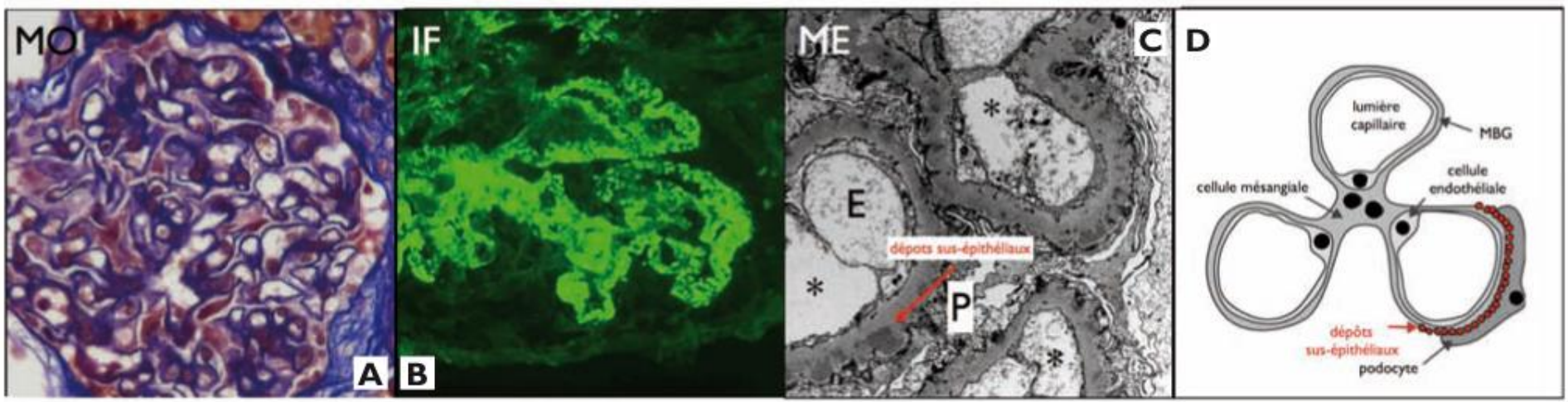
Colloque du vendredi 5 aout 2016



Dr Belén Ponte, PD
Cheffe de clinique scientifique
Service de néphrologie

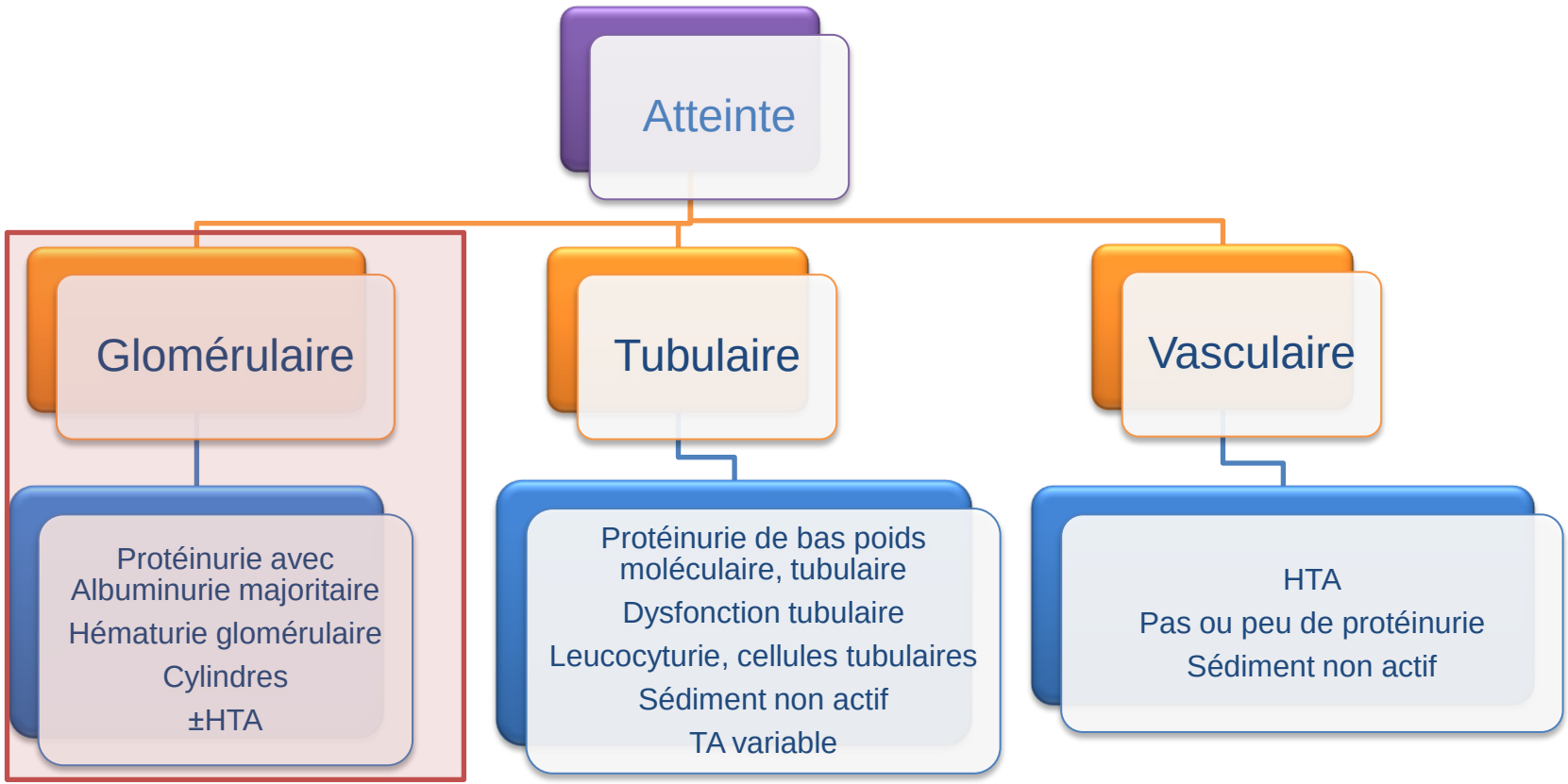
1. Hypothèses diagnostiques

✓ Diagnostic différentiel

✓GN membraneuse

✓Bilan étiologique

Définir le syndrome

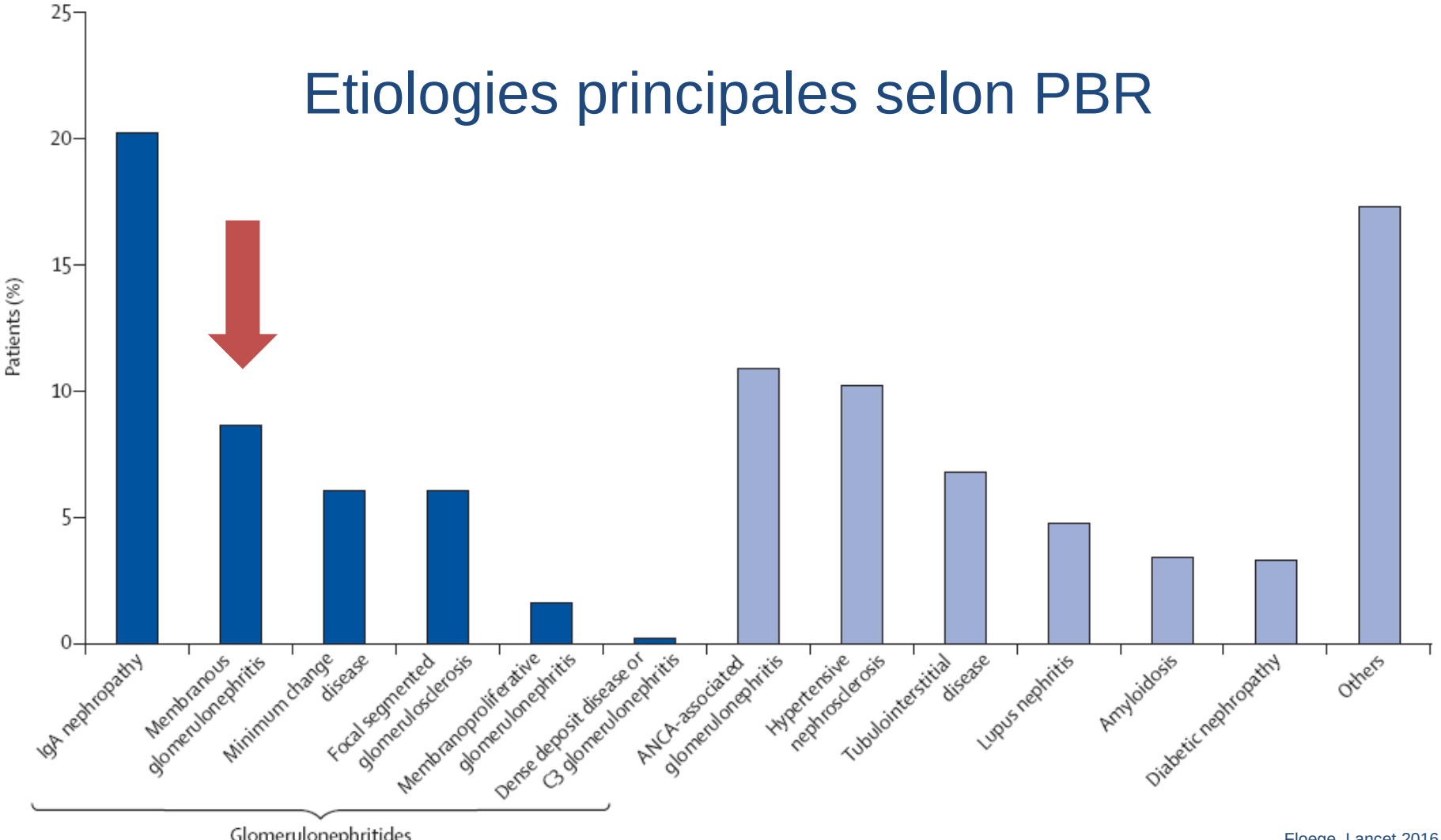


Atteinte glomérulaire

- **Syndrome néphrotique?**
  → Pur: pas d'altération de la fonction rénale, pas d'HTA, pas d'hématurie
  - ✓ Protéinurie glomérulaire (albumine) >3g/24h
  - ✓ Hypoalbuminémie < 30g/l
  - ✓ Oedèmes
  - ✓ Dyslipidémie

- **Syndrome néphritique? Glomérulonéphrite rapidement progressive?**
  → Altération rapide de la fonction rénale
  - ✓ Insuffisance rénale aiguë
  - ✓ Protéinurie glomérulaire (albumine)
  - ✓ Hématurie glomérulaire
  - ✓ HTA
  - ✓ surcharge hydro-sodée, oedèmes
  - ✓ Possibles signes extra-rénaux

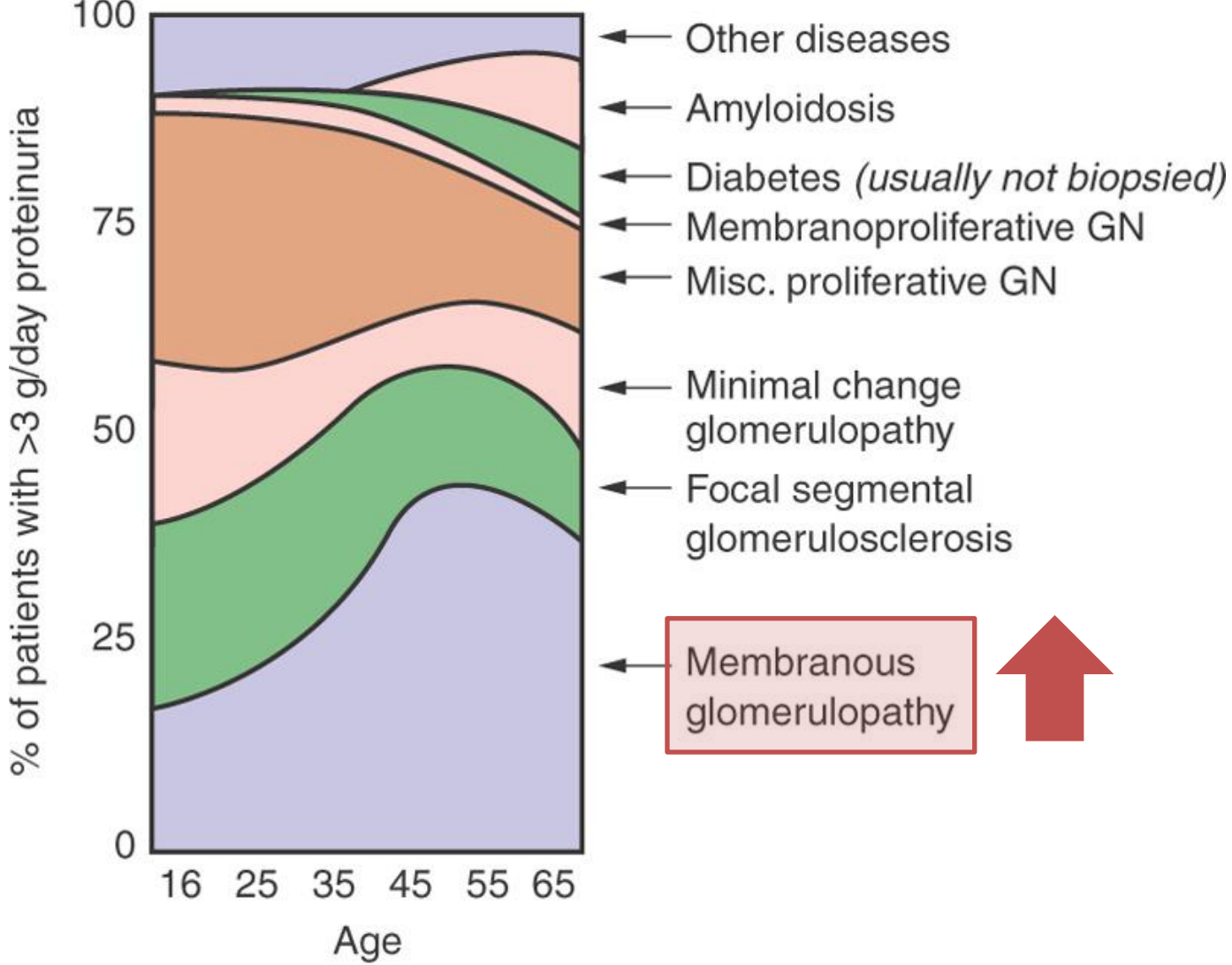
Etiologies principales selon PBR



Floege. Lancet 2016

Syndrome néphrotique: DD

Renal diseases	
Primary glomerular diseases	**Secondary glomerular diseases**
• Minimal-change nephropathy • Focal segmental glomerulosclerosis • Membranous nephropathy • IgA nephropathy • Membranoproliferative glomerulonephritis • Crescentic glomerulonephritis • Hereditary nephropathies	• Diabetes mellitus • Immune-mediated glomerulonephritis amyloidosis • Paraproteinemias • Viral infections (HBV, HCV, HIV) • Paraneoplastic-associated glomerulonephritis
Vascular nephropathies	**Tubulointerstitial nephropathy**
• Thrombotic microangiopathy • Preeclampsia • Benign nephroangiosclerosis • Malignant nephroangiosclerosis	• Chronic tubulointerstitial nephropathy • Acute tubulointerstitial nephropathy • Acute tubular necrosis • Cast nephropathy
Induced by drug administration	
• NSAIDs • Drugs for rheumatic diseases (gold and penicillamine) • Bisphosphonates • Lithium • Interferon • Bevacizumab	


100
75
50
25
0
% of patients with >3 g/day proteinuria
16 25 35 45 55 65
Age
Other diseases
Amyloidosis
Diabetes (usually not biopsied)
Membranoproliferative GN
Misc. proliferative GN
Minimal change glomerulopathy
Focal segmental glomerulosclerosis
Membranous glomerulopathy

Glomérulonéphrite membraneuse

- ✓GN I la + fréquente adulte : 1 cas/100’000 patients-année (USA)
- ✓Primaire (70-80%) ou secondaire
- ✓Homme: Femme = 2:1
- ✓Pic 50-60 ans

- ✓60-80% se manifesteavec SN
- ✓20-40% protéinurie sans SN mais 60% progressent en SN
- ✓50% hematurie microscopique, sans cylindres

- ✓ 1/3 Rémission spontanée dans les 6 mois
- ✓ 1/3 garde protéinurie non néphrotique et 1/3 progresse en IRC
- ✓ Récidive post-greffe +++

Maladies auto-immunes
- Lupus érythémateux disséminé
- Syndrome de Goujerot-Sjögren
- Thyroïdite d'Hashimoto
- Cirrhose biliaire primitive
- Sarcoïdose

Infections
- Hépatite B
- Hépatite C
- Syphilis
- Lèpre
- Filariose
- Paludisme

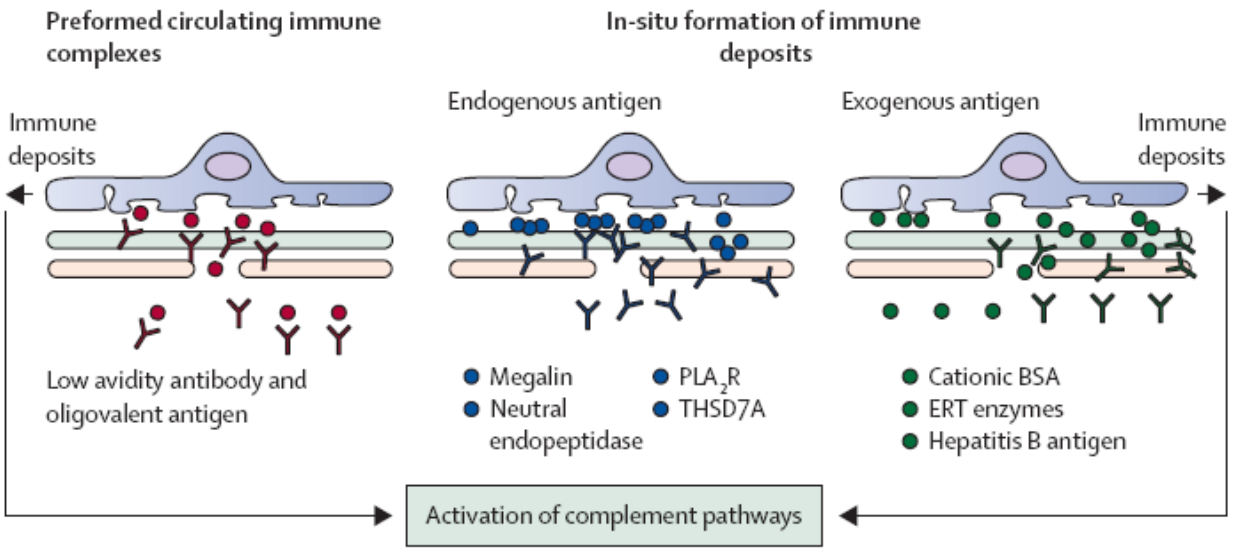
Médicaments
- Sels d'or
- D-pénicillamine
- Captopril
- Sels de mercure
- Anti-inflammatoires non stéroïdiens

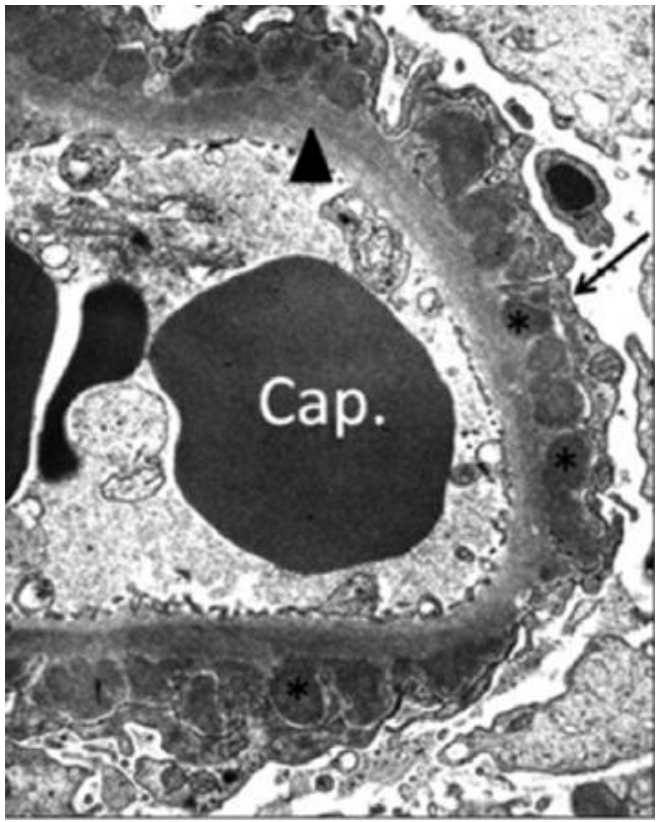
Néoplasies
- Adénocarcinome (sein, poumon, prostate, colôn, estomac, pancréas, foie)
- Mélanome

Lymphome non hodgkinien

70% → Idiopathique

Pathologie





Ronco. Lancet 2015

Bilan étiologique SN

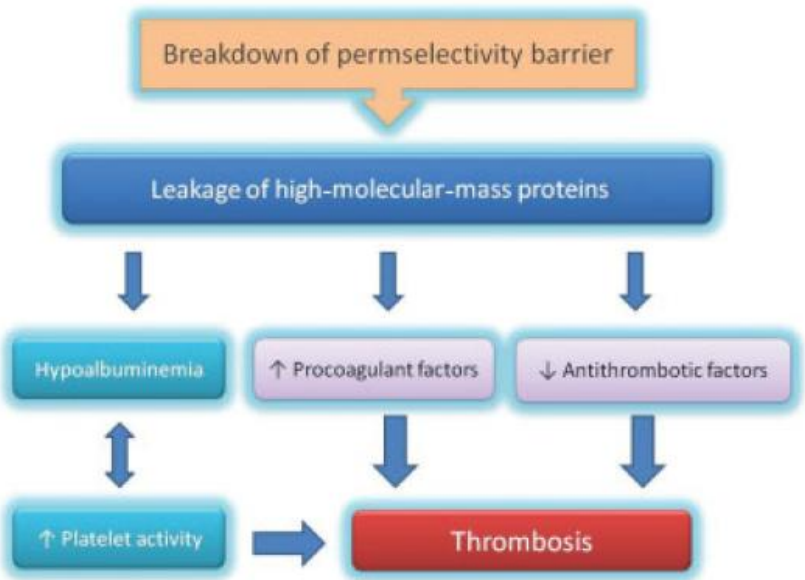
- **Anamnèse, examen clinique**
  - Atteinte extrarénale
  - Recherche tumeur solide, lymphome ou infection
  - Recherche de médicaments
  - Race patient: APOL1
  - Anamnèse familiale
- **Bilan paraclinique**
  - FSC; CRP; chimie complète et bilan lipidique, glycémie
  - HIV, HBV, HCV
  - Immunofixation et dosage chaines légères
  - FAN (ANCA), FR
  - Complément: c3, c4, ch50
  - Cryoglobulinémie
  - Anti PLA2R pour membraneuse
- **Us Doppler rénal**
- **PBR**

2. Complications

Complications du SN

- Protéinurie
- Hyperlipidémie
- Hypoalbuminémie
- Anémie
- hypocalcémie
- Déficit en vit D
- Oedèmes
- Hypertension
- Infectieux
- Os
- Thrombo-embolique
- Cardio-vasculaires

Thrombose



- Genetic predispositions
- Prior idiopathic thromboembolic events
- Obesity
- Severe heart failure
- Serum albumin < 20 g/L
- Abdominal, orthopedic, or gynecologic surgery
- Intercurrent illness or immobilization
- Membranous nephropathy
- Elevated lipoprotein(a)
- Antiphospholipid autoantibodies
- Central venous catheter
- Intravascular volume depletion
- Use of diuretics or steroids
- Steroid-resistant nephrotic syndrome

Endogenous antithrombotic factors	Procoagulant/prothrombotic factors
• Antithrombin III • Protein C • Protein S • Tissue factor pathway inhibitor	• Fibrinogen • Factor V, factor VIII • Platelet reactivity • von Willebrand factor • Fibrinolytic system and plasminogen activator inhibitor

Barabano. Sem Thromb Hemost 2013

Thrombose

Study	MN	MPGN	MCD	FSGS	Other
Llach *et al.* (22)	230.0 (20/69)	22.2 (6/27)	20.0 (2/10)	25.0 (1/4)	9.8 (11/41)
Chugh *et al.* (13)	42.9 (3/7)	20.0 (1/5)	26.3 (5/19)	0 (0/5)	25 (2/8)
Wagoner *et al.* (27)	51.9 (14/27)	NS	NS	NS	NS
Velasquez *et al.* (26)	60.0 (3/5)	40.0 (4/10)	NS	28.6 (2/7)	50 (2/4)
TOTAL	37.0 (40/108)	26.2 (11/42)	24.1 (7/29)	18.8 (3/16)	28.3 (15/53)
TOTAL for combined MPGN, MCD, and FSGS	—	——————24.1 (21/87)——————			—

Data are shown as percentages with thromboembolism (number with thromboembolism/number of patients in category). MN, membranous nephropathy; MPGN, membranoproliferative GN; MCD, minimal change disease; NS, not studied.

Etude de cohorte sur 898 patients avec GNM ont identifié risque de 7.2%
Temps médian: 3.8 mois. FR indépendant: albumine<28g/L

Kerlin. CJASN2012
Lionaki. CJAS 2012

3. Biopsie rénale

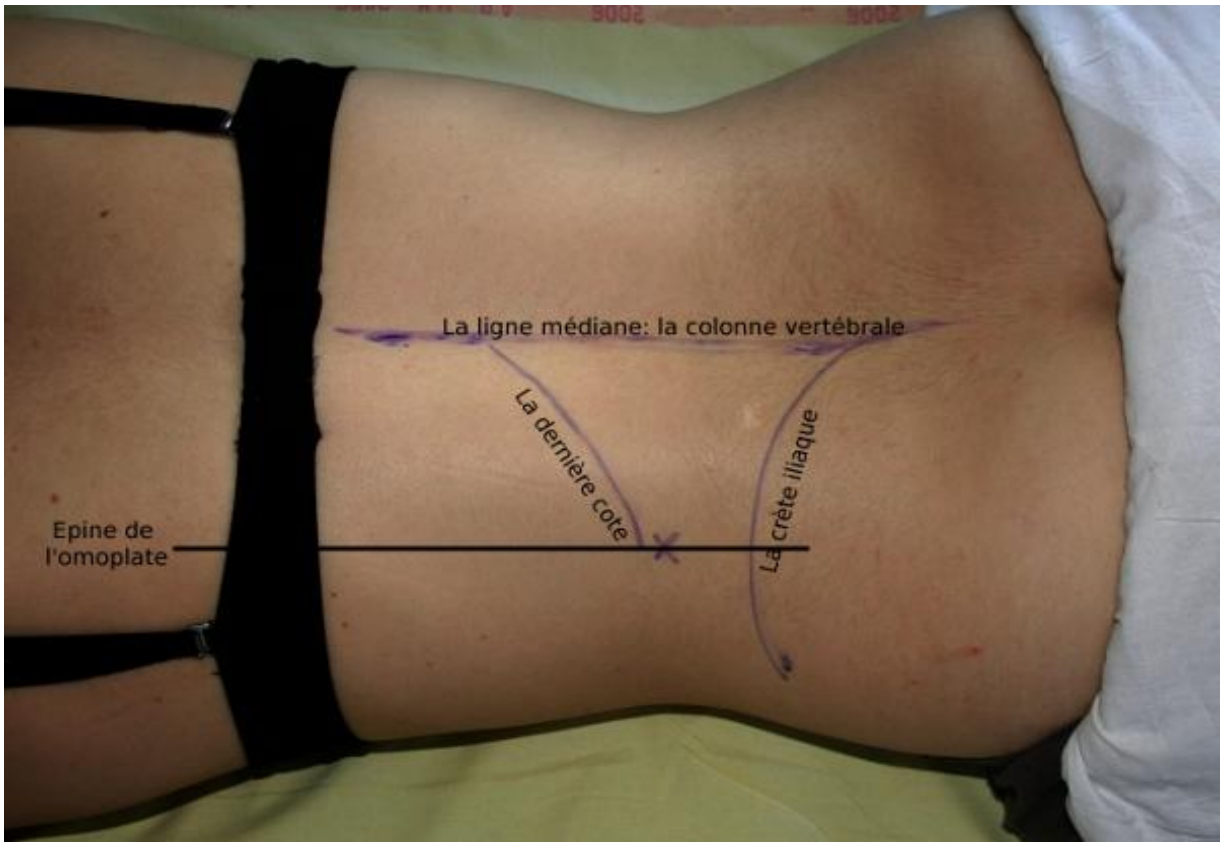
✓ Technique

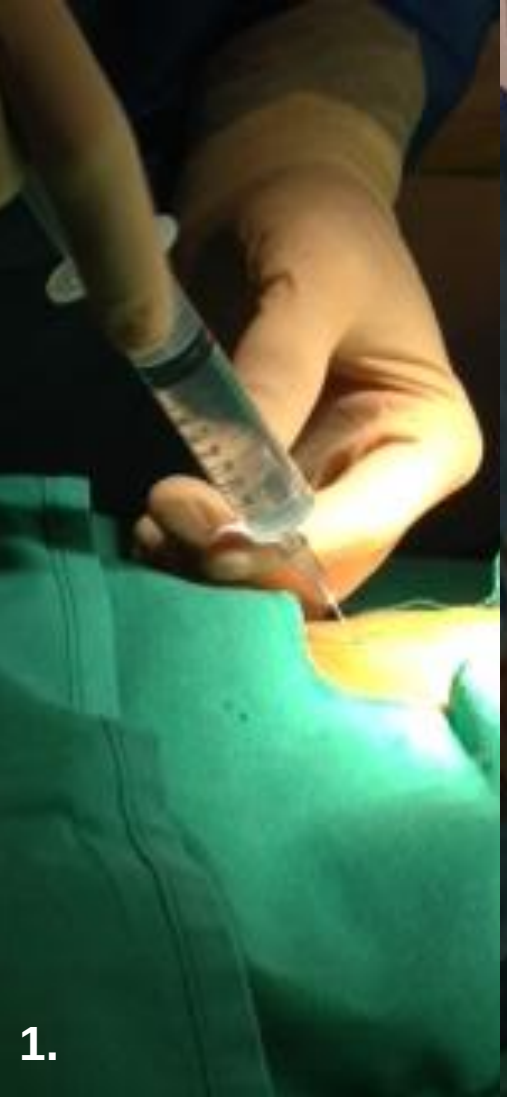
✓Indications /Contre-indications

✓Complications

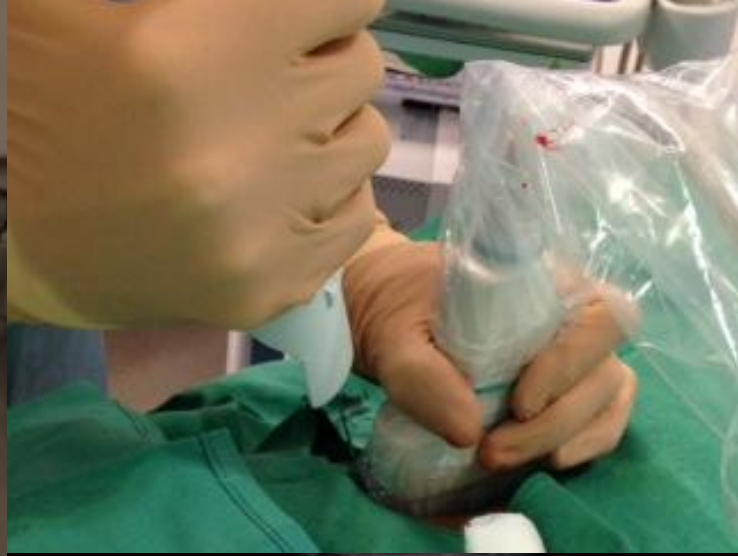
✓Membraneuse

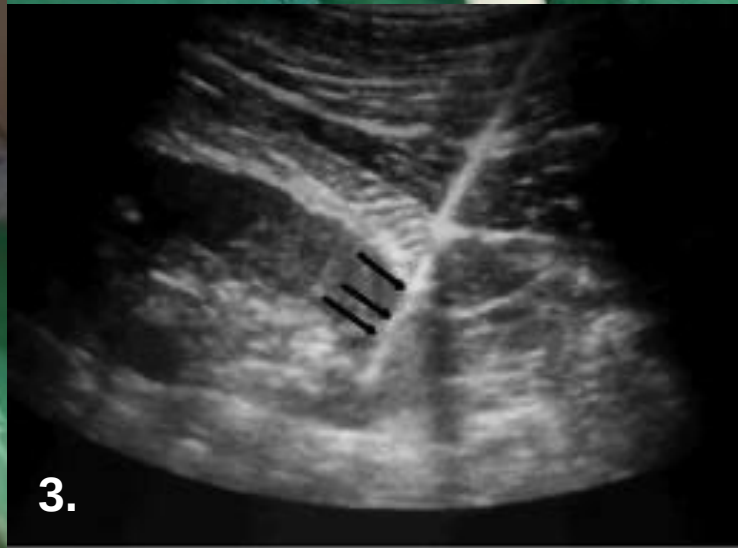
Technique


La ligne médiane: la colonne vertébrale
La dernière cote
La crête iliaque
Epine de
l'omoplate

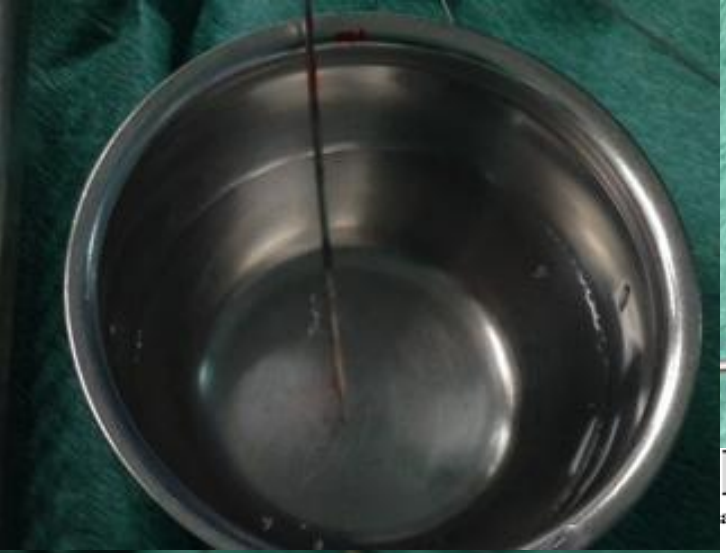

1.

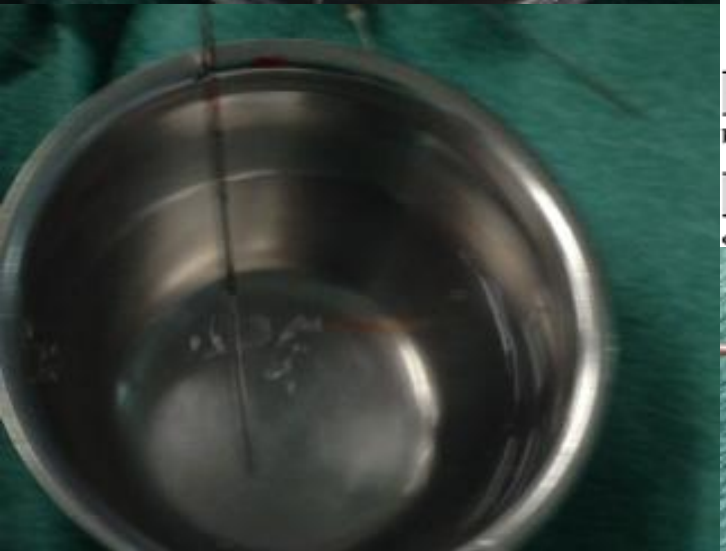

2.

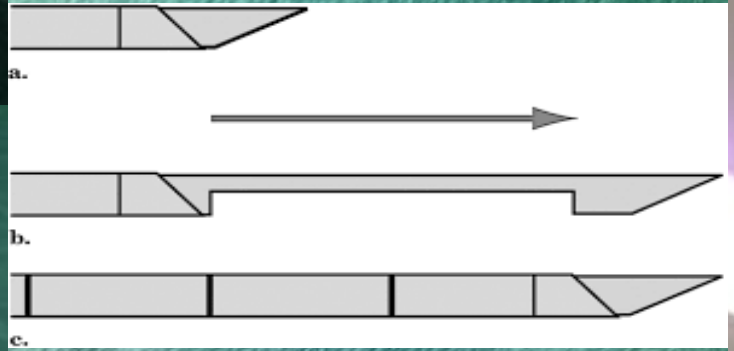


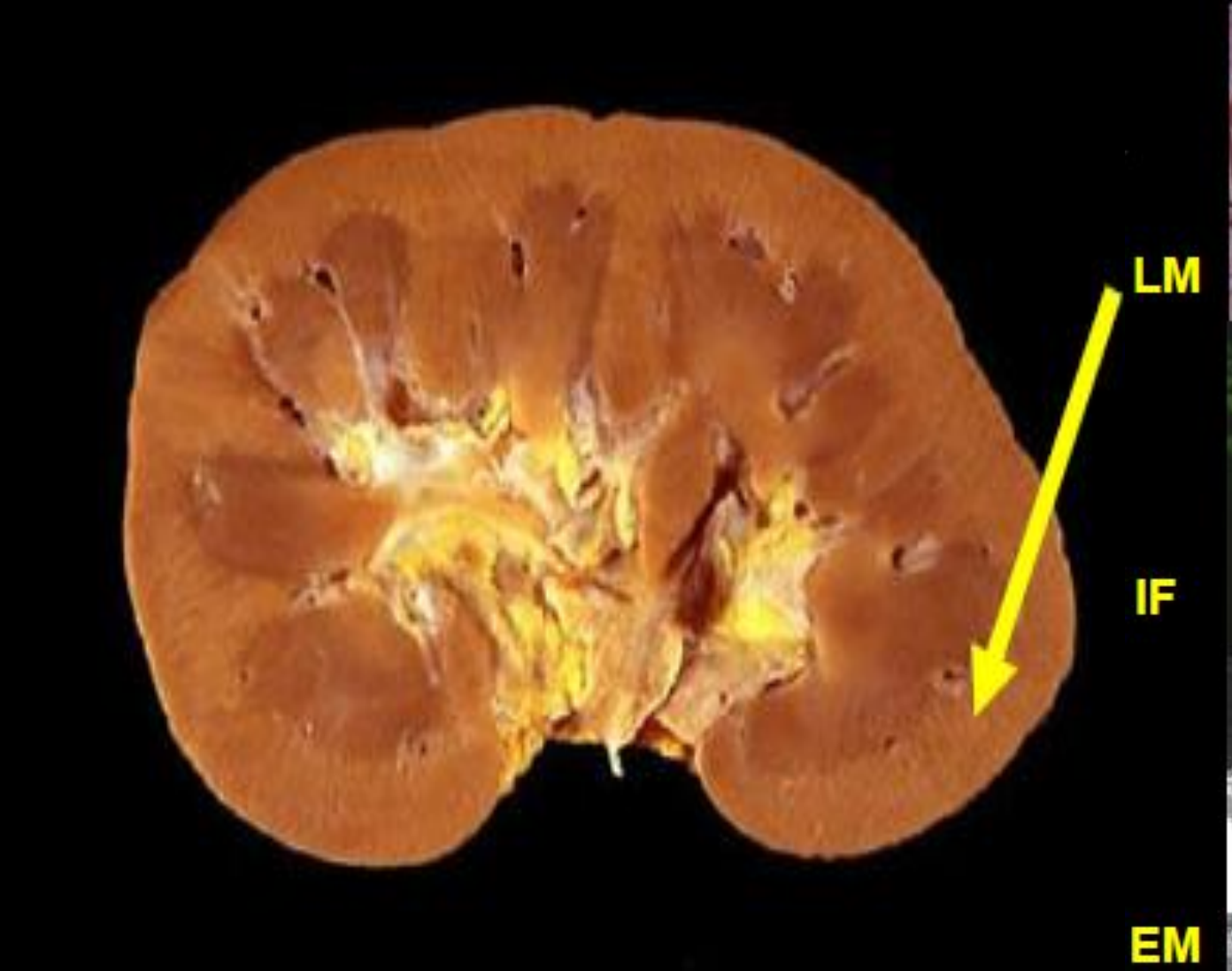

3.

Transport in NaCl
3 fragments

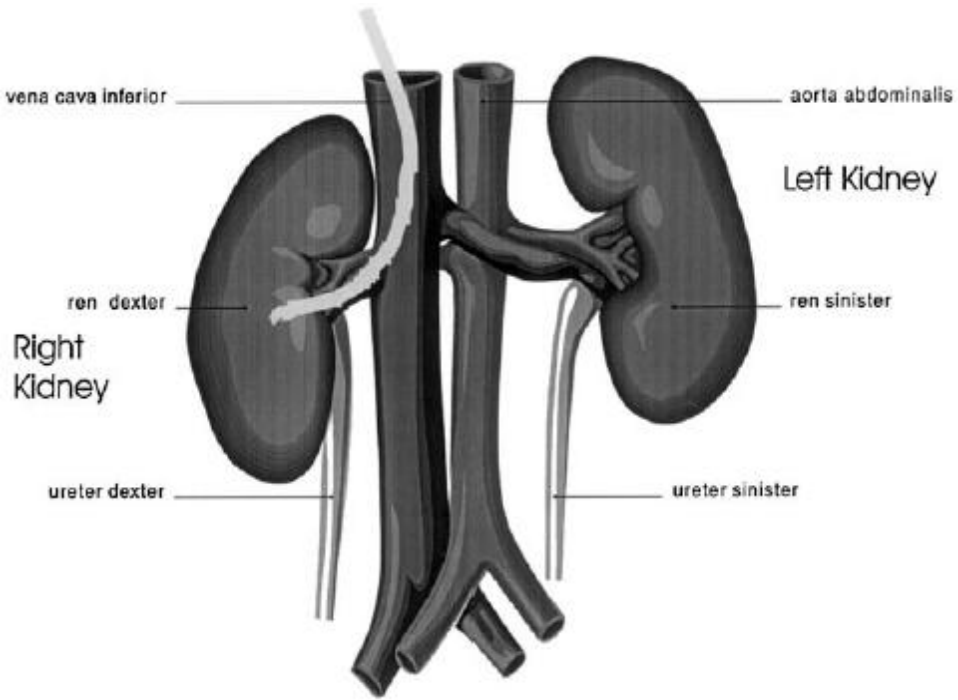







LM
IF
EM

Transjugulaire



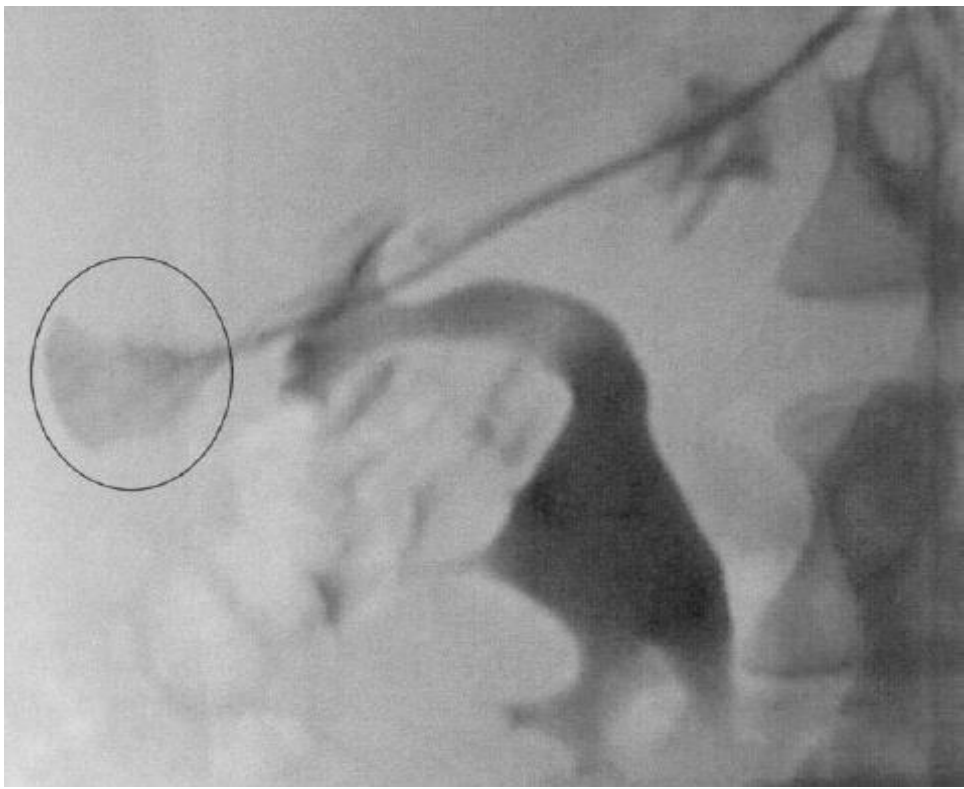
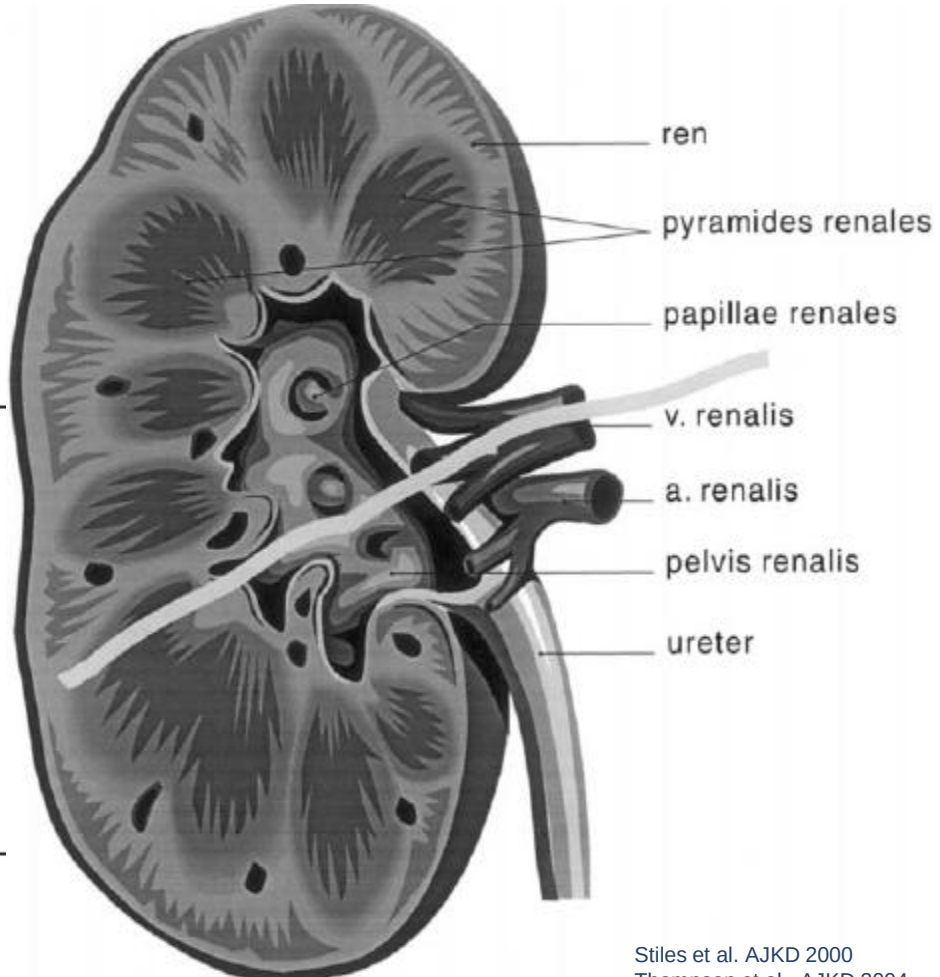


Table 2. Indications for Transjugular Route

Abnormal coagulation (9)
Warfarin therapy (4)
Failed percutaneous kidney biopsy (2)
Single functioning kidney (5)
Simultaneous liver and kidney biopsy (2)
Uncooperative: confused or ventilated (3)
Massive hepatosplenomegaly and myelodysplasia (1)
Known renal microaneurysms (1)



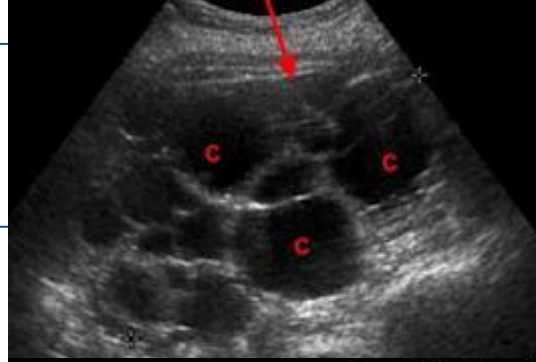
Stiles et al. AJKD 2000
Thompson et al. .AJKD 2004

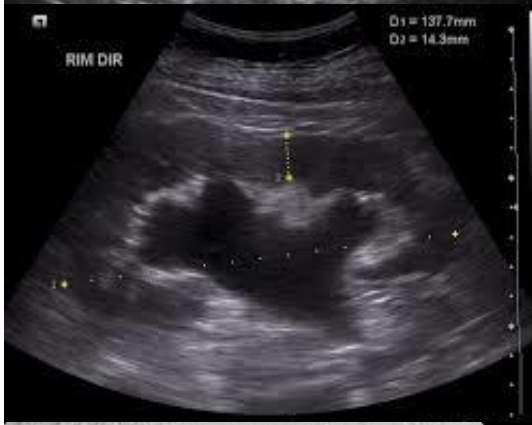
Indications

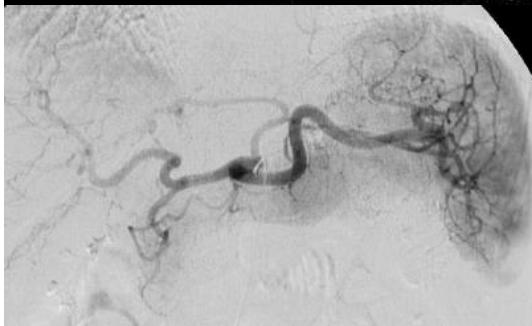
- Diagnostique
  - Hématurie glomérulaire et/ou protéinurie
  - Syndrome néphrotique ou néphritique
  - IRA d'origine peu claire
  - Glomérulonéphrite rapidement progressive
  - IRC peu claire
  - Maladie immunologique ou paranéoplasique avec atteinte rénale
- Contrôler la réponse au traitement

Contre-indications

- Relative:
  - Reins de petite taille, rein unique
  - Multiples kystes, masse rénale
  - Hydronephrose, infection
  - HTA non contrôlée
  - Grossesse
- Absolue:
  - Diathèse hémorragique
  - Patient non collaborant







Complications

Microhematuria	90-100%
Pain	12-18%
Macrohematuria	2-10%
Relevant hematoma	2-7.8%
Need of transfusion	0.4-6%
AV fistula	5-10%
Other tissue lesion	<5%
Surgical Intervention Nephrectomy	<0.2% 1/2000-1/5000
Death	0.1%

	n	Hours Post-Biopsy				
		≤ 4	≤ 8	≤12	≤24	>24
Total	91	42%	67%	85%	89%	11%
Minor complication	46	46%	67%	80%	87%	13%
Major complication	45	38%	67%	89%	91%	9%

Whitthier. JASN 2012.
Tondel. CJASN 2012
Chung. BMC Nephrology 2014
Simard. Nephron Extra 2014

Complications

Type of Complication	All Patients (%) (9288)	Adults (%) (8573)	Children (%) (715)	*P* Value
Gross hematuria	1.9 (178)	1.9 (167)	1.5 (11)	0.44
Blood transfusion	0.9 (79)	0.9 (78)	0.1 (1)	0.03[a]
Surgery/arterial embolization	0.2 (18)	0.2 (17)	0.1 (1)	0.73
Complications[b]	2.6 (215)	2.7 (233)	1.8 (13)	0.15
Major complications[c]	0.9 (88)	1.0 (86)	0.3 (2)	0.06

Needle Thickness	14 Gauge	16 Gauge	18 Gauge	Unknown	Total
N total	858	2146	4998	744	8746
Percent total	9.8	24.5	57.1	8.5	100
Percent (*N*) complications[a]	2.6 (22)	2.0 (43)[b]	3.0 (151)	2.3 (17)	2.7 (233)
Percent (*N*) major complications[c]	0.6 (5)	1.2 (25)	0.9 (46)	0.8 (6)	0.9 (82)
Percent (*N*) gross hematuria	2.2 (19)	1.0 (22)[d]	2.4 (118)	1.6 (12)	2.0 (171)
Percent (*N*) blood transfusions	0.2 (2)	1.1 (23)	0.9 (43)	0.7 (5)	0.8 (73)
Percent (*N*) surgery/angiographic embolization	0.4 (3)	0.2 (5)	0.1 (7)	0.3 (2)	0.2 (17)
Percent representative tissue	94.6	93.5	94.5	94.9	94.3
Median number of glomeruli (range)	12 (0–86)[d]	12 (0–61)[d]	9 (0–76)	11 (0–69)[d]	10 (0–86)

Tondel. CJASN 2012

Complications – technique

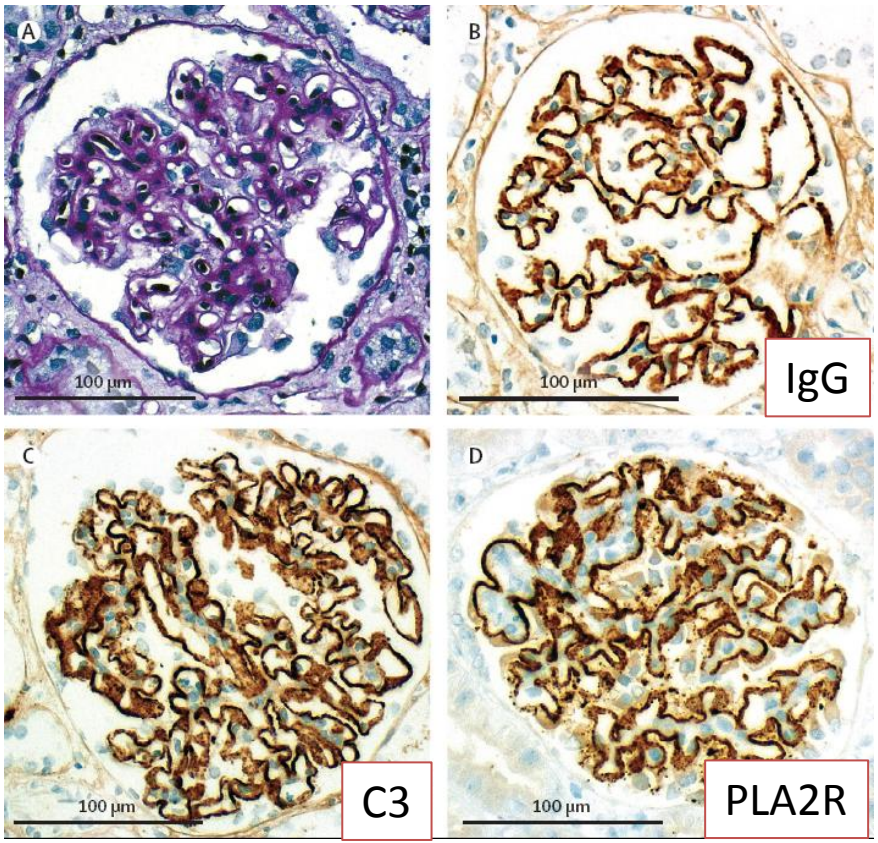
Table 3. Comparison of Techniques for Renal Biopsy in High-Risk Patients

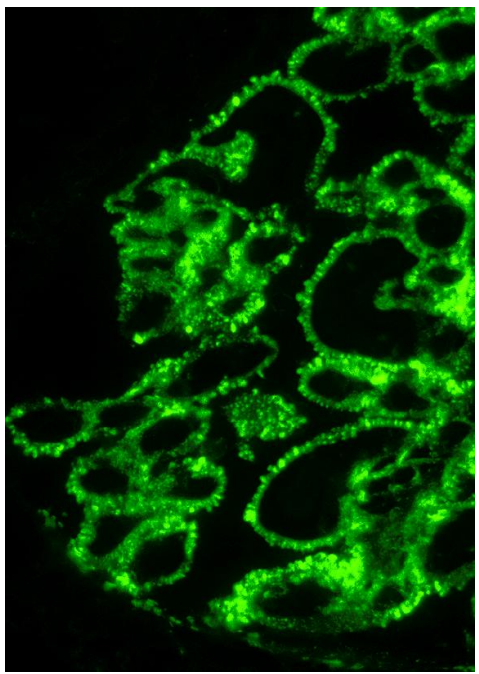
	General Anesthesia	Adequacy	Bleeding Risk	Recovery Time	Complexity, Cost
Open	Yes	5	1	5	5
Laparoscopic	Yes	5	1	3	4
Transjugular	No	2	2	1	3
Percutaneous	No	4	5	1	1

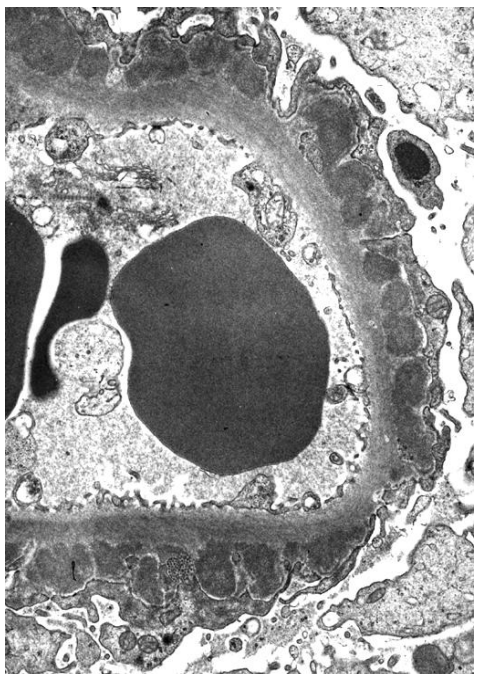
NOTE. Relative scale of 1 to 5, with 1 the lowest score and 5 the highest score.

Stiles et al. AJKD 2000

GN Membraneuse: PBR







PBR: DD primaire vs secondaire

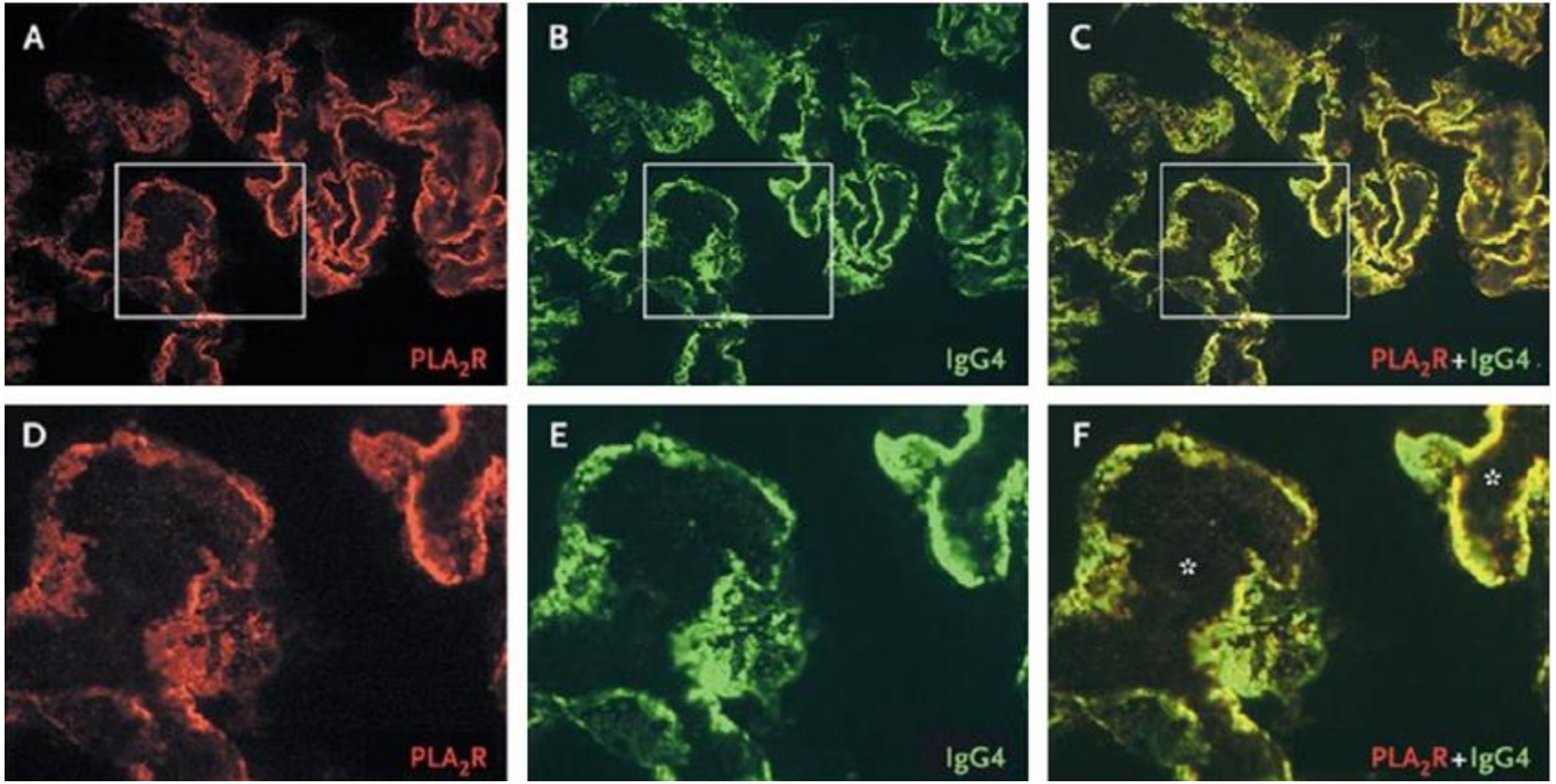
	Primary membranous nephropathy	Secondary membranous nephropathy
Location of Ig deposits by immunofluorescence microscopy	Subepithelial	Subepithelial and mesangial (SLE); extraglomerular Ig deposits (mostly SLE)
Ig isotypes	IgG only	IgG, often associated with IgA and IgM (so-called full house) in class V lupus nephritis
Ig subclass	Mostly IgG4, variable amounts of IgG1	Mostly IgG1 and IgG2; IgG4 is uncommon
Complement	C3, C4; rarely C1q (<20%)	C3, C4, and C1q (SLE)
Electron dense deposits by electron microscopy	Subepithelial and intramembranous	Subepithelial, intramembranous, and mesangial (SLE); tubuloreticular inclusions (SLE)

SLE=systemic lupus erythematosus.

Table 1: **Comparison of immunopathological characteristics of primary (idiopathic) and secondary membranous nephropathy**

Ronco. Lancet 2015

PLA2R et IgG4



4. PLA2R et anti-PLA2R

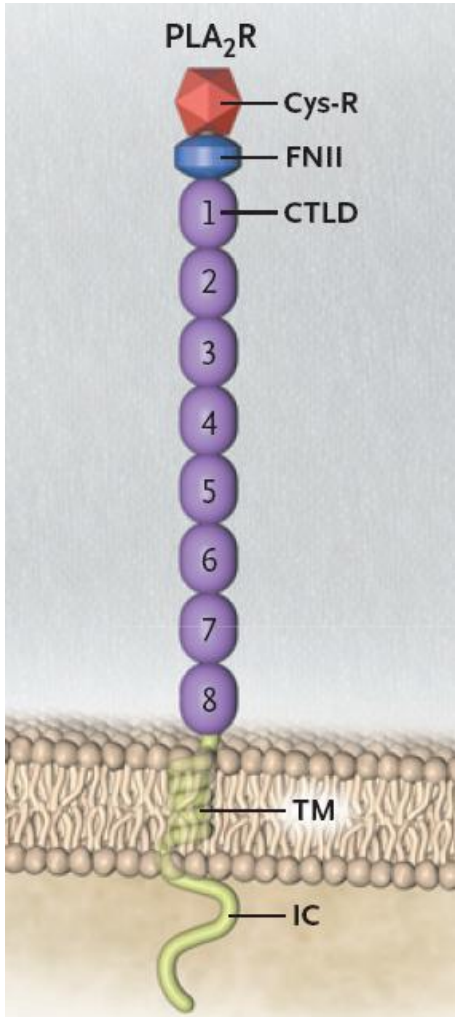
- ✓ test diagnostic
- ✓Spécificité
- ✓Pronostic
- ✓monitoring

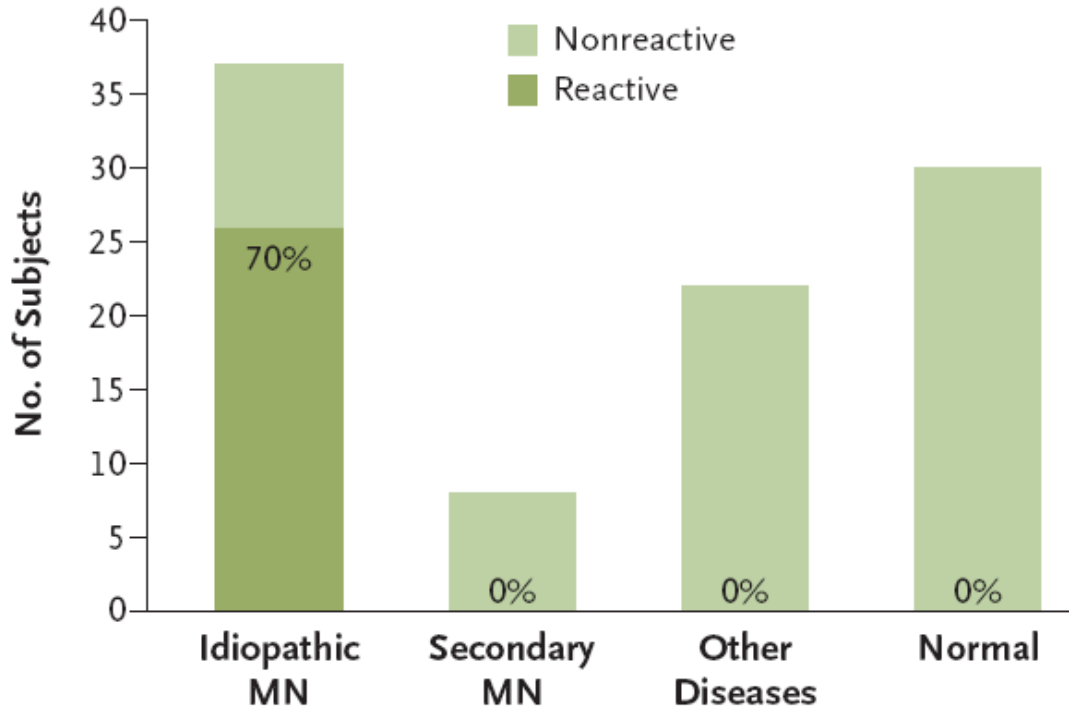
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2009 VOL. 361 NO. 1

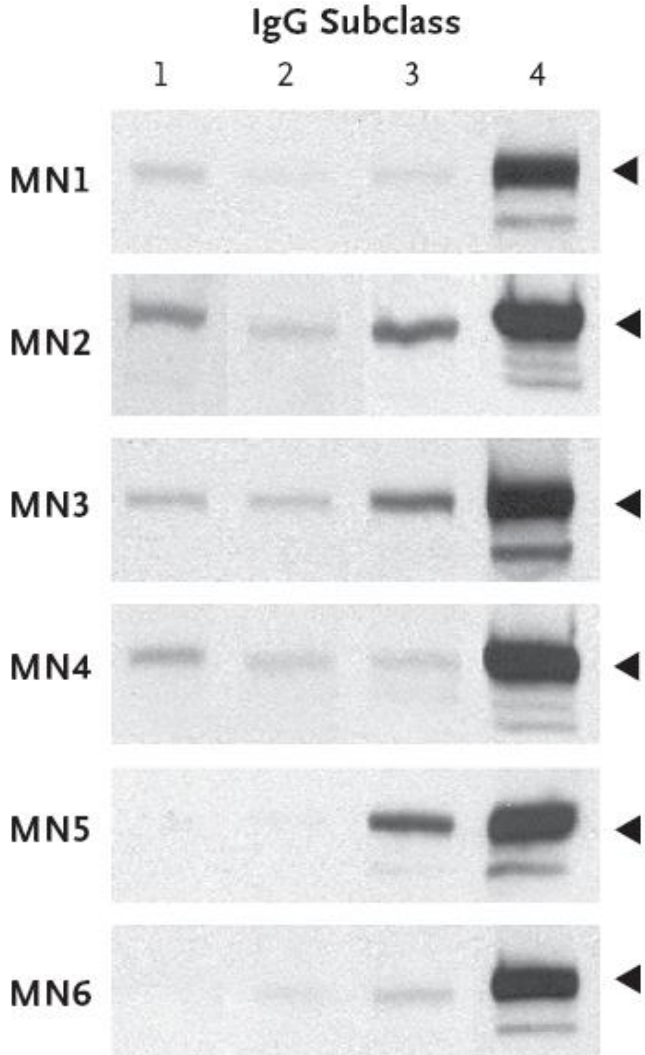
M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

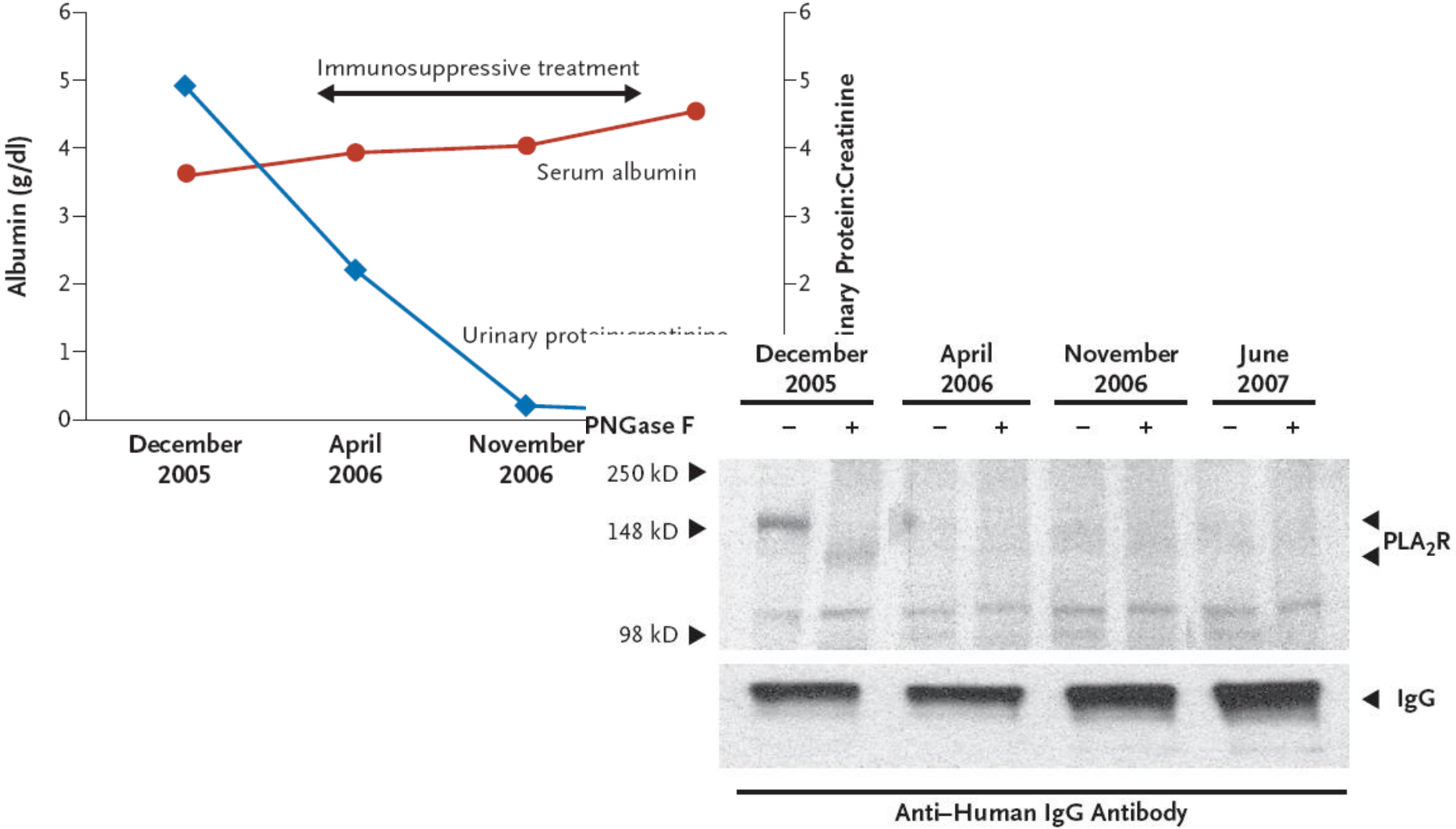
Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.



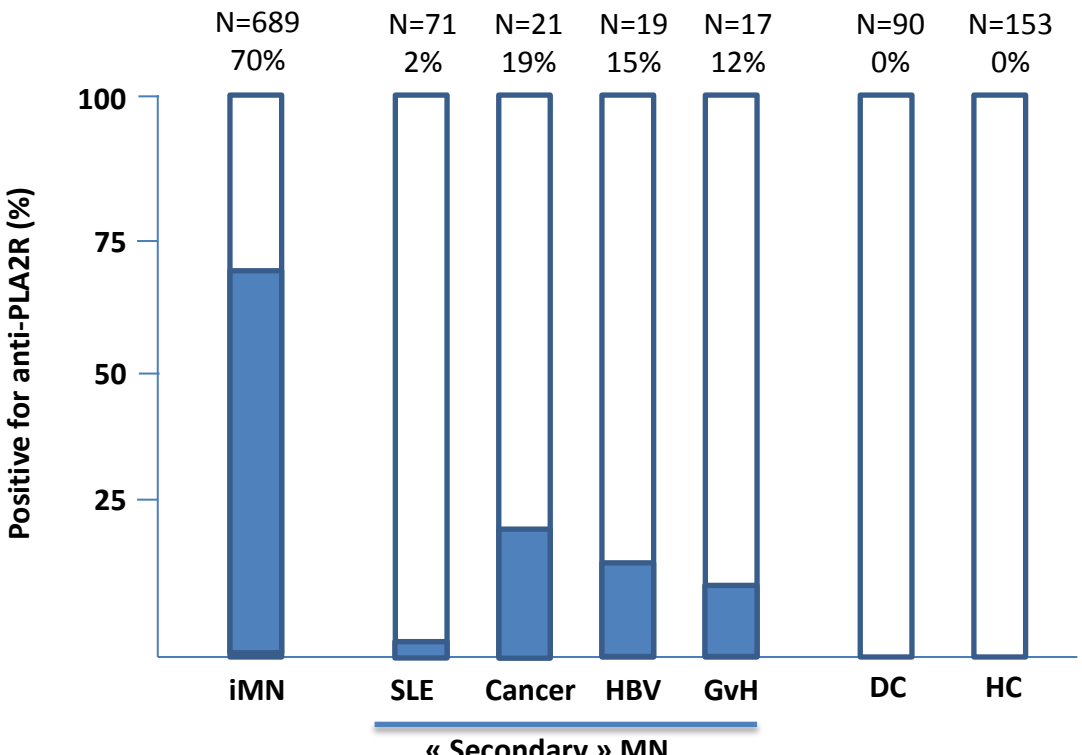


No. of Subjects				
Reactive serum	26	0	0	0
Nonreactive serum	11	8	22	30




Albumin (g/dl)
6
5
4
3
2
1
0
Immunosuppressive treatment
Serum albumin
Urinary protein:creatinine
December 2005
April 2006
November 2006
inary Protein:Creatinine
December 2005
April 2006
November 2006
June 2007
PNGase F
– + – + – + – +
250 kD
148 kD
98 kD
PLA2R
IgG
Anti–Human IgG Antibody

Sensibilité des tests sanguins

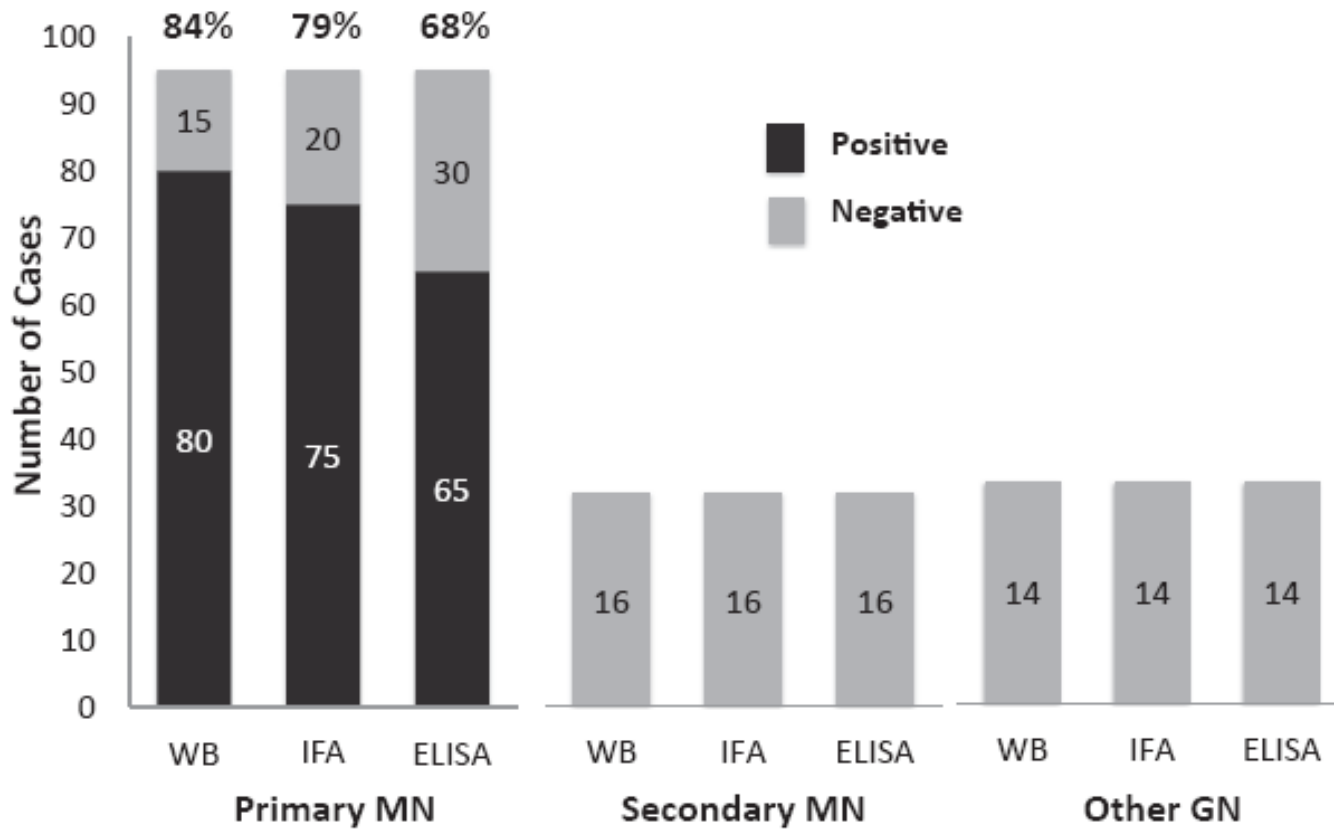


Meta-analyse:
15 études, 2212 patients

- **Specificity = 99%**
  (95% CI : 96-100%)
- **Sensitivity = 78%**
  (95% CI :66-87%)

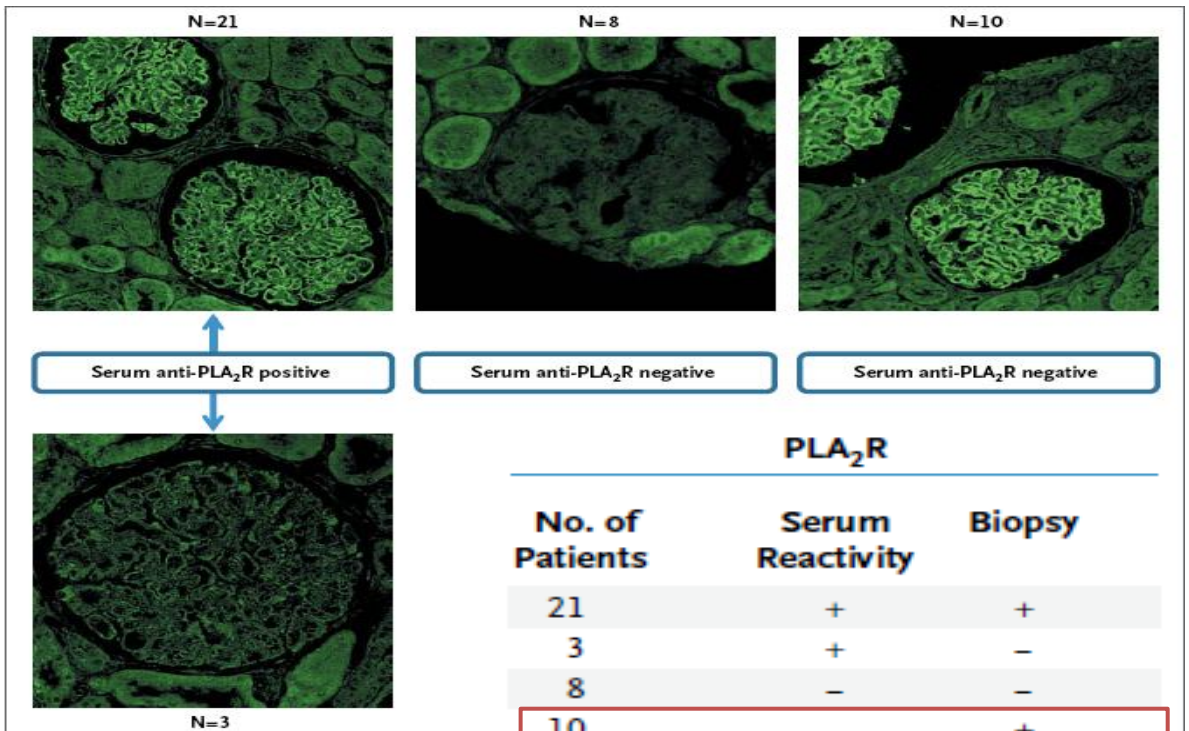
Plos one 2014

Sensibilité des tests - technique



Beck. AJKD2016

Détection Ag PLA2R biopsie



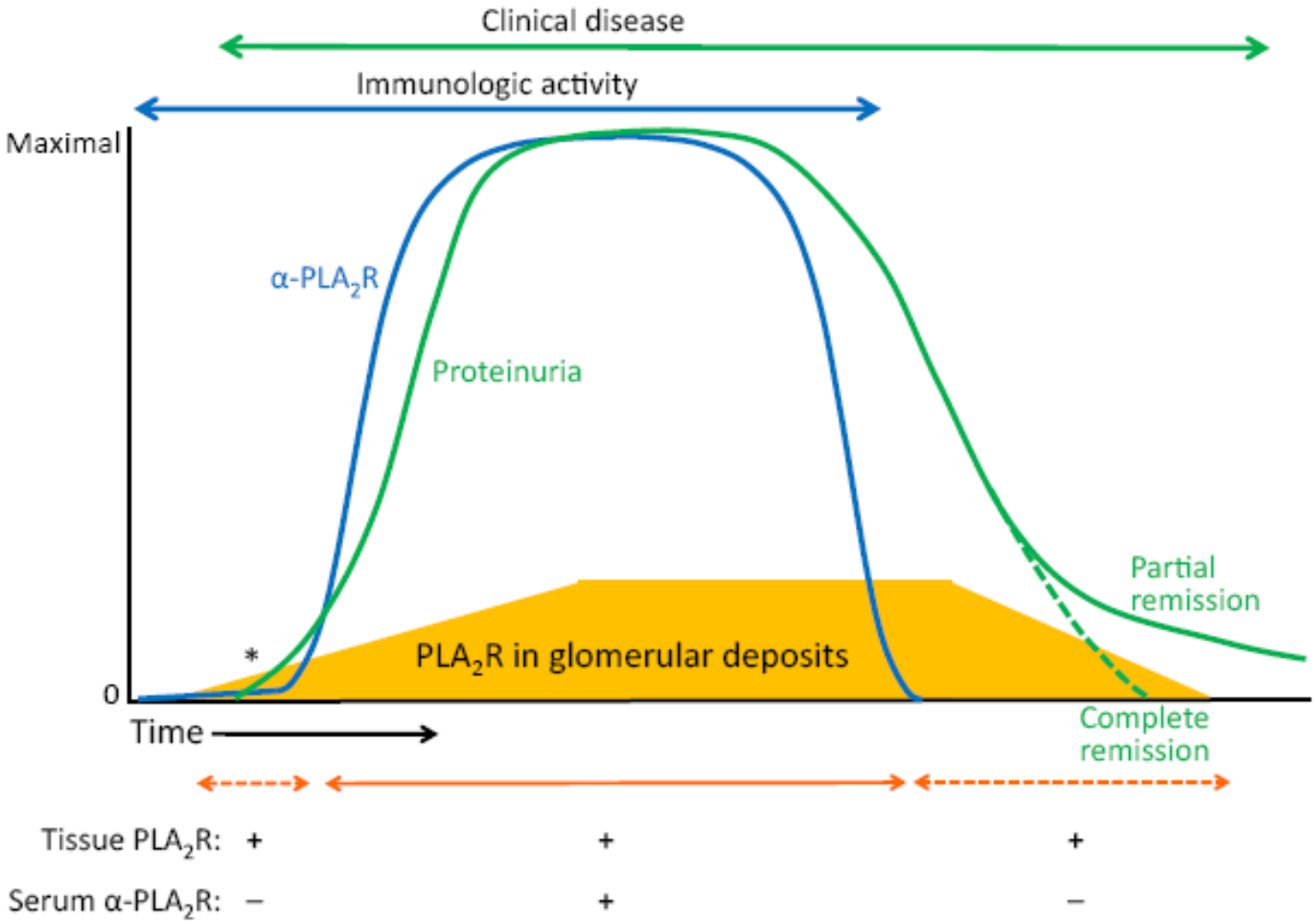
PLA$_2$R		
No. of Patients	Serum Reactivity	Biopsy
21	+	+
3	+	–
8	–	–
10	–	+
42	+24	+31
	57%	74%

Tenon cohorte 2000-2014
n = 106 (84 iMN ; 22 sMN)

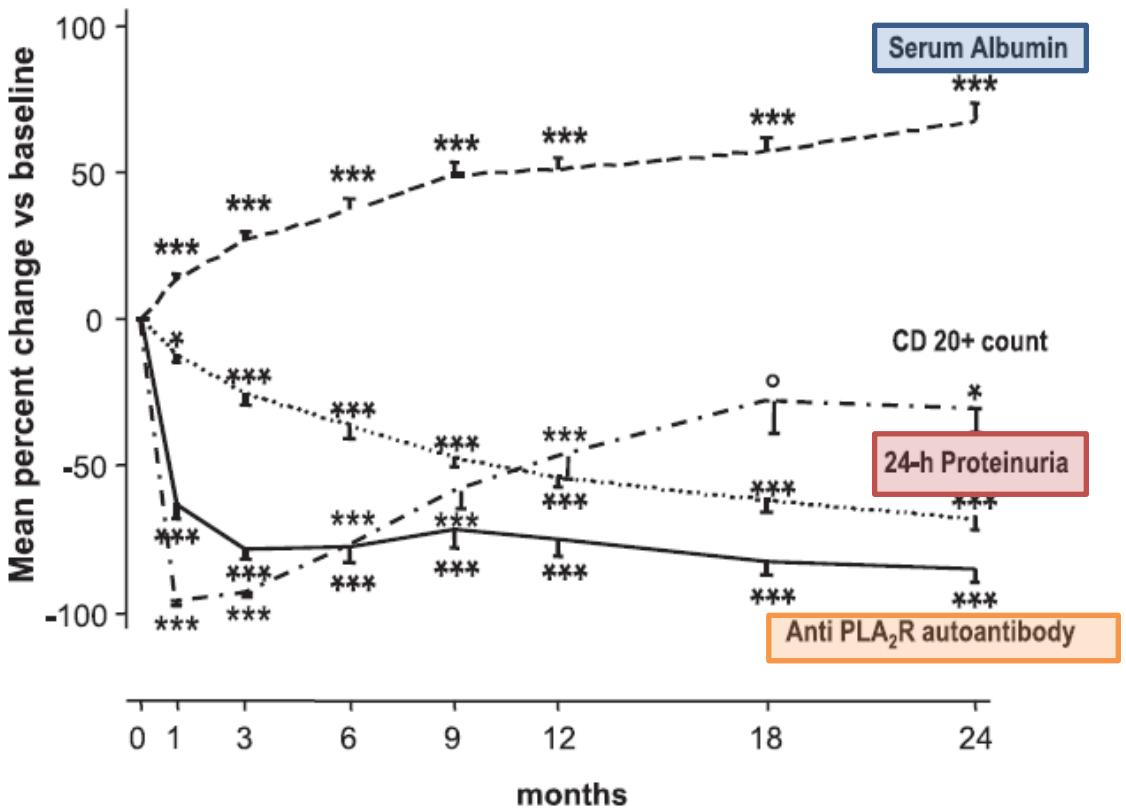
✓Sb PLA2R - Ag : 86%
✓ Sb aPLA2R-Ab : 76%

Pourcine et al, unpublished

Hofstra et al, J Am Soc Nephrol, 2012
Ruggenenti e J Am Soc Nephrol, 2015


Clinical disease
Immunologic activity
Maximal
α-PLA2R
Proteinuria
Partial remission
PLA2R in glomerular deposits
*
0
Time
Complete remission
Tissue PLA2R: + + +
Serum α-PLA2R: – + –

Prédiction outcome



Ruggeneti. JASn 2015
Beck. .JASn 2011

Prédiction rémission selon titre

Selon ELISA

Outcome	aPLA$_2$R=41–175 U/ml (*n*=26)	aPLA$_2$R=176–610 U/ml (*n*=26)	aPLA$_2$R>610 U/ml (*n*=27)	*P* Value
Partial remission	11 (42%)	8 (31%)	11 (41%)	NS
Complete remission	7 (27%)	9 (35%)	8 (30%)	NS
Renal failure	1 (4%)	3 (12%)	5 (19%)	NS
Persistent proteinuria	7 (27%)	6 (23%)	3 (11%)	NS
Spontaneous remission[a]	10 (38%)	8 (31%)	1 (4%)	<0.01

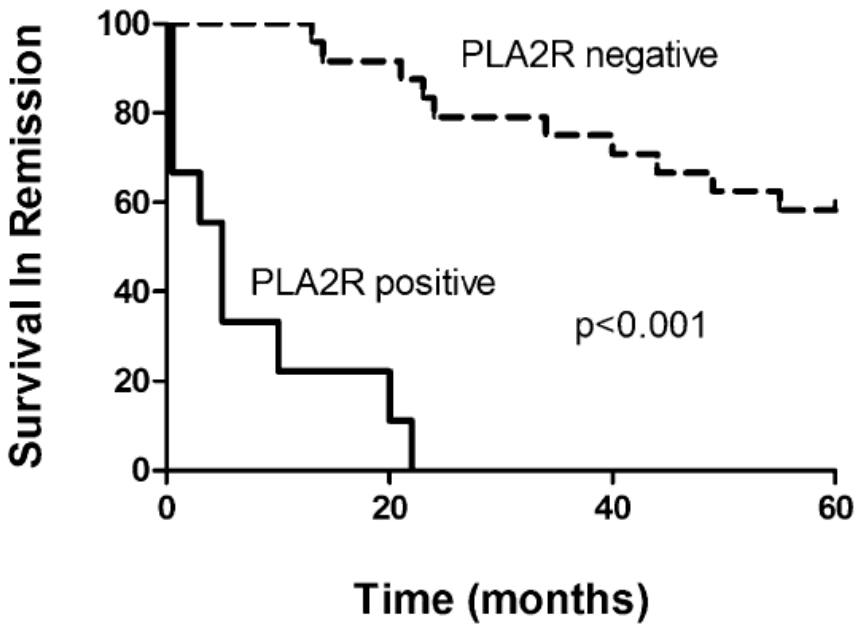
Selon IIFT

Outcome	aPLA$_2$R=1:10 or 1:32 (*n*=27)	aPLA$_2$R>1:100 (*n*=29)	aPLA$_2$R>1:100 (*n*=23)	*P* Value
Partial remission	10 (37%)	11 (38%)	9 (39%)	NS
Complete remission	6 (22%)	10 (35%)	8 (35%)	NS
Renal failure	1 (4%)	4 (14%)	4 (17%)	NS
Persistent proteinuria	10 (37%)	4 (14%)	2 (9%)	NS
Spontaneous remission[a]	8 (30%)	10 (35%)	1 (4%)	0.03

Hostra. JASN 2012

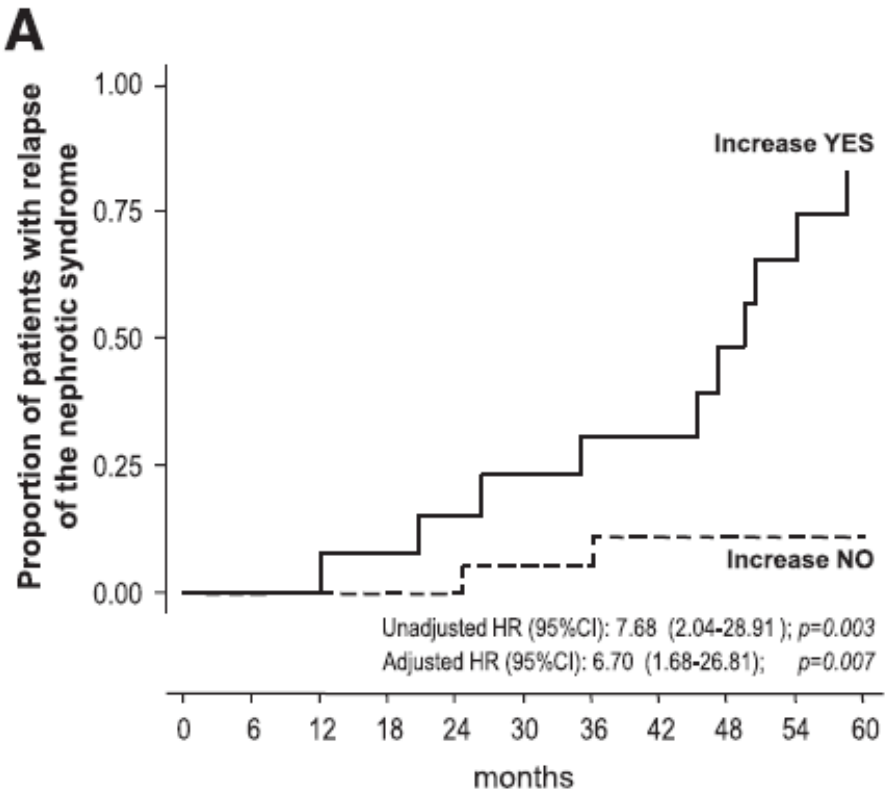
Prédiction Récidive

A 5 ans, 58% anti-PLA2R neg en fin de traitement sont toujours en rémission



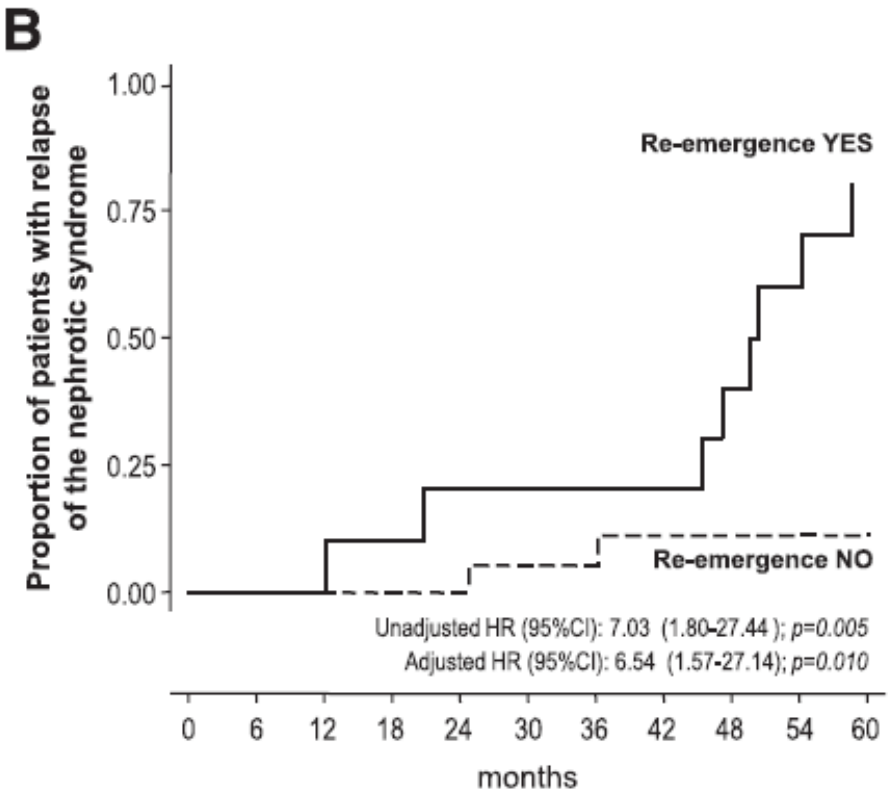
PLA2R positive	9	2	0	0
PLA2R negative	24	22	18	14

Bech. CJASnN2014



Patients at risk

Increase NO	31	31	27	26	24	16	16	12	12	11	10
Increase YES	13	13	13	12	11	10	9	8	6	4	2



Patients at risk

Emergence NO	31	31	27	26	24	16	16	12	12	11	10
Emergence YES	10	10	10	9	8	8	8	8	6	4	2

Ruggenenti. JASn 2015

- ✓ Anti-PLA2R + peuvent précéder protéinurie et manifestations cliniques
- ✓ PBR peut être positive avant serum
- ✓ Taux élevées: - rémissions spontanées ou réponse au traitement
- ✓ Taux élevés: + récidive ou progression

Kanigicherla Kidney Int 2013
Hofstra JASN 2012
Ruggenenti JASN 2015; Hoxha PLoS One 2014+ JASN 2014

To be continued…

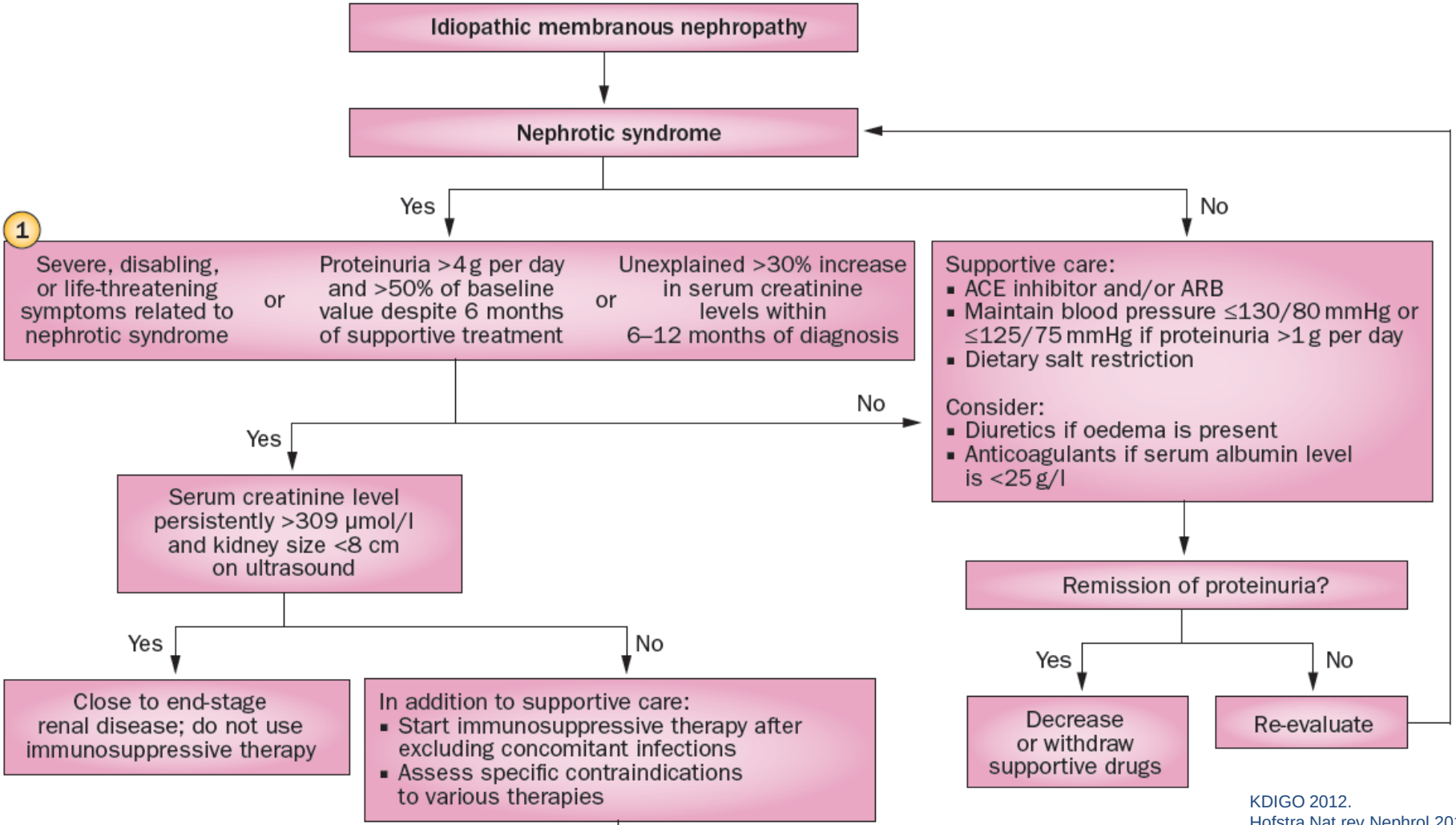
- Anti-PLA2R à la place de la PBR?
- Monitoring anti-PLA2R durant et après le traitement?
- Traitement à l'ère des anti-PLA2R?

5. Traitements

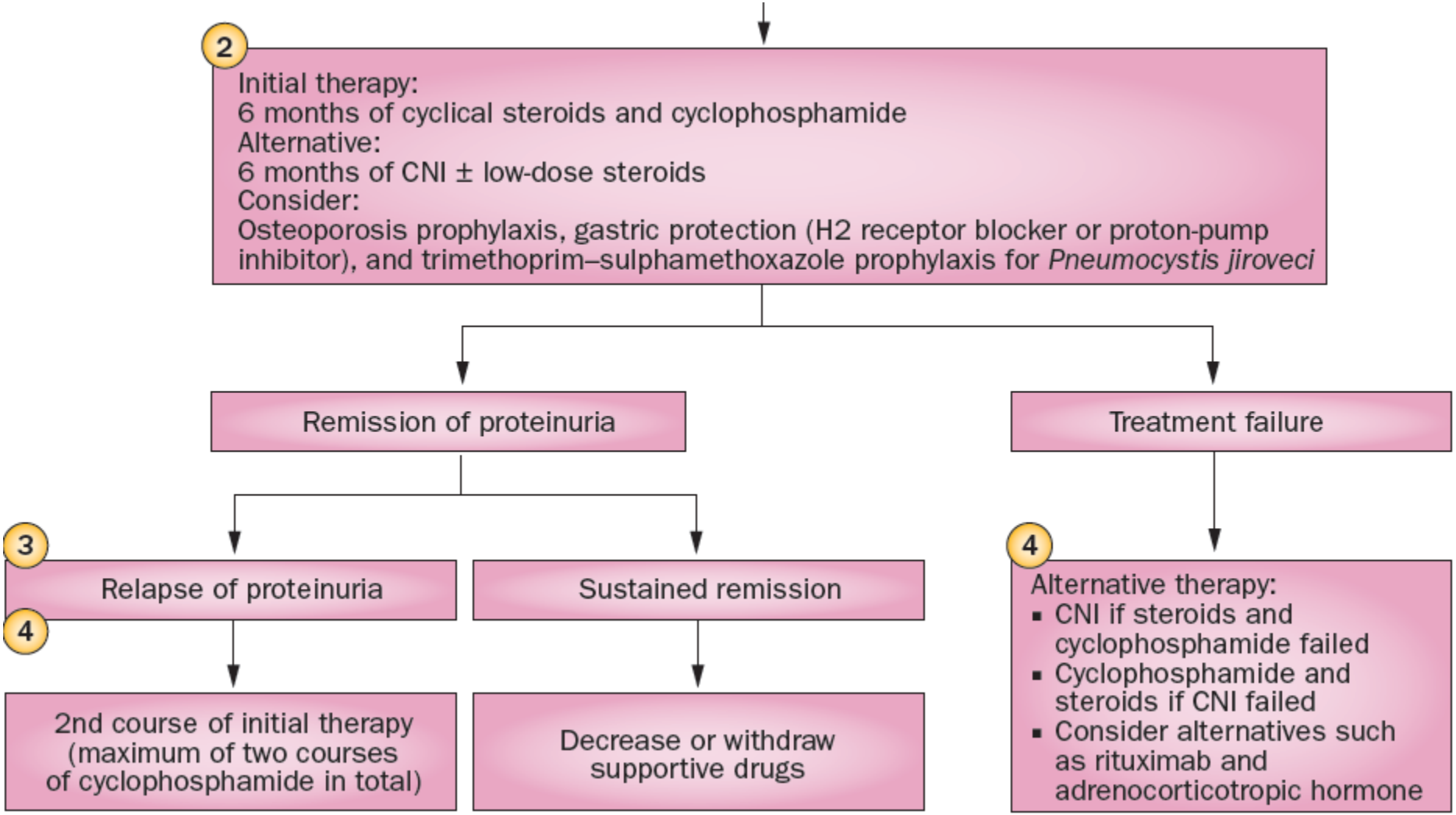
- ✓ traitement de « soutien »
- ✓Immunosuppresseur

Complication	Recommendations
Proteinuria	Specific treatment according to primary disease
	In all cases: ACE inhibitors or ARBs increased to maximum dose depending on biological and clinical tolerance
	If age <55 or no comorbidities: evaluate ACE and ARB combination
	If refractory proteinuria, consider spironolactone
Oedema	Low salt diet
	Amiloride in children
	Sequential diuretic blockade in adults (loop diuretics, thiazide, spironolactone or amiloride)
Hyperlipidaemia	Lipid profile
	Statin if pathological or severe long lasting nephrotic syndrome
Hypertension	ACE inhibitors or ARBs as first choice
	Thiazides or calcium channel blockers in association
	Low salt diet
Hypoalbuminaemia	High protein diet not indicated
	0.8–1 g/kg/day
Thromboembolic risk	Prophylactic anticoagulation if immobilisation
	Full-dose anticoagulation if thrombotic event or membranous nephropathy and severe hypoalbuminaemia (alb <20 g/l)
	In other cases of NS: to be discussed depending on bleeding risk
Anaemia	Anaemia evaluation
	Erythropoietin if required
	Target haemoglobin 11–12 g/l
Infections	High index of suspicion
	Antipneumococcal and influenza vaccinations
Bone metabolism	Vitamin D and calcium
	Bisphosphonates if steroids and/or pathological osteodensitometry

De Seigneux. Swiss medical weekly 2008



KDIGO 2012.
Hofstra Nat rev Nephrol 2013


2
Initial therapy:
6 months of cyclical steroids and cyclophosphamide
Alternative:
6 months of CNI ± low-dose steroids
Consider:
Osteoporosis prophylaxis, gastric protection (H2 receptor blocker or proton-pump inhibitor), and trimethoprim–sulphamethoxazole prophylaxis for *Pneumocystis jiroveci*
Remission of proteinuria
Treatment failure
3
Relapse of proteinuria
Sustained remission
4
2nd course of initial therapy (maximum of two courses of cyclophosphamide in total)
Decrease or withdraw supportive drugs
4
Alternative therapy:
▪ CNI if steroids and cyclophosphamide failed
▪ Cyclophosphamide and steroids if CNI failed
▪ Consider alternatives such as rituximab and adrenocorticotropic hormone

Merci de votre attention