldosterone antagonists is associated with an increased risk of hyperkalemia and gynecomastia.*
- *However, this combination has shown significant mortality benefits in patients with heart failure.*

CALCIUM CHANNEL BLOCKERS

- *Non-dihydropyridine calcium channel blockers (NDCCBs), diltiazem, and verapamil decrease proteinuria*
- *The newer NDCCBs, such as efonidipine and benedipine, used in combination with ARBs, have reduced proteinuria.*

PeerJ Publishing

Comparative proteinuria management of different angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for normotensive patients with CKD: a Bayesian network meta-analysis

Systematic review | Drugs and Devices | Global Health | Internal Medicine | Nephrology | Public Health

Huizhen Ye*, Zhihao Huo*, Peiyi Ye, Guanqing Xiao, Zhe Zhang, Chao Xie, Yaozhong Kong

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- Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are blood pressure-lowering agents, but they are also being used to control proteinuria in early chronic kidney disease (CKD) patients.
- The combination therapy of olmesartan plus temocapril appeared to be the most efficacious for reducing proteinuria in normotensive CKD patients and IgA nephropathy
- In normotensive diabetic nephropathy, monotherapy with the ACEI enalapril seems to be the most efficacious intervention for reducing albuminuria

HYPERTENSION

- *Hypertension control-prevent cardiovasular and renal complications*
- *MDRD study-patients with protienuria have better outcomes if BP reduced to 125/75mm hg*
- *High-dose diuretics with moderate dietary sodium restriction are usually an essential part of the treatment*
- *In case of primary hypertension –weight normalization ,salt restriction,smoking cessation,*

HYPERLIPIDEMIA

- *Dietary restriction alone has only modest effects on hyperlipidemia in glomerular disease, particularly nephrotic syndrome.*
- *If pt **age <50yrs** /early ckd - Statins alone*
- *If pt **age>50yrs**/late ckd - Statin or **Statin+Ezetimibe***

PROTEINURIA

- *Progressive loss of renal function observed in many glomerular diseases can largely be prevented if proteinuria can be reduced to levels below 0.5 gm/day*

- *Agents used to reduce urinary protein excretion do so hemodynamically, by either blocking efferent arteriolar constriction (ACE inhibitors or ARBs) or reducing preglomerular pressure (most other classes of antihypertensive drug)*

- *Combination of ACE inhibitors and ARBs has additive antiproteinuric effect with low risk in younger patients with glomerular proteinuria But is **contraindicated** in **old** and **dm patients***

- *If proteinuria persists despite maximum allowed or tolerated doses of ACE inhibitors or ARBs, a low dose of an aldosterone antagonist may overcome aldosterone breakthrough and reduce proteinuria*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes

Edmund J. Lewis, M.D., Lawrence G. Hunsicker, M.D., William R. Clarke, Ph.D., Tomas Berl, M.D., et al., for the Collaborative Study Group*

September 20, 2001
N Engl J Med 2001; 345:851-860
DOI: 10.1056/NEJMoa011303

Abstract

BACKGROUND

It is unknown whether either the angiotensin-II–receptor blocker irbesartan or the calcium-channel blocker amlodipine slows the progression of nephropathy in patients with type 2 diabetes independently of its capacity to lower the systemic blood pressure.

METHODS

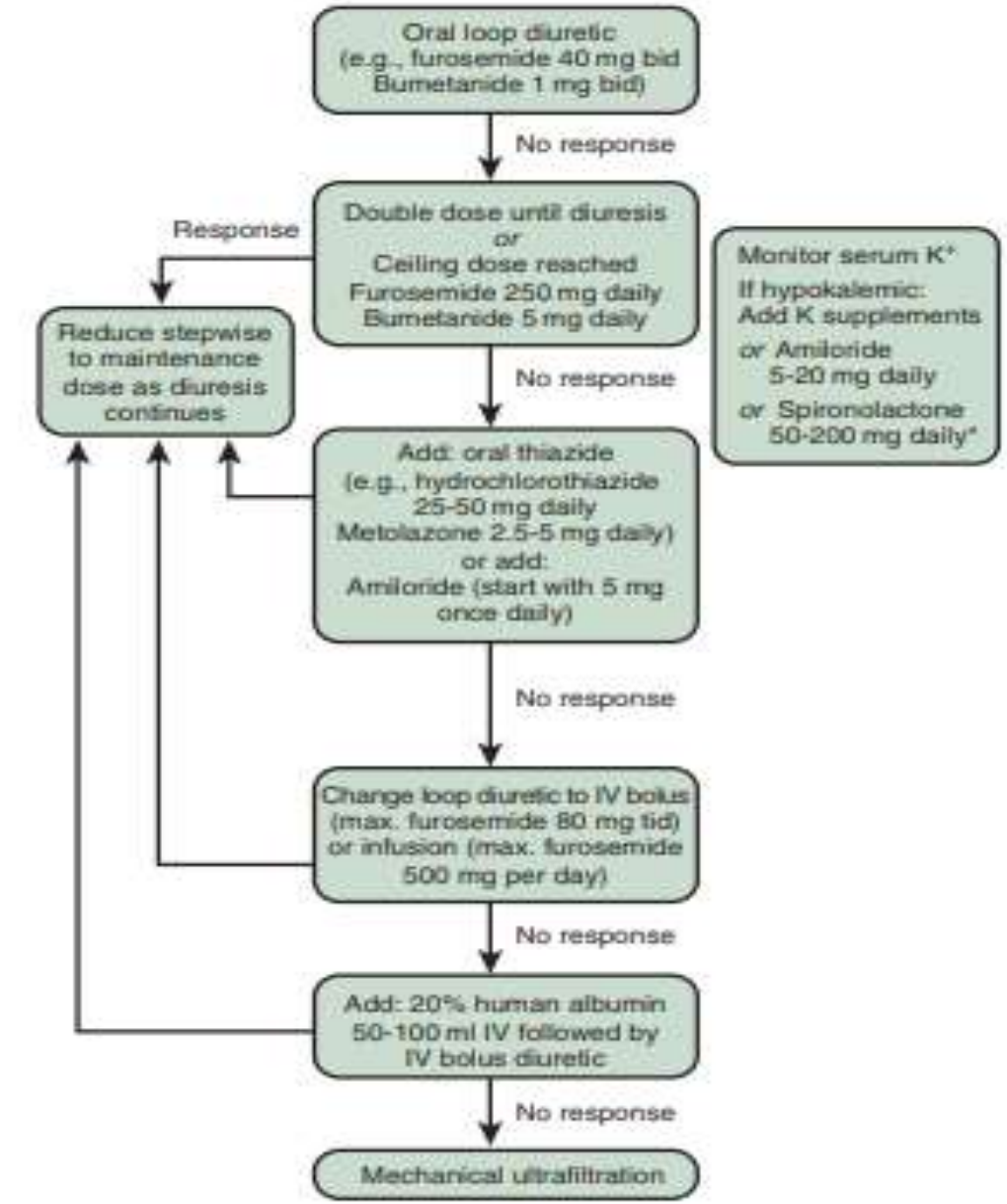
We randomly assigned 1715 hypertensive patients with nephropathy due to type 2 diabetes to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mm Hg or less in all groups. We compared the groups with regard to the time to the primary composite end point of a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death from any cause. We also compared them with regard to the time to a secondary, cardiovascular composite end point.

The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the primary composite end point that was 20 percent lower than that in the placebo group (P=0.02) and 23 percent lower than that in the amlodipine group (P=0.006). The risk of a doubling of the serum creatinine concentration was 33 percent lower in the irbesartan group than in the placebo group (P=0.003) and 37 percent lower in the irbesartan group than in the amlodipine group (P<0.001). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23 percent lower than that in both other groups (P=0.07 for both comparisons). These differences were not explained by differences in the blood pressures that were achieved. The serum creatinine concentration increased 24 percent more slowly in the irbesartan group than in the placebo group (P=0.008) and 21 percent more slowly than in the amlodipine group (P=0.02). There were no significant differences in the rates of death from any cause or in the cardiovascular composite end point.

CONCLUSIONS

The angiotensin-II–receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes.

Management of Edema in Nephrotic Syndrome



- **NEPHROTIC EDEMA CORRECTION**
- *Diuretic +moderate salt restriction (60 to 80 mmol/24 h)*
- *In severe nephrosis, GI absorption of the diuretic may be uncertain because of intestinal wall edema, and intravenous diuretic by bolus injection*
- *Daily weight is the best measurement of progress; ideally it should decrease by no more than 1 to 2 kg/day*
- *In severe proteinuria-medical nephrectomy is done*
- *NSAID +ACE inhibitiors+Diuretics lead to AKI causing decreased proteinuria*
- *If medical nephrectomy fails B/L renal artery embolisation is done*

HYPOPROTEINEMIA CORRECTION

- *Adequate dietary protein should be ensured (0.8 to 1 g/kg/day) with a high carbohydrate intake to maximize use of that protein.*
- *In patients with heavy proteinuria, the amount of urinary protein loss should be added to dietary protein intake.*

HYPERCOAGULABILITY

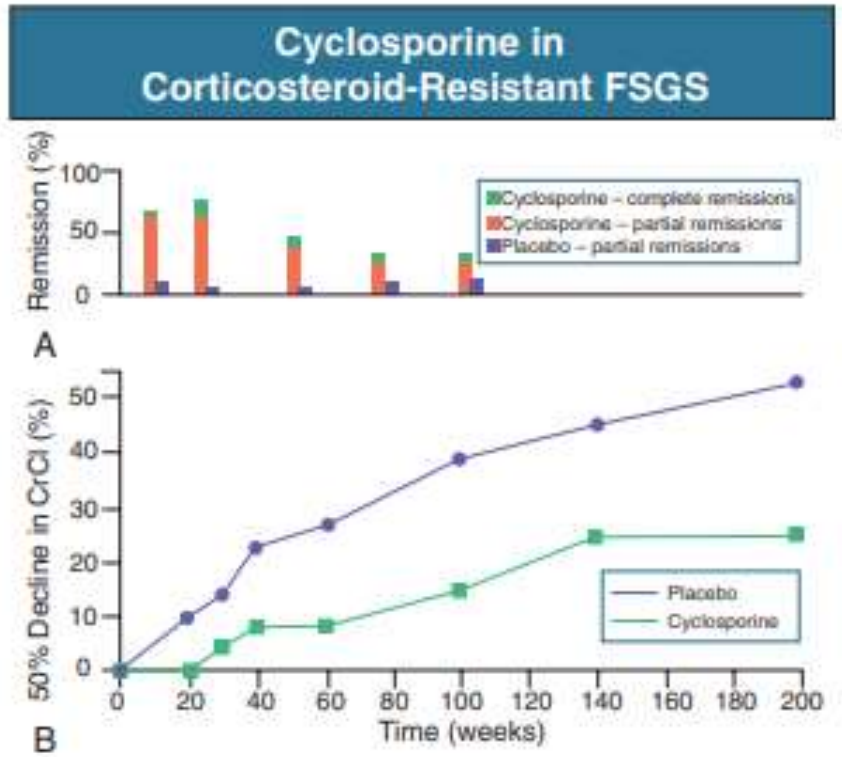
- *Risk for thrombotic events increases as serum albumin values decrease to less than 2.5 g/dl*
- *Risk is aggravated by immobilization due to edema*
- *Albumin 2-2.5,immobilization—prophylactic dose of anticoagulants*
- *Albumin <2gm/dl --full dose anticoagulation with LMWH or warfarin*
- *Target INR 2-3*

TREATMENT OF PRIMARY FSGS

- In FSGS with subnephrotic protienuria-ACEI/ARB
- BP<125/75mm hg
- *Primary FSGS with nephrotic syndrome- prednisolone 1mg/kg/day for 4-8wks*

- ***In steroid resistance or patient with C/I for steroids***-

- Oral cyclosporine 3-5 mg/kg/day for 4-6 months
- Tacrolimus 2-4 mg BID for 4-6 months
- Oral cyclophosphamide 2 mg/kg/day for 2-4 months
- Oral MMF 1-1.5 g bid for 4-6 months



- *Avoid using CNIs in patients with significantly reduced kidney function because of the potential nephrotoxicity of these drugs.*

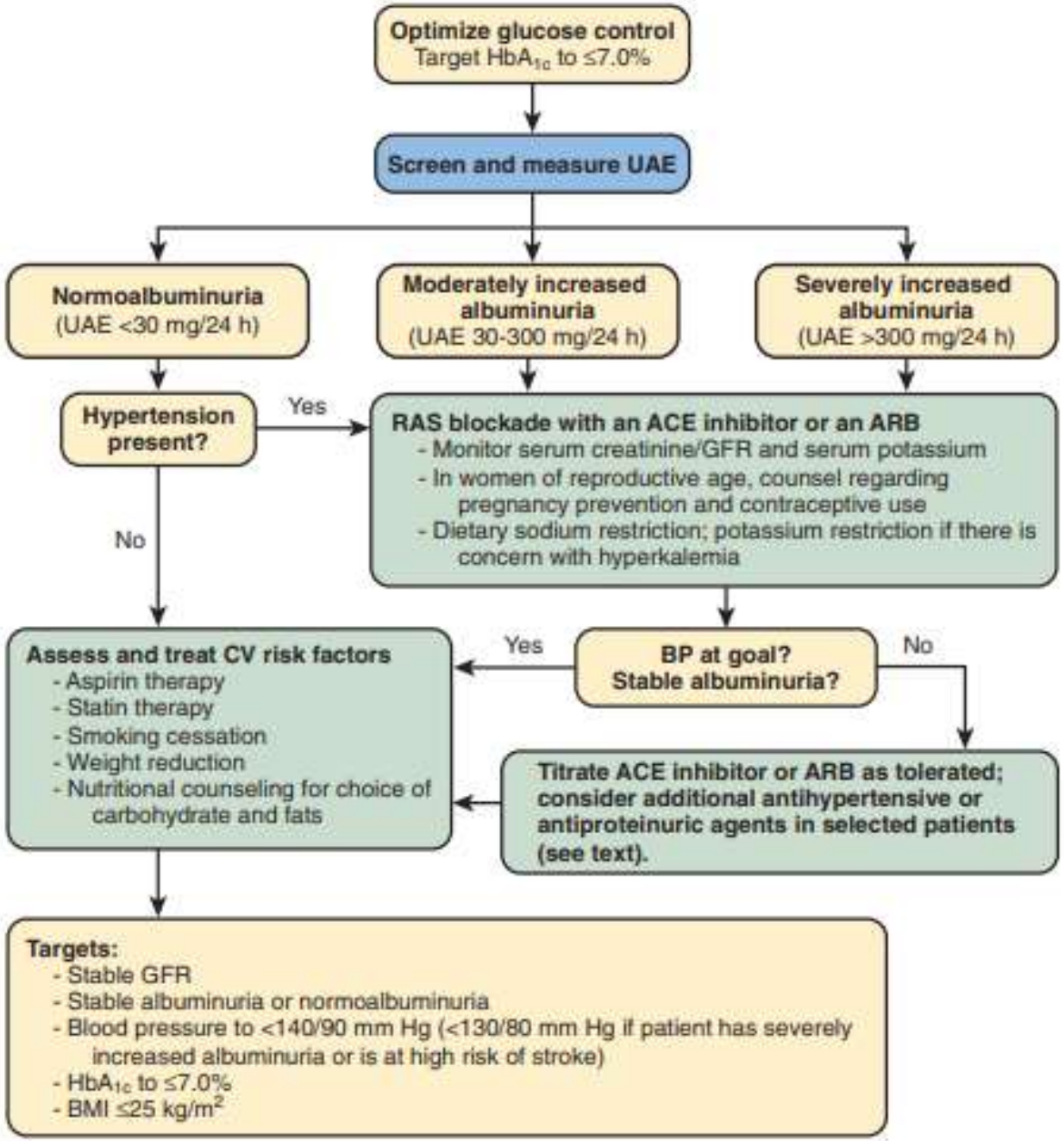
- *Administer prednisone 1 mg/kg per day (maximum dose 60 to 80 mg/day) with subsequent tapering of the dose. The full dose should be given once daily around 9 or 10 AM, to minimize **suppression** of the **hypophyseal-adrenal axis**.*

- *Patients who cannot be treated with either glucocorticoids or a CNI - Mycophenolate mofetil /enteric-coated mycophenolate sodium , rituximab, and ACTH gel are used*

PROTEINURIA IN DIABETES

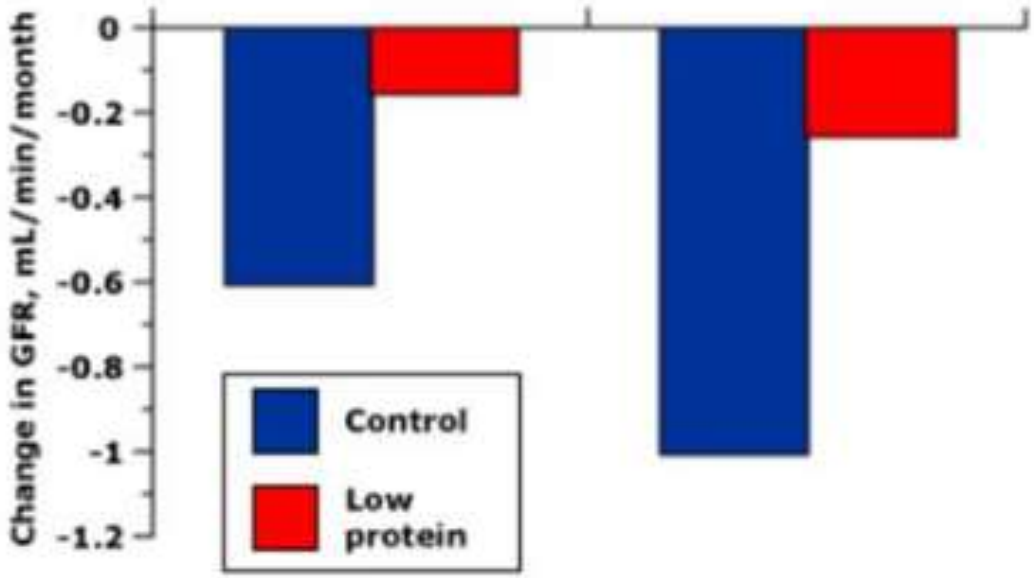
- *In diabetic patients with microalbuminuria.* ***Glycemic and blood pressure control****, particularly with ACE inhibitors, ARB's is beneficial*

- *They reduce both moderately increased albuminuria and progression to severely increased albuminuria*


Optimize glucose control
Target HbA1c to ≤7.0%
Screen and measure UAE
Normoalbuminuria
(UAE <30 mg/24 h)
Moderately increased albuminuria
(UAE 30-300 mg/24 h)
Severely increased albuminuria
(UAE >300 mg/24 h)
Hypertension present?
Yes
No
RAS blockade with an ACE inhibitor or an ARB
- Monitor serum creatinine/GFR and serum potassium
- In women of reproductive age, counsel regarding pregnancy prevention and contraceptive use
- Dietary sodium restriction; potassium restriction if there is concern with hyperkalemia
BP at goal? Stable albuminuria?
Yes
No
Assess and treat CV risk factors
- Aspirin therapy
- Statin therapy
- Smoking cessation
- Weight reduction
- Nutritional counseling for choice of carbohydrate and fats
Titrate ACE inhibitor or ARB as tolerated; consider additional antihypertensive or antiproteinuric agents in selected patients (see text).
Targets:
- Stable GFR
- Stable albuminuria or normoalbuminuria
- Blood pressure to <140/90 mm Hg (<130/80 mm Hg if patient has severely increased albuminuria or is at high risk of stroke)
- HbA1c to ≤7.0%
- BMI ≤25 kg/m2

Diabetic nephropathy

Graph showing effect of dietary protein restriction on progression of diabetic nephropathy



Dietary protein restriction - to about 0.6 g/kg per day or 30 to 40 percent lower than the control group - in two trials (left and right panels) of patients with type 1 diabetes and diabetic nephropathy led to a 75 percent reduction in the rate of loss of glomerular filtration rate (GFR) at 18 to 36 months.

Active Vitamin D Treatment for Reduction of Residual Proteinuria: A Systematic Review

Martin H. de Borst,[*] Reza Hajhosseiny,[†‡] Hector Tamez,[†] Julia Wenger,[†] Ravi Thadhani,[†] and David J.A. Goldsmith[⊠‡]

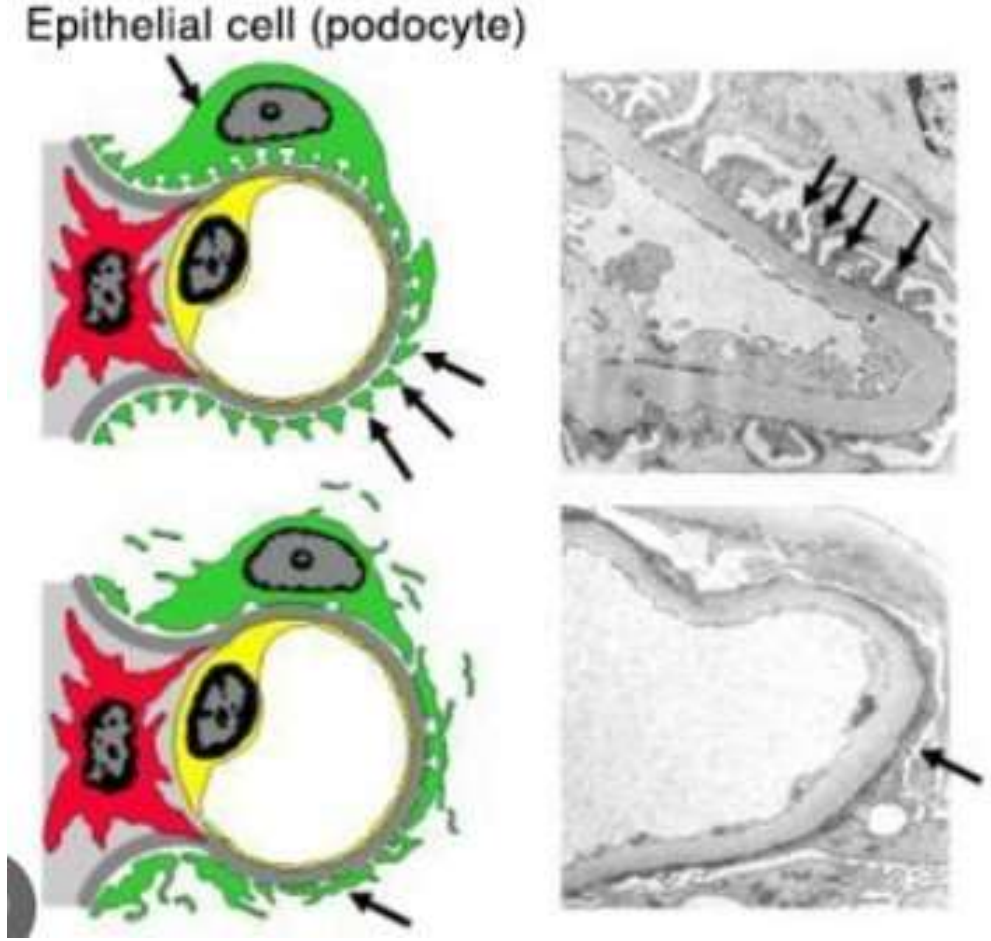
- **Active vitamin D analogs reduced proteinuria (weighted mean difference from baseline to last measurement was −16% [95% CI, −13% to −18%]) compared with controls (+6% [95% CI, 0% to +12%]; *P*<0.001)**

- **Proteinuria reduction was achieved more commonly in patients treated with an active vitamin D analog (204/390 patients) than control patients (86/298 patients; OR, 2.72 [95% CI, 1.82 to 4.07]; *P*<0.001).**

- **Thus, active vitamin D analogs may further reduce proteinuria in CKD patients in addition to current regimens**

Minimal Change Disease

- *It is a steroid-sensitive nephrotic syndrome in which the only structural abnormality is podocyte swelling and fusion of foot processes on EM*
- *Podocyte injury is associated with overexpression of angiopoietin-like-4 overexpression can be reduced with corticosteroids and N-acetyl-d-mannosamine.*
- *EM changes are also present in other nephrotic conditions but absence of light microscopic changes makes EM changes pathognomonic*



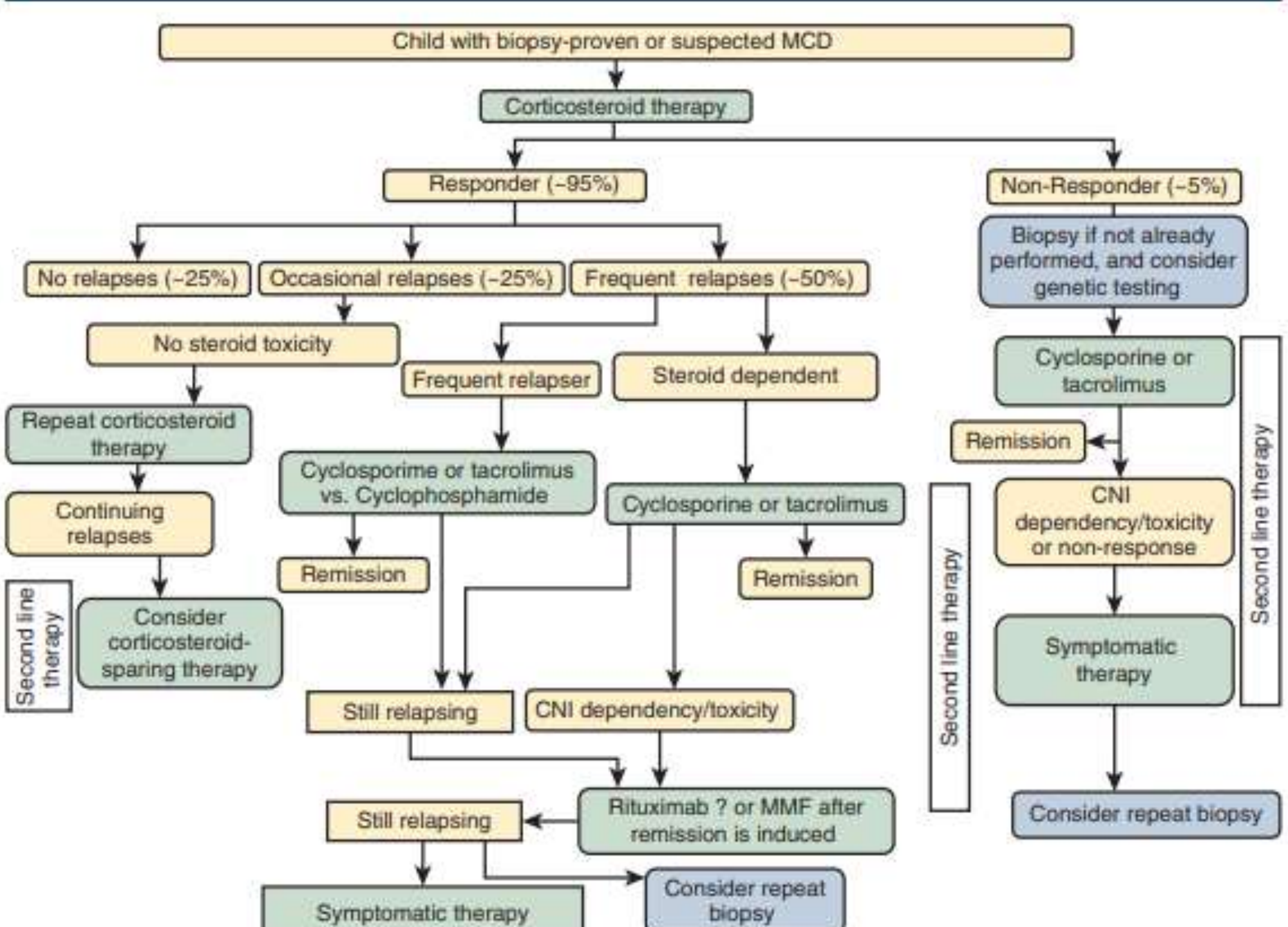
By electron microscopy, a normal glomerular capillary has separate foot processes (arrows).

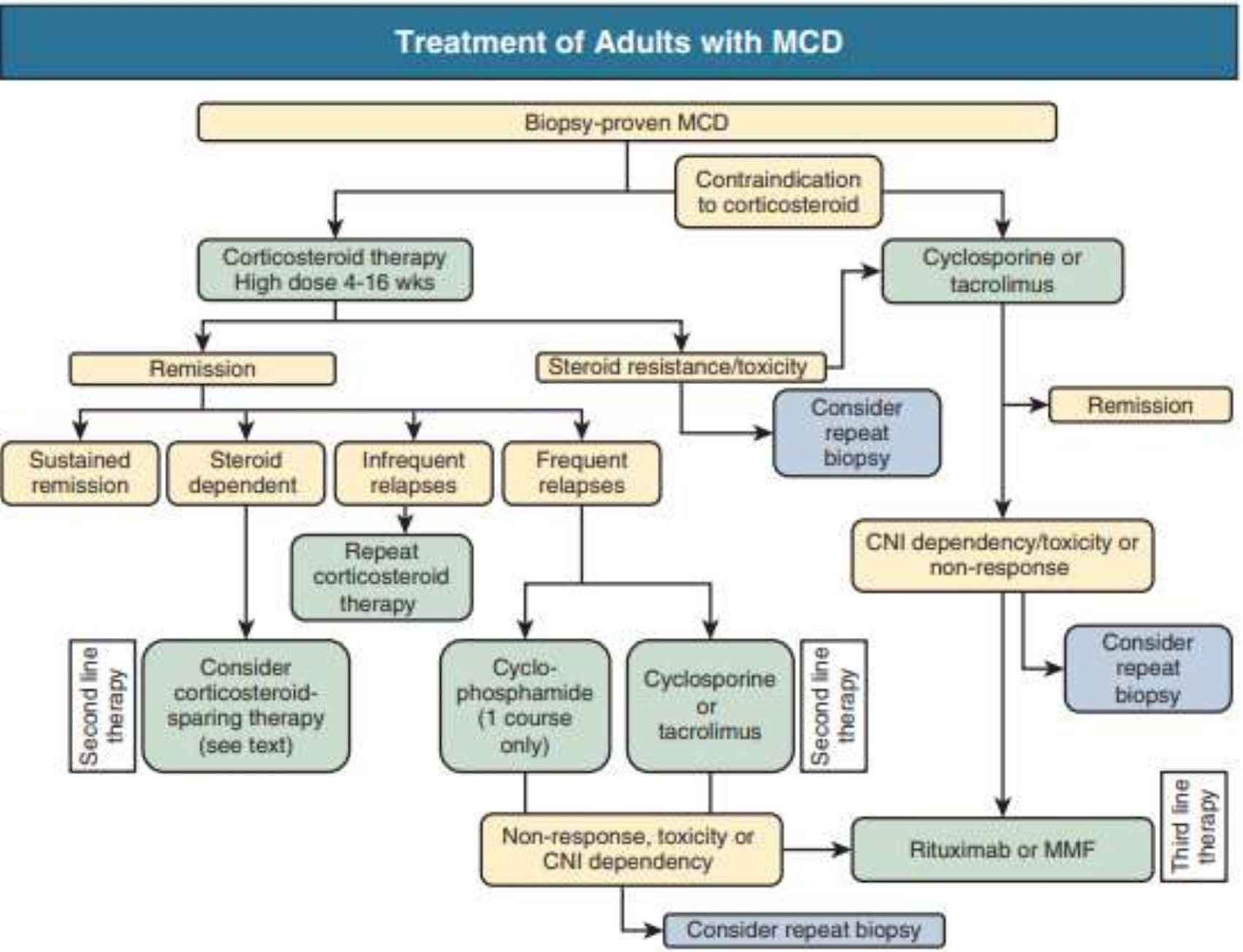
A minimal change disease glomerular capillary has fused foot processes (arrow).

TREATMENT

- *Low sodium diet to prevent edema*
- *Bed rest is contraindicated due to risk of thrombosis*
- *Thrombosis prophylaxis in hypoalbuminemia(albumin<2gm/dl)*
- ***IN CHILDREN***
- *INITIAL TREATMENT—Prednisolone-60mg/day for 4wks*
- *IN RELAPSE—Prednisolone –60mg/m2/day until response (maximum-4wks)*
- *Followed by prednisolone 40mg/m2/day --3days /wk for 4wks*

MC
TR
CH


Child with biopsy-proven or suspected MCD
Corticosteroid therapy
Responder (~95%)
Non-Responder (~5%)
No relapses (~25%)
Occasional relapses (~25%)
Frequent relapses (~50%)
Biopsy if not already performed, and consider genetic testing
No steroid toxicity
Frequent relapser
Steroid dependent
Cyclosporine or tacrolimus
Repeat corticosteroid therapy
Cyclosporime or tacrolimus vs. Cyclophosphamide
Cyclosporine or tacrolimus
Remission
Continuing relapses
Remission
Remission
CNI dependency/toxicity or non-response
Second line therapy
Consider corticosteroid-sparing therapy
Second line therapy
Second line therapy
Still relapsing
CNI dependency/toxicity
Symptomatic therapy
Rituximab ? or MMF after remission is induced
Still relapsing
Consider repeat biopsy
Symptomatic therapy
Consider repeat biopsy



MCD TREATMENT IN ADULT

- *Initial treatment- prednisolone 1mg/kg for upto16wks*
- *Frequent relapses- cyclophosphamide*
- *In cyclophosphamide therapy sperm banking and ova retrival should be done prior to treatment*

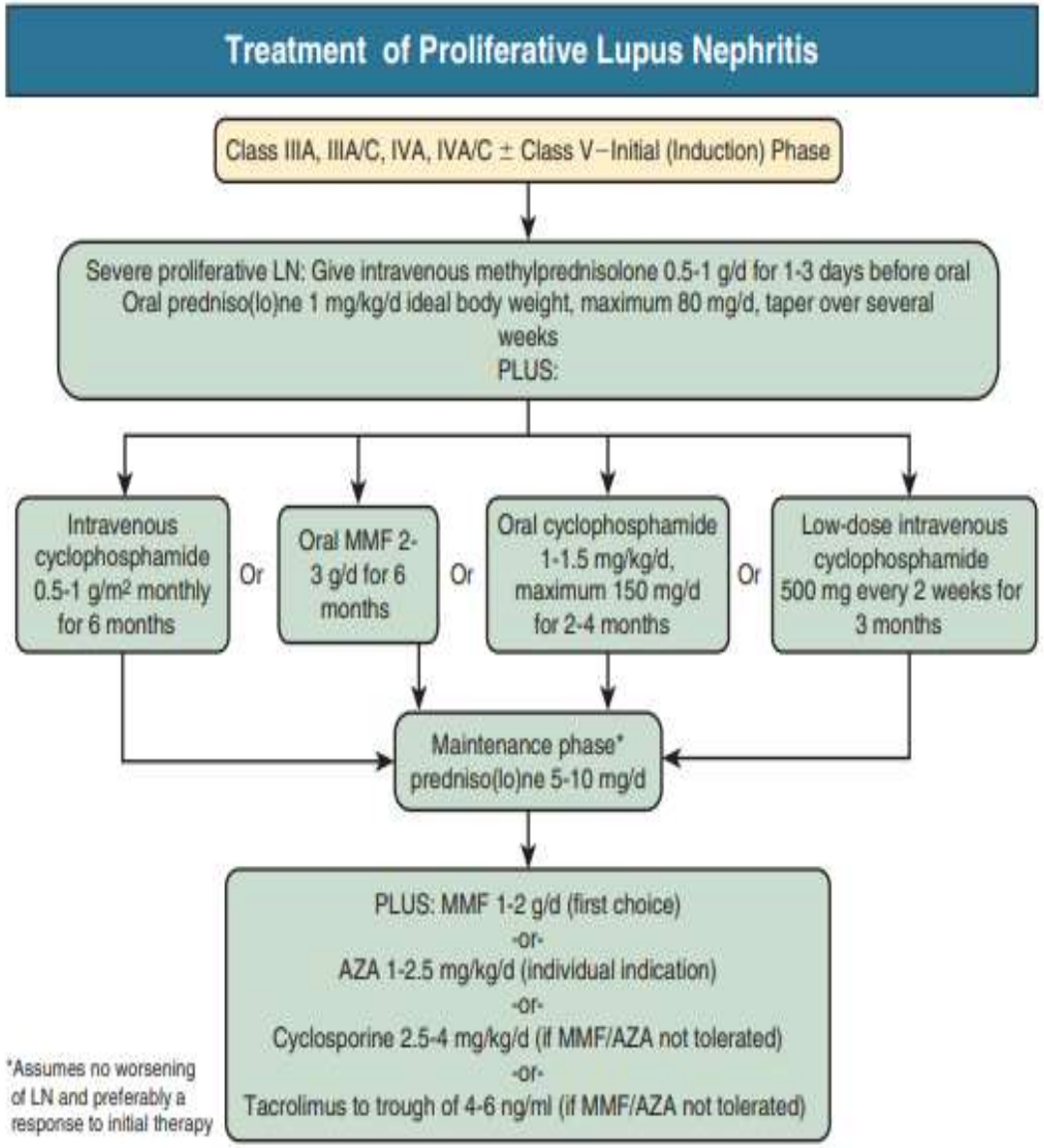
LUPUS NEPHRITIS

Treatment of lupus –2phases

1)Initial/Induction phase

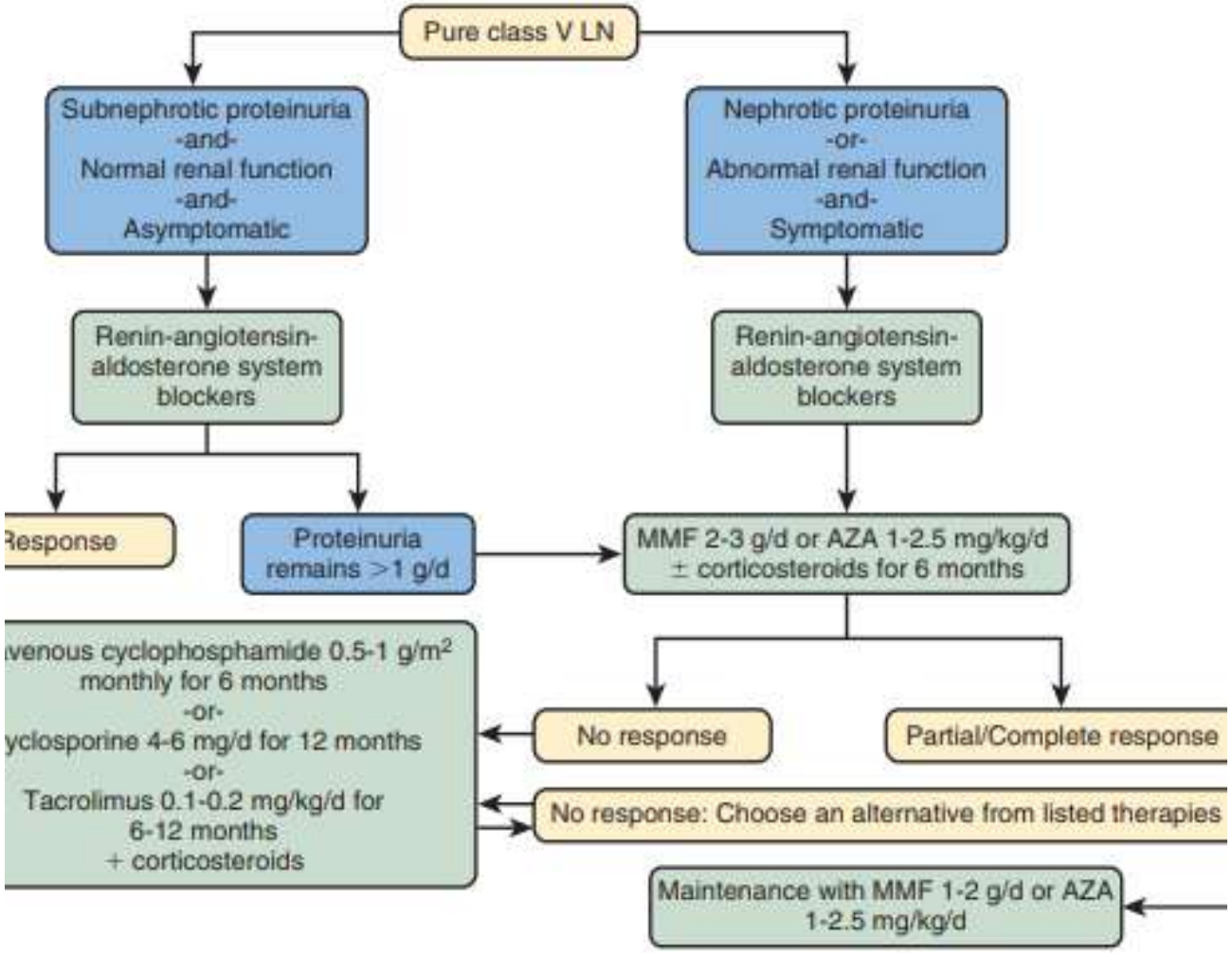
2)maintainence phase

- class I and II LN- immunosuppressive treatment of extrarenal lupus manifestation
- classes IIIA , IIIA/C IVA , IVA/C, V- high-dose corticosteroids plus an immunosuppressive agent



TREATMENT OF MEBMRANOUS LUPUS NEPHRITIS

- Steroids are not given in membranous lupus as kidney is already fibrosed



MEMBRANOUS NEPHRITIS

- ***Non immunosuppressive Therapy***
- *Conservative management of control of edema, hypertension, hyperlipidemia, and proteinuria.*
- ***Immunosuppressive Therapy***
- *When to use immunosuppresive therapy--persistent nephrotic-range proteinuria (>4 g/day) and the proteinuria has not declined more than 50% from baseline, over a minimum observation period of 6 months, despite maximum antihypertensive and antiproteinuric therapy*
- *criteria for early intervention are the presence of severe disabling or life-threatening symptoms related to the nephrotic syndrome or a rise in serum creatinine greater than 30% within 12 months*

- ***Cytotoxic Agents Combined With Corticosteroids***
- *methylprednisolone pulses 1 g intravenously for 3 days at the start of months 1, 3 and 5 followed by oral methylprednisolone 0.4 mg/kg/day for 27 days, and each cycle followed by 1 month of treatment with a cytotoxic agent (cyclophosphamide or chlorambucil)*
- *Cyclophosphamide is used more often because of better safety profile*
- ***Calcineurin Inhibitors***
- ***Mycophenolate Mofetil***
- ***Rituximab***