MANAGEMENT OF POST TRANSPLANT GLOMERULONEPHRITIS RECURRENCE

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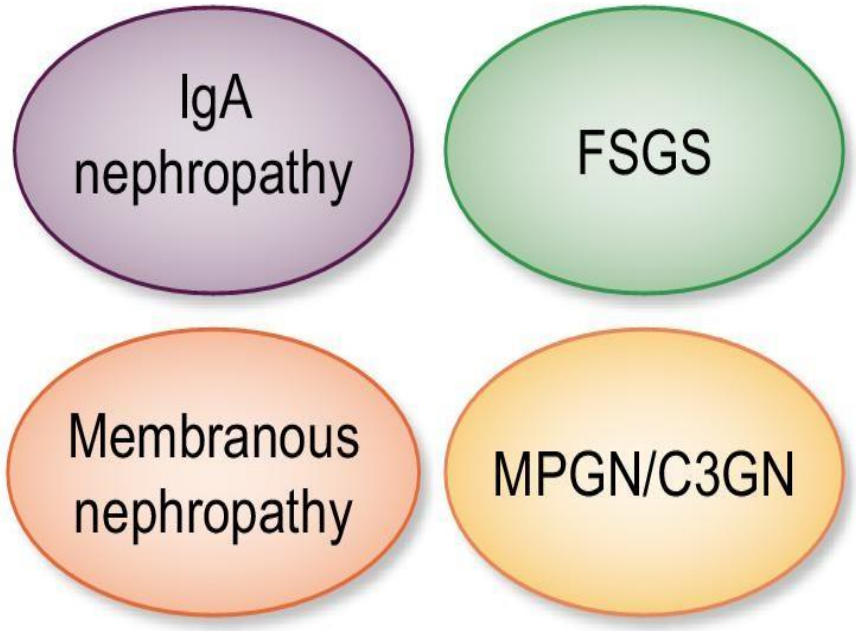
Four most common recurrent GNs:



Risk of clinically-significant recurrent disease

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CKJ Review

CKJ REVIEW

Post-transplant glomerular diseases: update on pathophysiology, risk factors and management strategies

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Recurrent glomerular disease after kidney transplantation: an update of selected areas and the impact of protocol biopsy

Possible factors that influence the recurrence of glomerulonephritis

Focal segmental glomerulosclerosis
Age of onset
Interval to end-stage renal disease
History of graft loss due to recurrent FSGS
Circulating permeability factors
Circulating urokinase receptor
Membranous glomerulonephritis
Anti-phospholipase A2 receptor antibody
Anti-glomerular basement membrane (GBM) antibody glomerulonephritis

Light chain deposition disease
AL-amyloidosis
Paraproteinaemic glomerulopathy
Free light chain detection, kappa/lambda ratio
Atypical HUS

Morozumi K, et al. Nephrology. 2014;19 suppl 3:6-10

Recurence rate of GN on kidney allograft

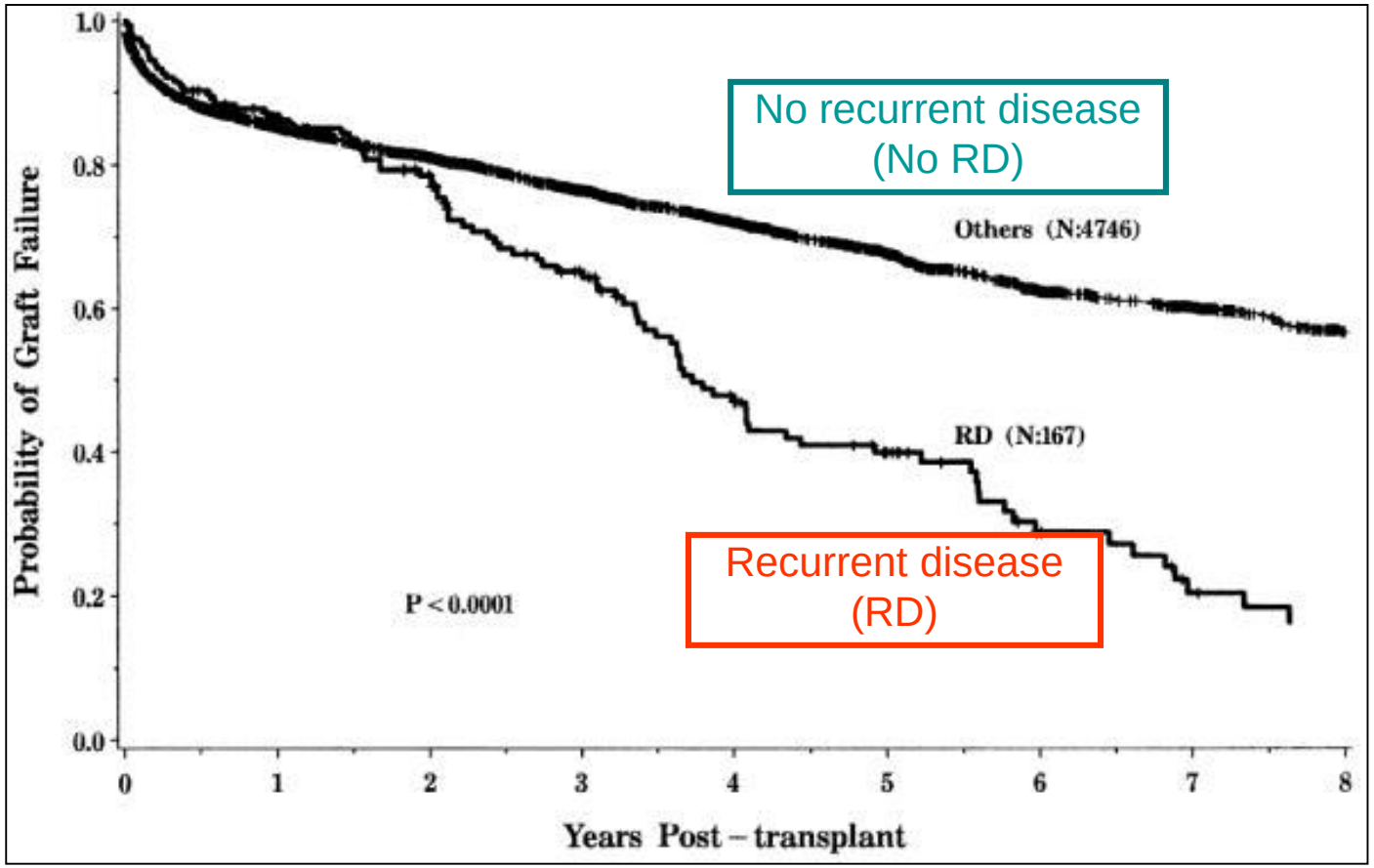
2,026 KTx recipients from 1990 to 2005; of these
36% had biopsy-proven GN,
8% had presumed GN, and
56% had disorders other than GN

Estimate of *de novo* / recurrence of GN post transplantation:

- **5 y : 5.5%**
- **10 y : 10.1%**
- **15 y : 15.7%**

Chalimpamontree et al. JASN, 2009

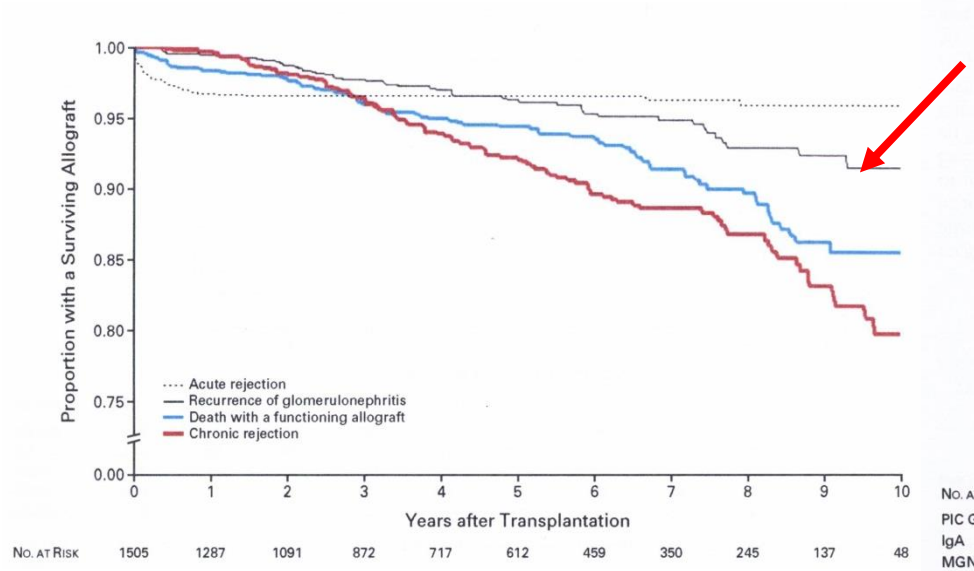
Glomerulopathies : outcome of kidney allograft with regards to recurrence

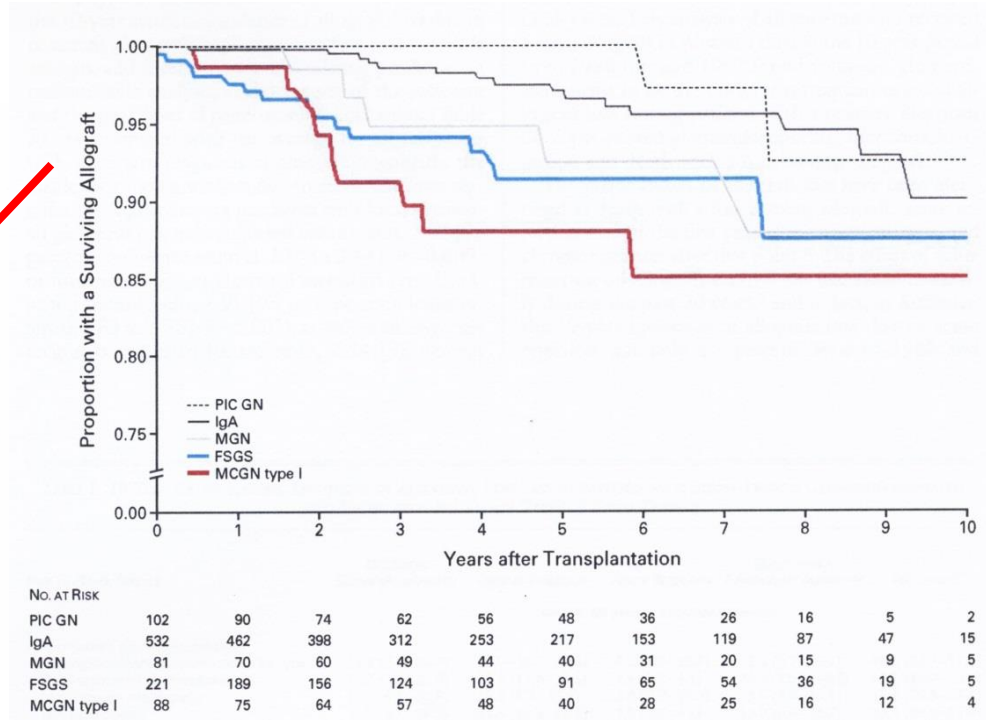


Hariharan S et al. Transplantation 1999

Incidence of kidney alloraft loss due to recurrence of glomerulopathy : 8.4% at 10y

- 1505 KTx recipients with biopsy-proven GN
- 1st KTx between 1988 and 1997
- Recurrence confirmed by kidney biopsy





Allograft Loss Due to Recurrence of Glomerulonephritis, Acute Rejection, Chronic Rejection, and Death with a Functioning Allograft.

Allograft Loss Due to Recurrence of Glomerulonephritis, According to the Type of Glomerulonephritis.

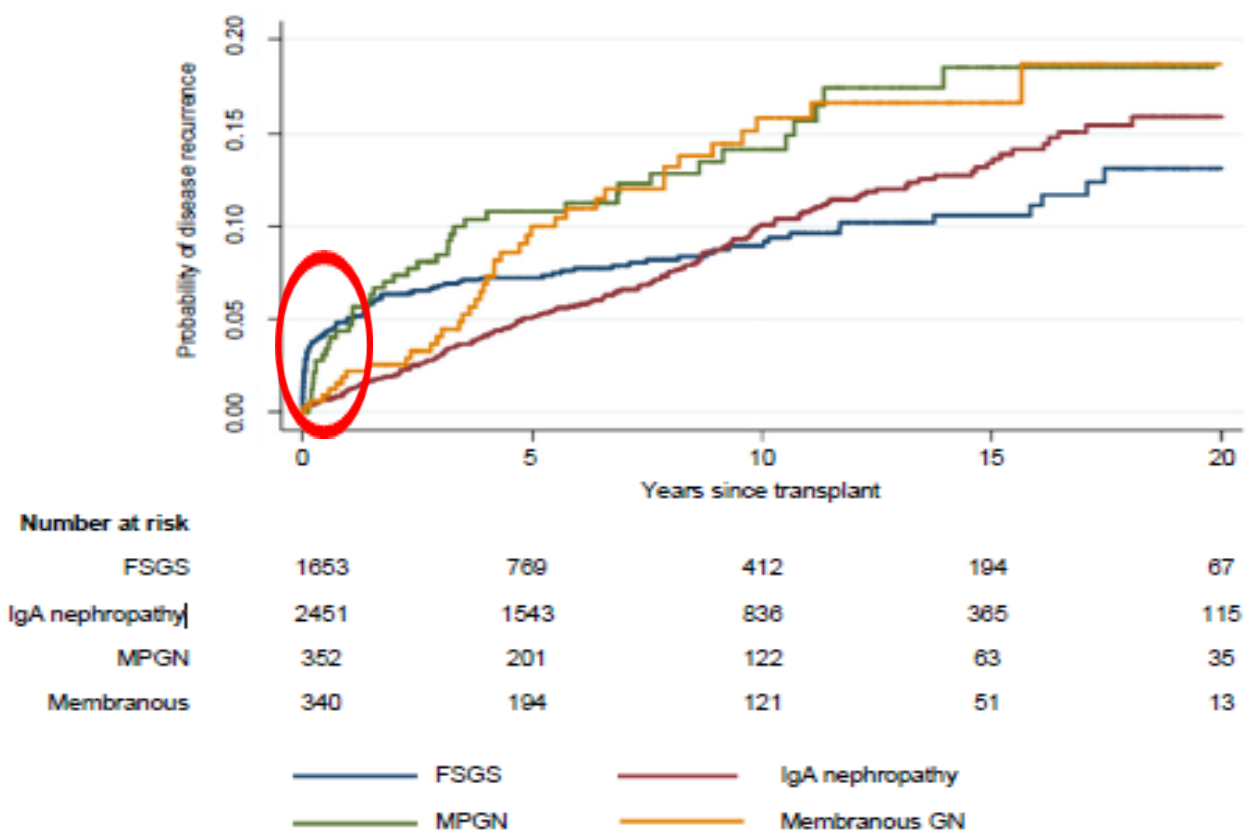
Briganti EM et al. NEJM 2002

Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

- **ANZDATA registry**
  - 6,597 patients with biopsy-proven GN on native kidneys who received a kidney Tx between 1985 and 2014,
    - ✓ 2,501 IgA nephropathy
    - ✓ 1,403 FSGS
    - ✓ 376 MN
    - ✓ 357 MPGN

Allen PJ, et al. Kidney International 2017;92:461–469

Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

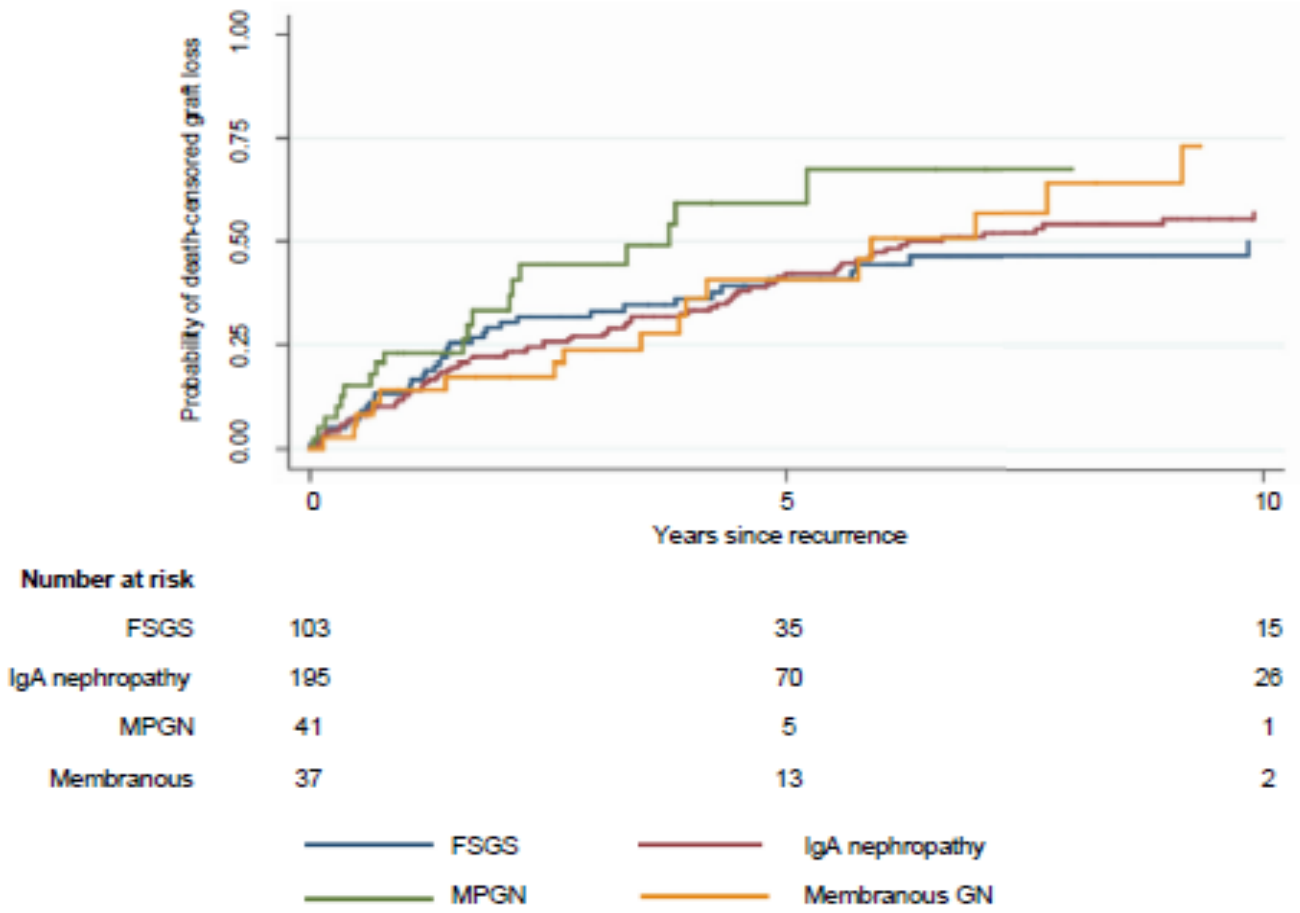


Kaplan–Meier **estimates of disease recurrence,** stratified by glomerulonephritis (GN) types: focal segmental glomerulosclerosis (FSGS), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and membranous GN.

Allen PJ, et al. Kidney International 2017;92:461–469

Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

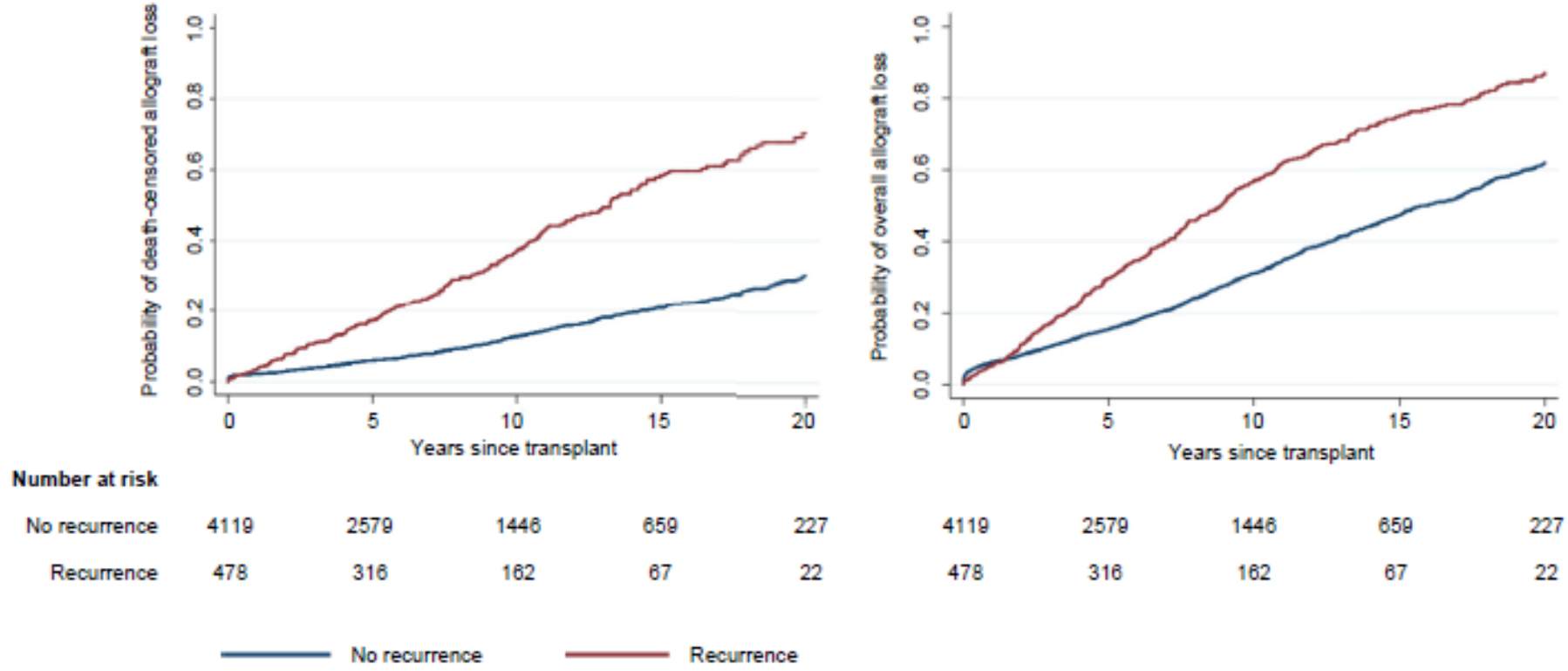
Allograft survival after recurrence, stratified by glomerulonephritis (GN) type: focal segmental glomerulosclerosis (FSGS), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), and membranous GN.



Allen PJ, et al. Kidney International 2017;92:461–469

Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

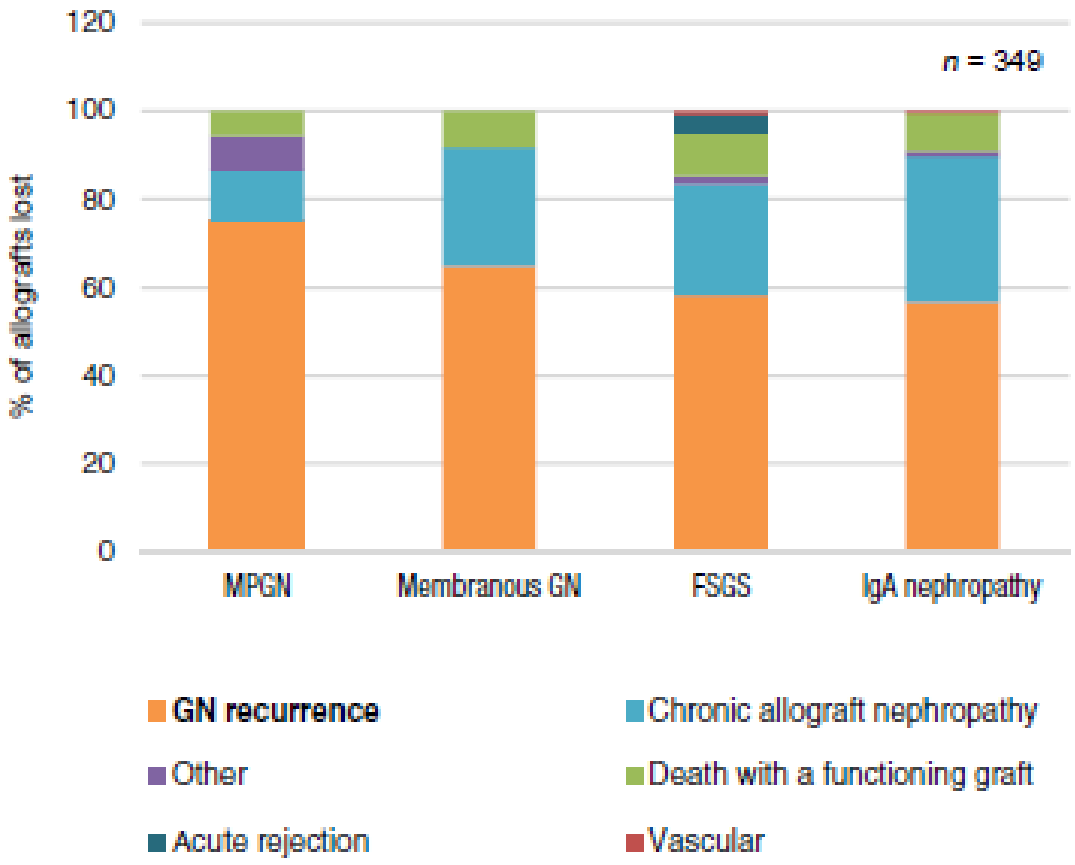
Kaplan–Meier estimates of **overall and death-censored allograft loss** in those with and without recurrent glomerulonephritis



Allen PJ, et al. Kidney International 2017;92:461–469

Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

Causes of allograft loss in recipients with recurrent glomerulonephritis (GN). FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.



Allen PJ, et al. Kidney International 2017;92:461–469

General considerations with regards to kidney transplantation - KTx (4)

- **IgA glomerulopathy**
  - Primary GN
  - Diffuse mesangial deposition of IgA, usually IgA1

IgA GN is one of the most common recurrent GN after KTx

General considerations with regards to kidney transplantation

- **IgA glomerulopathy**

➲ Because of the lack of clear definition for recurrence, the latter is reported in approximately 33% of patients (9 to 61%)

➲ Recurrence may also increase with time post-transplantation

General considerations with regards to kidney transplantation

- **IgA glomerulopathy**

  The diagnosis of recurrence is made 3 years post transplant (hematuria and low grade proteinuria).

  - **Eurotransplant registry data :**
    - 107 IgA KTx vs. 7,935 KTx for other diseases.
    - ➲ 10-year death-censored graft survival identical except in those IgA GN patients that were HLA 58 DR3 (52.5% vs 69.1%;p=0.009)
  - **Single centre case-control study** (106 IgA GN KTx and 212 non-IgA GN KTx patients) : 10-year graft survival : similar.

General considerations with regards to kidney transplantation

- **IgA glomerulopathy**
  - Recurrence occurs more frequently :
    - In younger patients
    - In those with rapid progression of the original disease
    - In related transplants
  - Posttransplant immunosuppression does not affect the recurrence rate excepted the choice of induction therapy (basiliximab : 41% recurrence, Thymoglobulines : 9% recurrence, *(Berthoux et al. Transplantation 2008*)

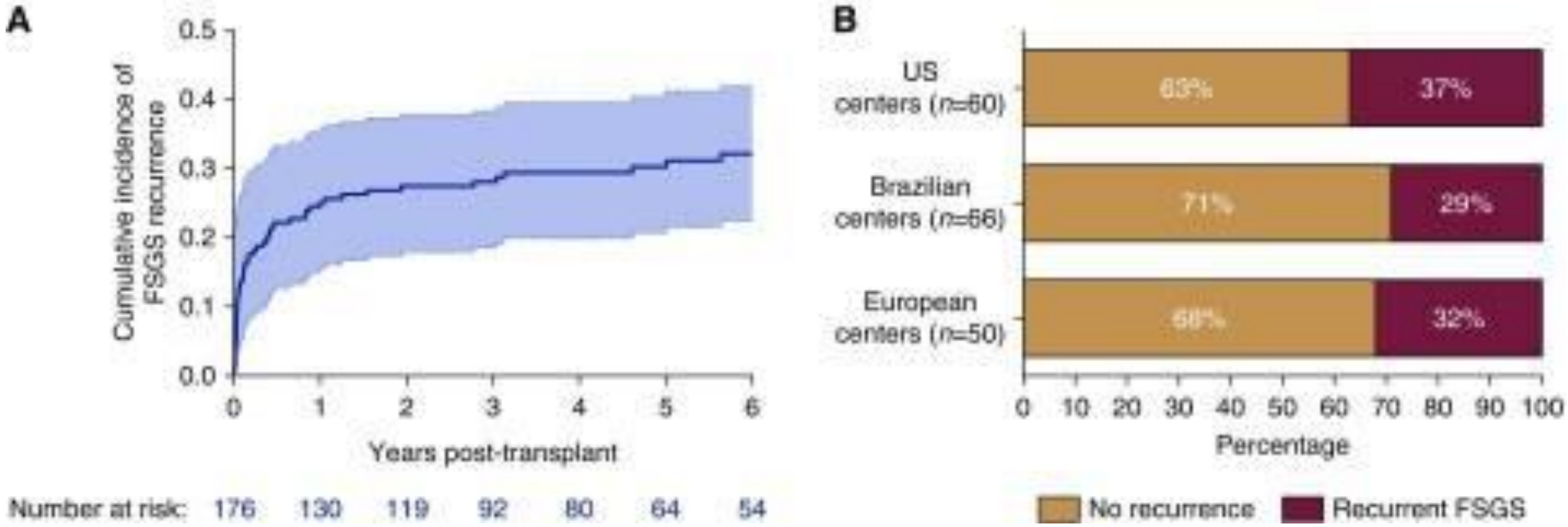
Steroids, antithymocyte globulins and recurrence of IgA nephropathy

- Single-center retrospective study on IgA glomerulopathy
  - Among 3311 kidney transplant patients 124 were transplanted for biopsy-proven IgA nephropathy
    - 27 pts (22%) had biopsy-proven recurrence of IgAN
  - Of these 124 pts, 49 (39.5%) had steroid-free immunosuppression
  - MPA use had a protective effect (HR= 0.42:0.19-0.95; p=0.03)
  - The use of sirolimus as well as the non-use of steroids were significantly associated with IgA recurrence

Von Visger JR, et al. Clin Transplant 2014;28:845-54

MCD/FSGS

Recurrence of FSGS after Transplant

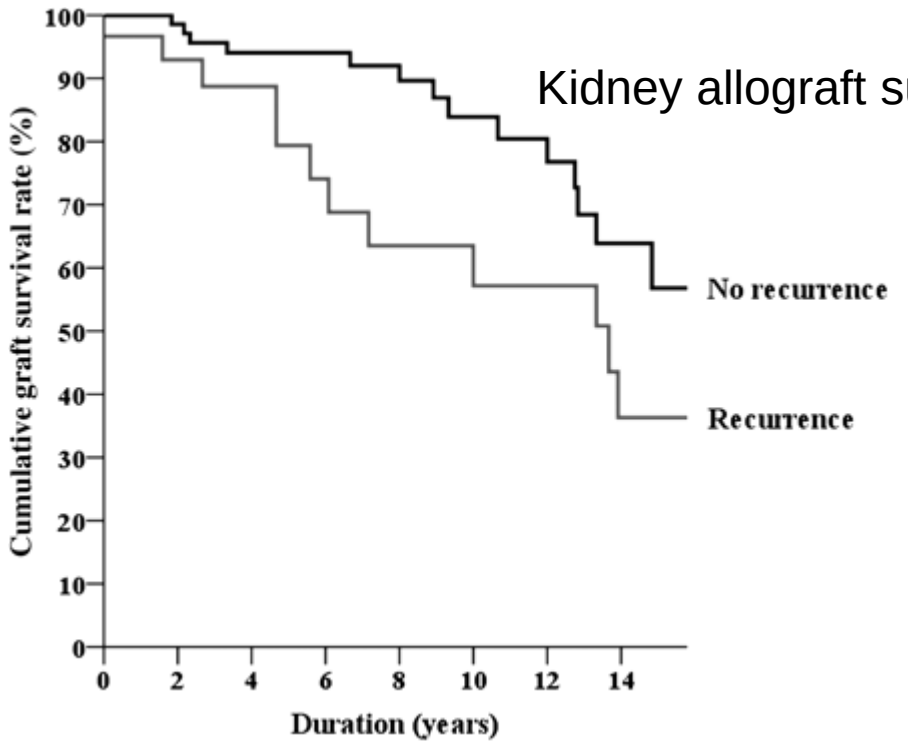


Audrey Uffing et al , JASN, 2020; 15(2):247-56

- **Idiopathic FSGS :**
  - Children and adults
  - Recurrence rate :
    - around 50% on the first transplant
    - around 100% if it had already recurred on a previous graft
  - ➲ 2 patterns post transplant :
    - Immediate recurrence with heavy proteinuria as soon as the allograft recovers function
    - Late recurrence several months /years post KTx;
  - ➲ Recurrence negatively affects allograft survival
  - ➲ Is recurrence mediated by a circulating factor ?
  - ➲ What about familial FSGS (NPHS2 mutation)? Almost no recurrence

Focal and segmental glomerular sclerosis (FSGS)

Multicentric study (South Korea); 47 FSGS adult pts and 60 FSGS paediatric pts

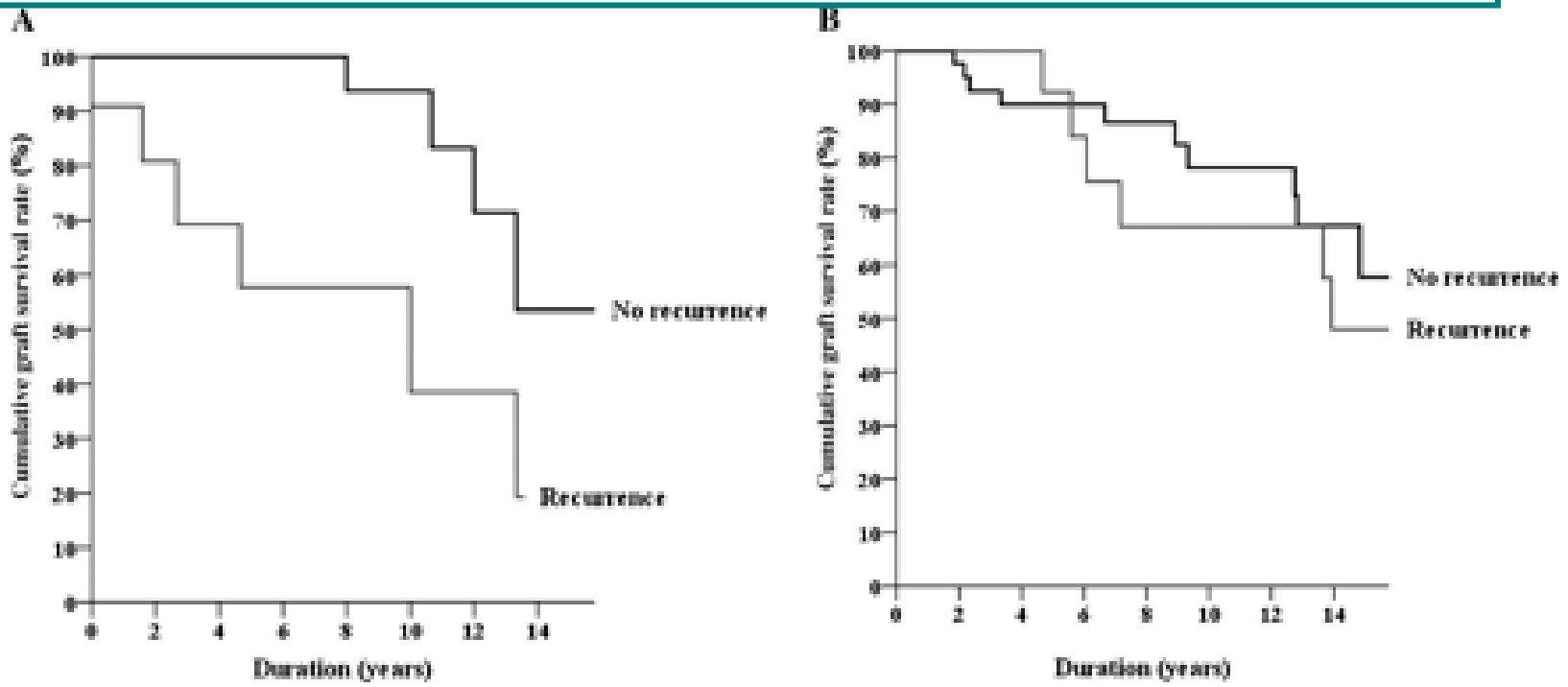


Kaplan–Meier curves of **graft survival in recipients with and without recurrence of focal segmental glomerulosclerosis.** The patients in the recurrence group have a poorer graft outcome than in the non-recurrence group (P = 0.037 by the log-rank test).

Hwang JH et al. NDT 2012;27:2559-65

Focal and segmental glomerular sclerosis (FSGS)

FSGS in adults | FSGS in paediatrics



The impact of recurrent focal segmental glomerulosclerosis on the **overall graft outcome** in A-FSGS group (**A**) and C-FSGS group (**B**). **While recurrence affected the graft outcome in the adulthood-onset group (P = 0.005), recurrence was not associated with the graft outcome in the childhood-onset group (**P = 0.558 by the log-rank test).

Hwang JH et al. NDT 2012;27:2559-65

Recurrence of nephrotic syndrome following kidney transplantation is associated with initial native kidney biopsy findings

- Multicenter study on recurrence of nephrotic syndrome after KTx for steroid-resistant NS (SRNS)-related ESKD (2006-2015)
  - ➢ 158 pediatric patients :
    - → 64 (41%) had recurrence :
      78% of patients with late SRNS
      39% of patients with primary SRNS
    - → According to native kidney histology :
      MCD → 76% recurrence
      FSGS → 40% recurrence
    - ↳ In multivariate analysis MCD histology (vs. FSGS) predicted disease recurrence (OR; 95% CI : 5.6;1.3-23.7)

Pelletier JH, et al. Pediatric Nephrology 2018;33:1773-1780

How to prevent FSGS recurrence ?

- **Idiopathic FSGS: management**
  - Prevention, i.e. to treat the recipient before transplantation
  1. ***Living donor :***
     - Start treatment around 10 days before KTx :
       - IV ciclosporine (« trough levels » at around 300 ng/mL)
       - Steroids (1 mg/kg/d)
       - Rituximab 375 mg/m² (D -10)

       Or Cyclophosphamide IV 1g (D -10)
       - 1 plasmapheresis (or immunoadsorption) session pre-KTx
     - Post transplant immunosuppression : IV ciclosporine (10 days then orally), steroids, mycophenolate mofetil (MMF)
       - Plasmapheresis : only when albuminuria > 500 mg/d

How to prevent FSGS recurrence ?

2. ***Deceased donor :***

- Start treatment as early as possible, i.e. a **few hours pre-transplant**:
  - IV ciclosporine
  - Steroids (1 mg/kg/d)
  - 1 plasmapheresis session
  - Then Rituximab IV 375 mg/m²
- Post transplant immunosuppression : IV ciclosporine (10 days then orally), steroids, MMF or mycophenolic acid
- Post transplant plasmapheresis : only when albuminuria > 500 mg/d

The effect of peri-transplant plasmapheresis in the prevention of recurrent FSGS

- Single center study including 57 children with FSGS
  - Before 2006 : no pretransplant TPE
  - After 2006 : pretransplant TPE (3 sessions if live-KTx ; 1 session if cadaveric-KTx) with FFP + 5 sessions every other day posttransplant

↳ Incidence (27% vs 26%) and time to recurrence of FSGS on kidney allograft was similar.

Verghese PS, et al. Pediatric Transplantation. 2018;22:e13154.

Rituximab and Therapeutic Plasma Exchange in Recurrent Focal Segmental Glomerulosclerosis Postkidney Transplantation

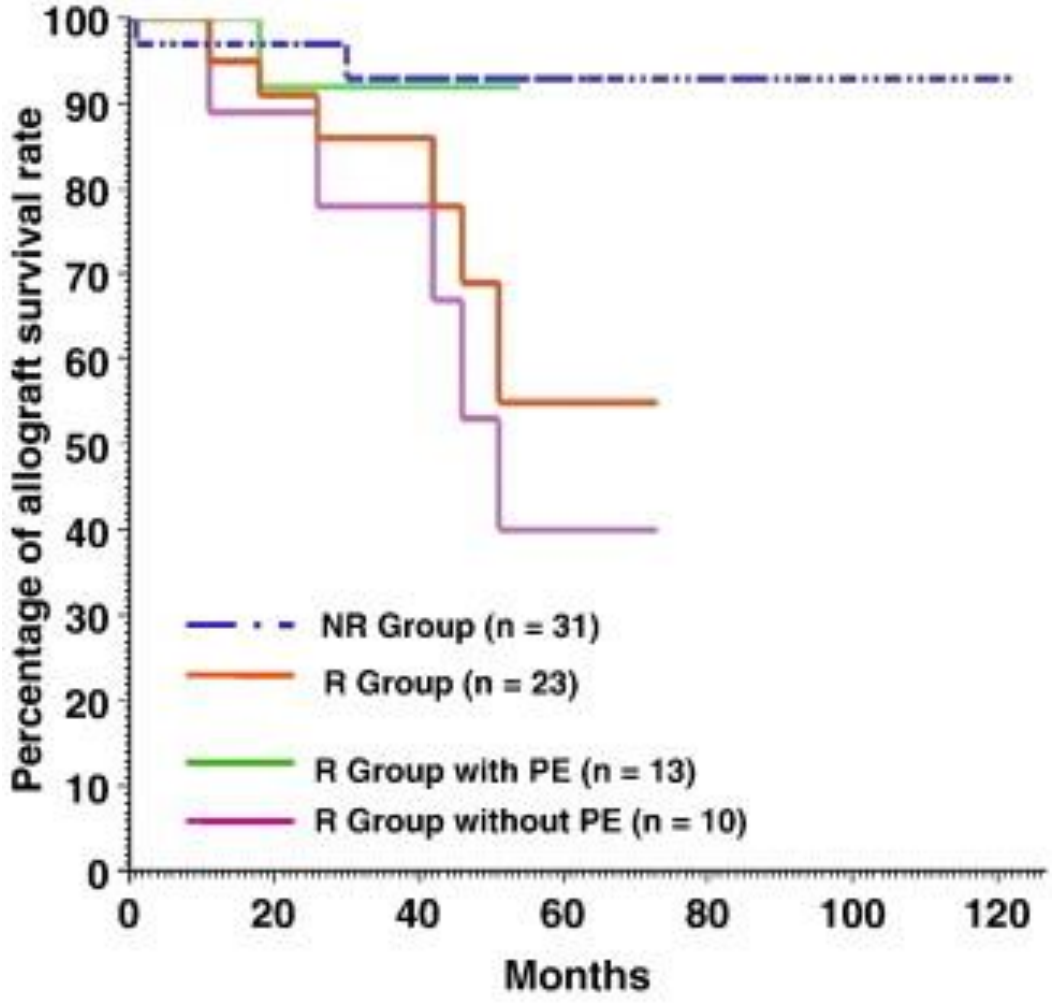
- 66 FSGS patients who underwent KTx
  - ➢ 37 patients at risk of FSGS recurrence received preventive therapy with TPE and/or rituximab

    → 62% of patients with preventive therapy developed recurrence vs. 51% of those without preventive therapy (p=0.21).

Alasfar S, et al. Transplantation 2018;102 (3):e115-e120

Focal and segmental glomerular sclerosis (FSGS)

Impact of plasma exchange on allograft survival rate: the Necker experience.



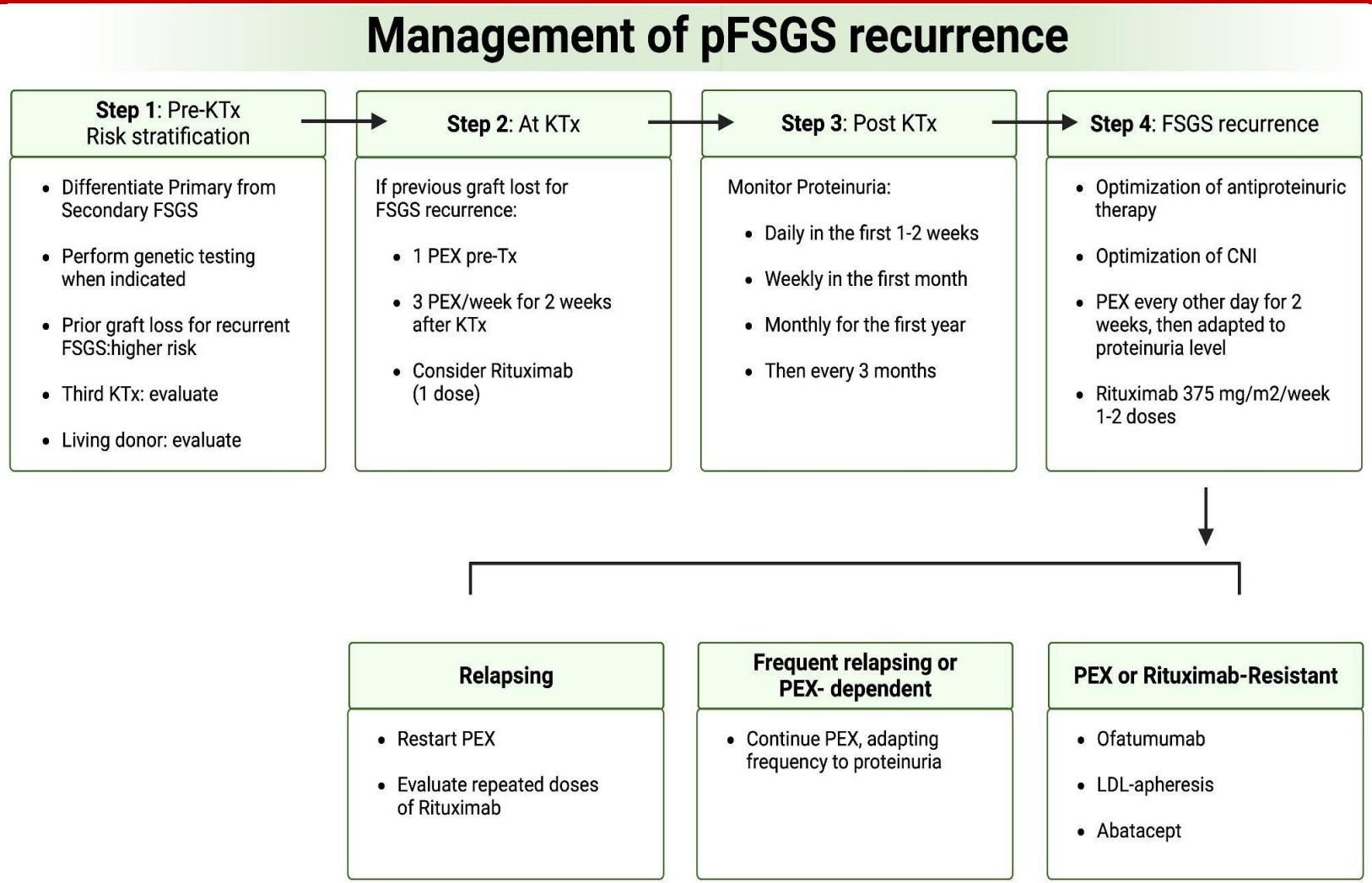
They retrospectively studied the allograft survival rate of patient with (R group) or without (NR group) FSGS recurrence from January 1994 to December 2004.
In case of recurrence, they separated patients according to PE status in their therapeutic approach.

Canaud G, et al. Transplant Rev, 2010

FSGS recurrence : treatment

- **Treatment of the recurrence of FSGS :**
  - Rituximab infusion (375 mg/m²) or cyclophosphamide IV (1g) up to 4 times
  - Daily plasmapheresis (or daily immunoadsorption)
    - How many sessions ? It is guided by the albuminuria rate
    - ≈ 50% of remission
  - In case of no remission despite of the previous therapies try oral GALACTOSE

Algorithm for pFSGS recurrence in KTx.



Clin Kidney J, Volume 17, Issue 12, December 2024, sfae320, https://doi.org/10.1093/ckj/sfae320

Membranous nephropathy

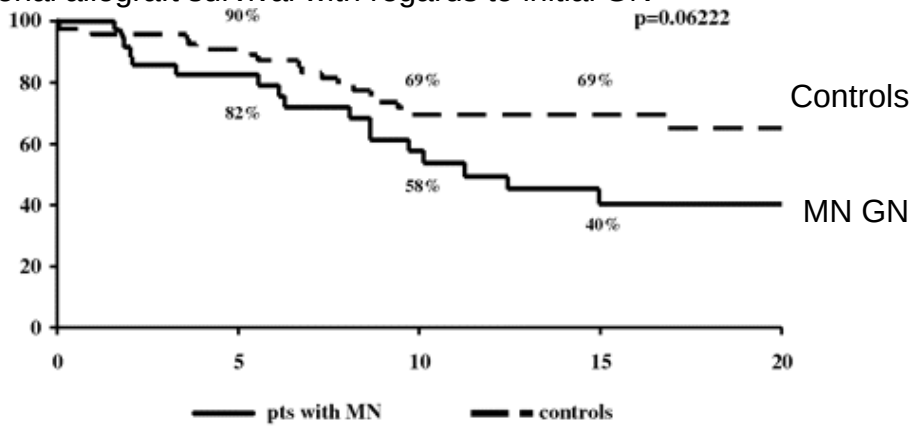
Membranous Glomerulopathy (MN)

- The allograft may demonstrate :
  - Recurrence of MN is usually seen in 30 to 40% of patients
  - *De novo* MN (occurring more frequently than recurrent MN)
  - *Recurrence* :
    - Between 6 to 36 months posttransplantation
    - May be silent (detected by protocol biopsies)
    - Is associated with a progressive increase rate of proteinuria
    - No predictive factors, except auto-antibodies to M type PLA2 receptors when present at pretransplant

Membranous Glomerulopathy (MN)

Monocentric study; 35 first KT pts (1975-2008) matched with a controled group of 70 1st KT pts; posttransplant follow-up: 117 +/- 86 months

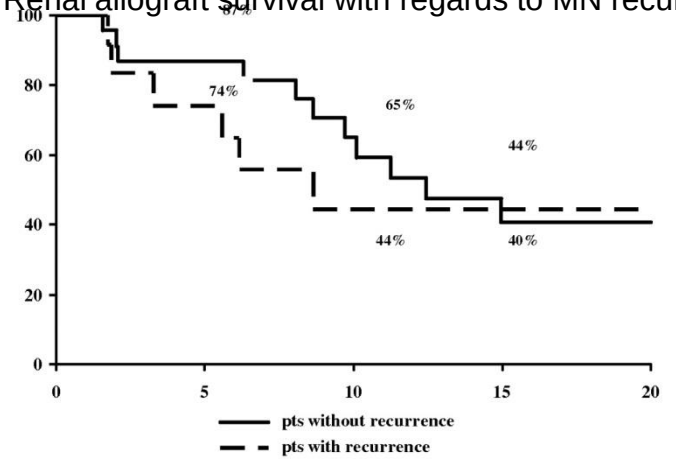
Renal allograft survival with regards to initial GN



Pts at risk	5 years	10 years	15 years	20 years
pts with MN	25	14	8	2
controls	52	34	19	6

Kaplan–Meier estimates of renal survival probability censored for death in renal transplanted patients with membranous nephropathy (solid line) and in controls (dashed line).

Renal allograft survival with regards to MN recurrence



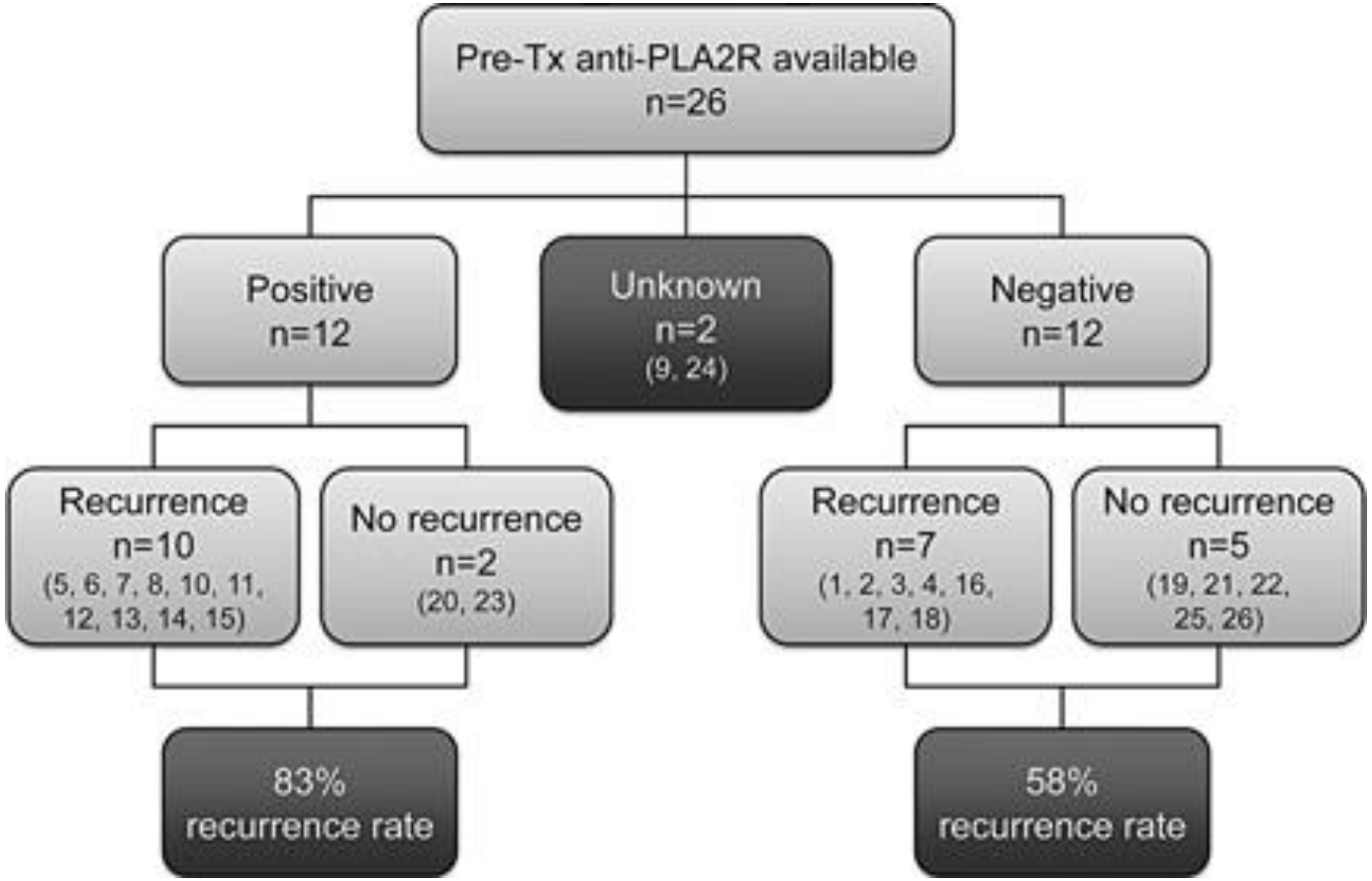
Pts at risk	5 years	10 years	15 years	20 years
pts without recurrence	16	11	6	2
pts with recurrence	8	3	2	0

Kaplan–Meier estimates of renal survival probability censored for death in renal transplanted patients without recurrence (solid line) and in those with recurrence of membranous nephropathy (dashed line).

Moroni G, et al. NDT 2010;25(10):3408-15

Anti-phospholipase A_2 receptor antibodies in recurrent membranous nephropathy

Distribution of pre-Tx anti-PLA2R in those with and without MN recurrence .

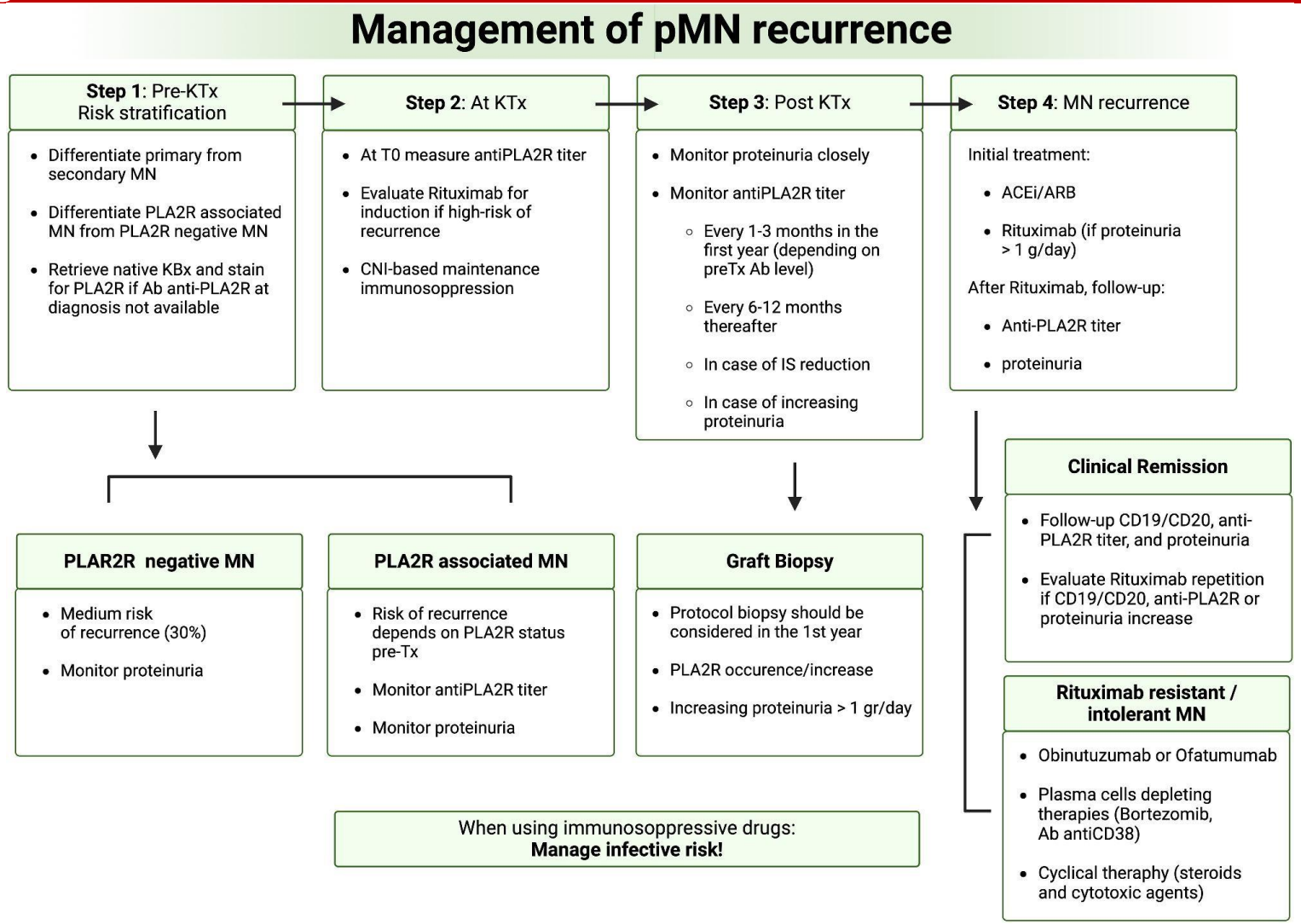


Kattah A, et al. AJT. 2015;15:1349-59

Membranous Glomerulopathy (MN)

- Treatment :
  - ARB and / or ACEIs
  - Rituximab therapy 1gr x 2
    - 35% complete remission
    - 40% partial remission
    - Resorption of electron-dense immune deposits in many responders.

Algorithm for primary MN recurrence in KTx. Complete clinical remission is defined as proteinuria <0.3 g/24 h with ...



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Membranoproliferative GN (MPGN)

- **MPGN is a “pattern of injury” rather than a disease**
  - **Idiopathic MPGN is rare**
- MPGN is a common feature of HCV-related glomerulopathy, with or without cryogobulinemia
- MGPN may be associated :
  - With complement pathway genetically-based dysfunction
  - Lupus
  - Monoclonal gammopathy
  - ➲ MGN recurrence varies according to the underlying disease

Membranoproliferative GN (MPGN)

- Dense deposit disease :

  - Electron dense transformation of the glomerular basement membrane and deposition of C3

  - Very often :

    - Low C3 levels

    - 70 to 80% have a circulating autoantibody to C3Bb known as C3 nephritic factor (C3Nef)

    - Some of them may have factor H or I deficiency

  - Very high risk of recurrence (≈ 100%)

New classification of Membranoproliferative GN (MPGN)

- ICGN: immune-complex-mediated glomerulonephritis:
  - Presence of ICs and complement components
- CGN: complement-mediated glomerulonephritis:
  - Absence of ICs; presence of C’ components

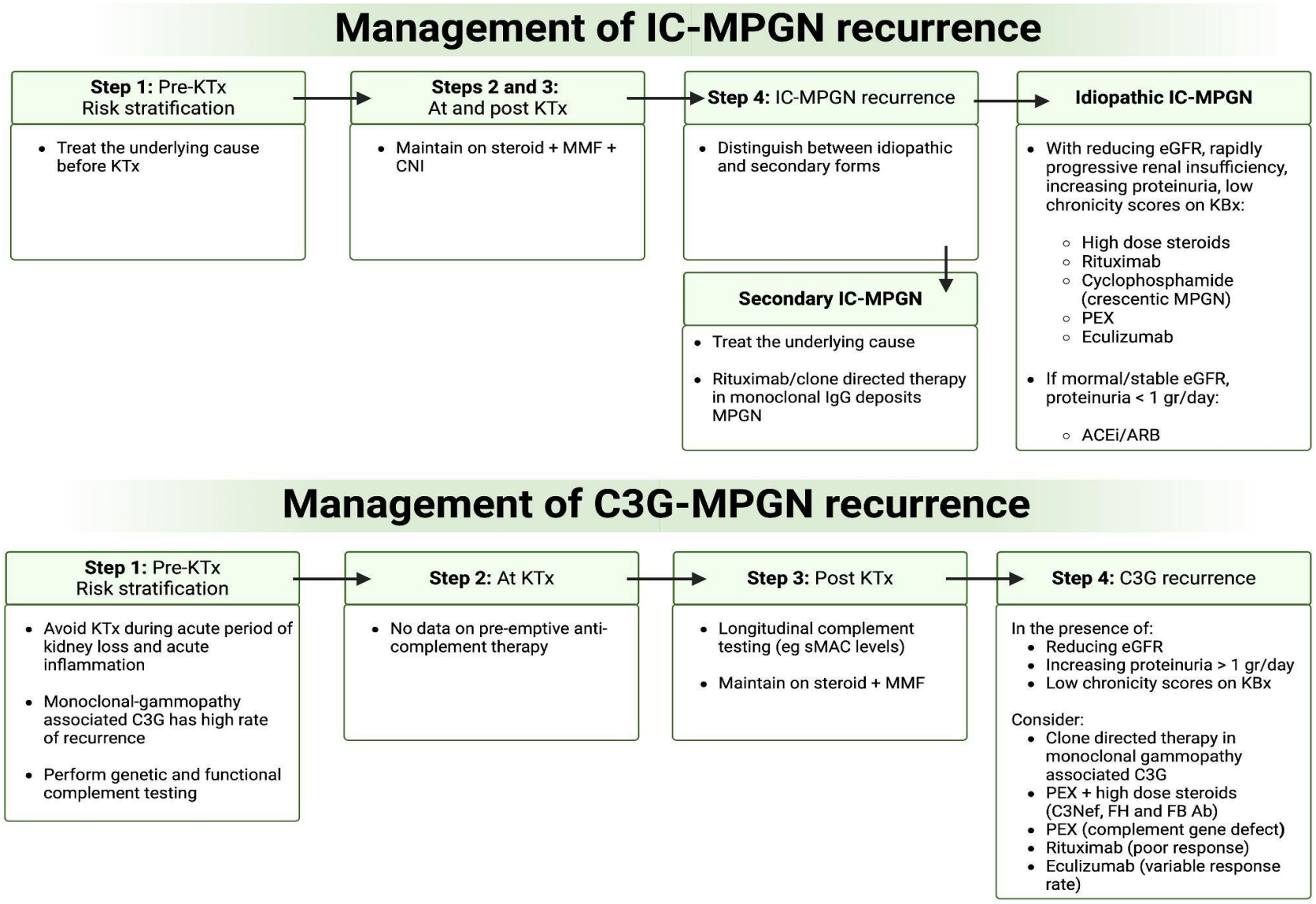
- Alasfar et al.:
  - Single-center retrospective study on 34 MPGN-related ESRD with 40 kidney transplants

Alasfar S. et al. BMC Nephrol. 2016;17:7

Membranoproliferative GN (MPGN)

- Treatment :
  - In case of factor H or I deficiency: prophylactic or therapeutic infusions of fresh frozen plasma (FFP)
  - In case of overt recurrence :
    - Plasmapheresis with FFP
    - Rituximab therapy ? Not sure..
    - Eculizumab therapy ? Certainly… cost issue.

Algorithm for IC-MPGN and CM-MPGN recurrence in KTx.



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Hemolytic and Uremic Syndrome (HUS)

- Two settings :
  - Typical HUS, i.e. postshiga toxin
    - No recurrence on the allograft
  - Atypical HUS (aHUS)
    - Recurrence on the allograft depends on the aetiology

Hemolytic and Uremic Syndrome (HUS)

- Outcome after kidney transplantation :
  - Deficit in MCP :
    - Almost no recurrence
  - Other situations : recurrence in 50% to 100% of cases
    - Avoid living kidney transplantation
    - Recurrence is prevented by eculizumab therapy in the long-term +++
    - In some cases combined liver + kidney transplantation can be performed.

Other nephropathies

Recurrence of glomerulopathies after kidney transplantation

- Lupus nephropathy : no recurrence
- Antiphospholipid syndrome:
    - Recurrence +++/ prevention by using mTOR-inhibitor-based immunosuppression
- ANCA-associated vsculitis
    - Low recurrence rate provided pretransplant ANCA titers are low
- Alport syndrome
    - No recurrence
- Goodpasture syndrome : no recurrence if pretransplant anti-GBM autoantibodies are negative
- Amyloidosis : high rate of recurrence

In conclusion (1)

To reduce the impact of recurrent GN, in clinical practice:

Identification of the original cause of kidney failure before KTx

Adequate information to patients about the risk of recurrence

Selection of appropriate pre-emptive therapy at KTx able to reduce disease recurrence in high-risk patients

Monitoring patient adherence to immunosuppressive

Conclusion (2)

Establishment of predictive markers of recurrence after KTx

Appropriate monitoring strategies to detect recurrent and de novo Glomerular Diseases at an early stage

Identification of appropriate therapies for recurrent and de novo GDs

Balance of benefits and risks of additional immunosuppressive therapies.

Thank You