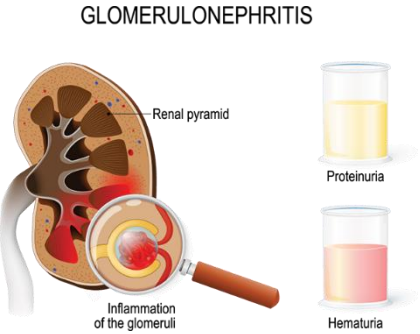


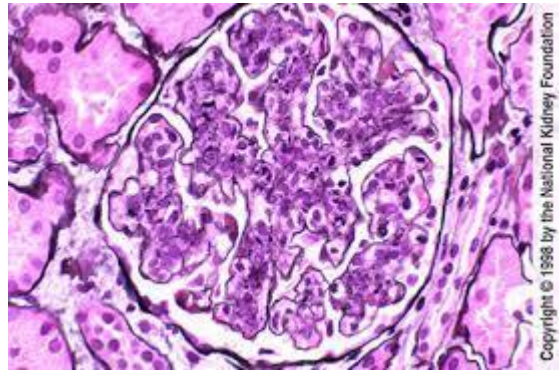
Recurrent Glomerulonephritis after Renal Transplantation

Professor Mojgan Mortazavi

Isfahan kidney diseases research center

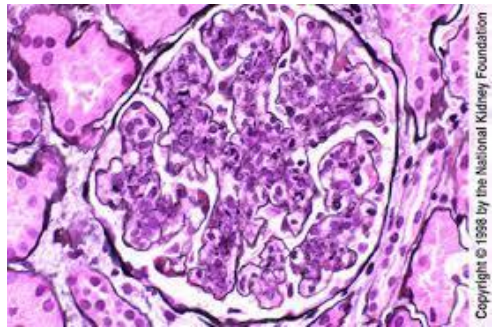
Isfahan university of medical sciences

Introduction



- Glomerulonephritis (GN) continues to be one of the main causes of end-stage kidney disease (ESKD) with an incidence rating from 10.5% to 38.2%.
- Recurrent GN, previously considered to be a minor contributor to graft loss, is the third most common cause of graft failure 10 years after renal transplantation.

introduction

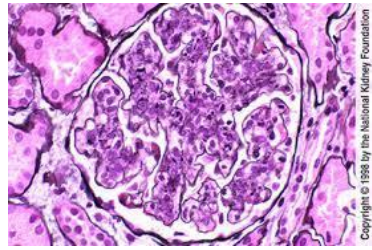


- Virtually every GN may recur after transplantation, however the impact and consequences of recurrence can be very different.

- recipient patients with anti-glomerular basement membrane (GBM) disease present recurrence rarely, but often exhibit rapid graft loss.
- recipient patients with C3 glomerulonephritis present recurrence in more than 50% of cases, although the disease is generally slowly progressive with a mean graft survival of 6.4 years from

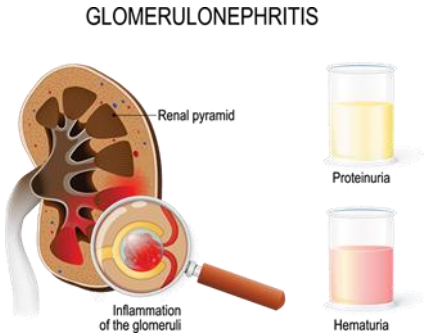
transplantation

Different type of recurrent GN



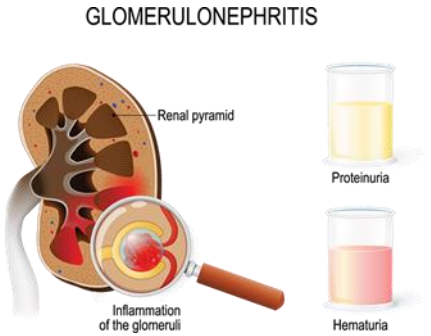
- 1- True recurrence (native and recurrent disease are the same at biopsy)
- 2-Transplant GN with unknown primary disease,
- 3-de novo GN (occurrence of new disease in the graft).

Recurrence of primary GN:



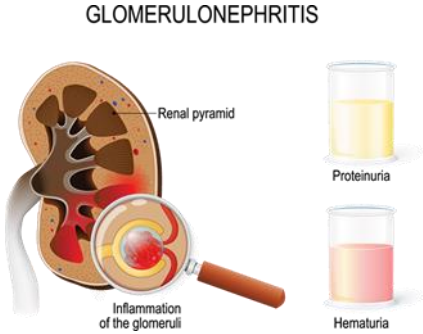
- Recurrent focal and segmental glomerulosclerosis (FSGS)
- Membrano-proliferative GN (MPGN)
- IgA nephropathy (IgAN),
- Henoch-Schonlein purpura
- Membranous Nephropathy (MN)

Recurrence of secondary GN:



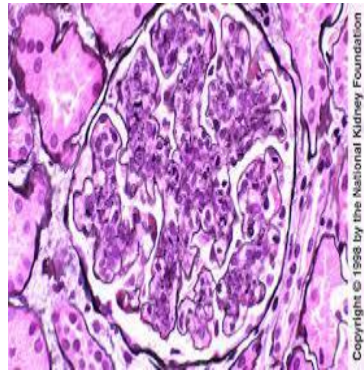
- Systemic lupus erythematosus (SLE)
- Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS-TTP)
- Small vessel vasculitis
- Anti-glomerular basement membrane (anti-GBM) disease

De novo GN



- De novo GN more frequently encountered are anti-GBM disease in patients with Alport syndrome
- MN
- FSGS

Factors may influence the risk for recurrence



- 1- First of all, type of glomerulonephritis(For example, lupus nephritis recurs in fewer than 10% of cases and graft loss

is uncommon, in contrast C3 glomerulopathy recurs in more than 50% of patients and graft loss is frequent)

- 2-Male gender
- 3-Early age
- 4- Duration on dialysis less than 5 years before transplant;

Clin. Transplant. ***2014****, 28, 368–376*

Clinical Features and Differential Diagnosis

- Clinical features of recurrence are often the same of native disease:

proteinuria, hematuria , deterioration in renal function

- Nevertheless, even chronic rejection may manifest with progressive deterioration of kidney function, proteinuria, and hypertension, potentially being clinically indistinguishable from recurrence

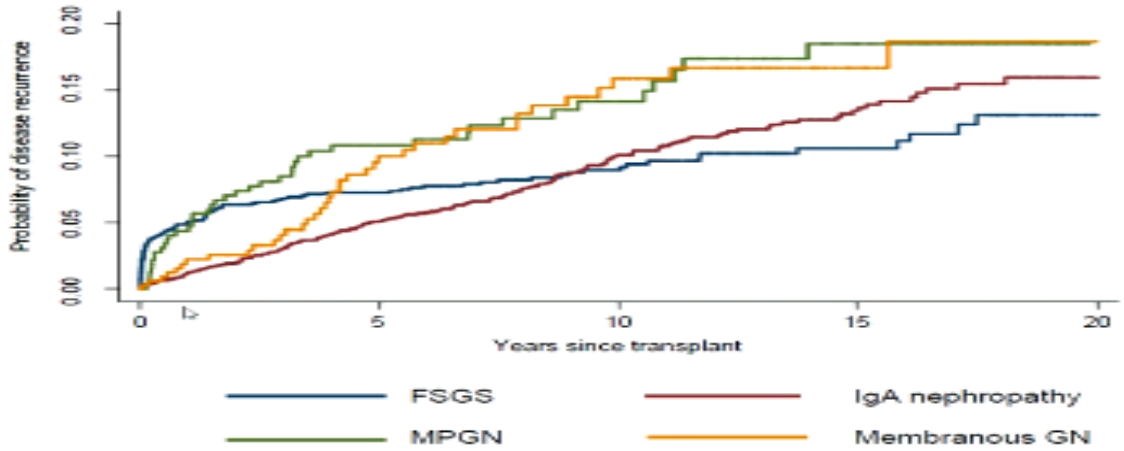
Renal biopsy

- Renal biopsy is essential, it can provide the diagnosis, excluding alternative diagnosis that may require different treatment, and provides some important information on the possibility of a future re-transplantation

Primary GN IgA Nephropathy (IgAN)

• IgAN recurs after renal transplantation in a percentage varying from 9% to 61%, depending on differences in follow-up duration and biopsy policies, and that recurrence leads to graft dysfunction in approximately 13% of patients and to graft loss in nearly 5% of cases

Kinetics of recurrence



Absolute risk very sensitive to biopsy policy (protocol vs. for cause)

Allen, Kidney Int 2017

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higher risk of recurrence in IgA nephropathy

- Younger age at renal transplantation,
- recipients of zero-HLA mismatched live-related donor kidney,
- steroid-avoidance or early steroid-withdrawal immunosuppressive regimens,
- male gender,
- rapidly progressive course of the original disease before transplantation,
- degree of proteinuria,
- HLA-B35/DR4, and
- higher levels of circulating Gd-IgA1 and IgA-IgG immune complexes and soluble CD89
- living related donor, and even with increased serum levels of IgA 6 months post-transplants
- number of crescents in the native biopsy and both the renal native survival

Clinical presentation of recurrence

- Is similar to primary IgAN with microscopic hematuria, proteinuria, slow decline kidney function

- Macroscopic and often microscopic hematuria, the hallmarks of

IgAN, are rarely present in recurrence at the time of the diagnosis, more often isolated proteinuria is

the only sign.

Histological features that shows severity of disease

The degree of severity of the disease depends on five histological features:

- Degree of mesangial hypercellularity,
- Segmental glomerulosclerosis,
- Endocapillary hypercellularity,
- Tubular atrophy and interstitial fibrosis,
- and cellular and/or fibrocellular crescents (MEST-C)

Oxford classification criteria

Treatment of recurrent IgAN

- To date, there are no specific therapies for recurrent IgAN yet. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) Transplant Guidelines has clarified the management of patients affected by recurrent IgAN, recommending the reduction of proteinuria and blood pressure control.

- Only one study demonstrated that the graft survival is increased by the use of angiotensin converting enzyme inhibitors

Treatment of recurrent IgAN(Roll of ATG)

- In the last few years there has been much discussion about how much induction therapy can affect the recurrence of this nephropathy.
- Bertoux et al. showed that the incidence of recurrence of IgAN at only 9% in patients with anti-thymocyte globulin (ATG) induction therapy, in comparison with 41% in patients without induction therapy

induction therapy and disease recurrence in renal transplant recipients with primary IgA nephropathy.

Transplantation **2008**, 85, 1505–1507. [CrossRef]

Management of recurrence

- Scarce data about specific management of IgAN recurrence (case reports, small series)
- Native-IgAN therapies ***could*** apply
  - *Non specific protective therapies (strict BP control, RAAS blockers, SGLT2 inhibitors)*
  - *Systemic steroids (+- pulse) are still debated (STOP-IgAN, TESTING)*
  - *Targeted-release budesonide (NEFIGAN, NEFIGARD)*

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13:00 - 16:45

Kidney transplantation

LEADING EUROPEAN NEPHROLOGY

Deutsche Gesellschaft für Nephrologie

Focal Segmental Glomerulosclerosis

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FSGS

- Typically only immune-mediated primary FSGS can recur on transplanted kidney
- It is critical to assess the native kidney disease, to distinguish primary FSGS from secondary forms or genetic FSGS

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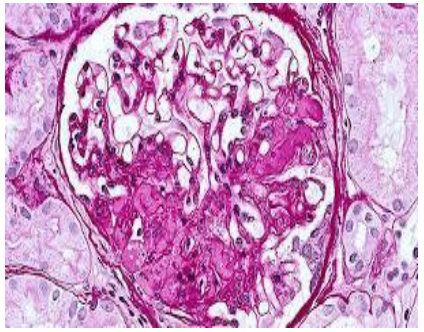
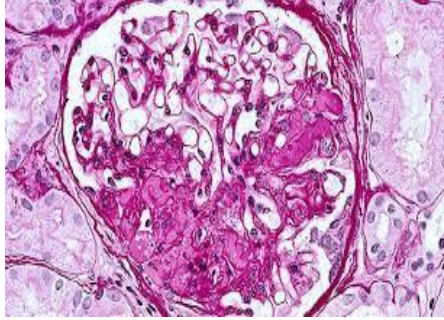
Focal and Segmental Glomerulosclerosis (FSGS)



Typically, only primary FSGS recurs after renal transplantation

Clinical Presentation of FSGS Recurrence



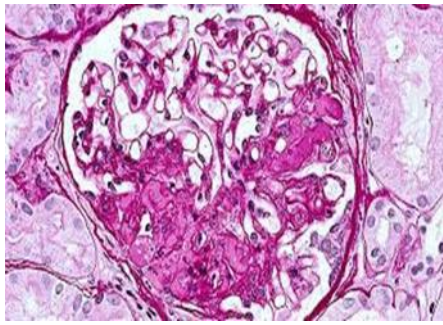
- There are two clinical manifestations of recurrent FSGS:

1- Early recurrence characterized by a massive proteinuria within 48–72 h after transplantation

2- Late recurrence, characterized by a progressive development of the nephrotic syndrome within months or years after surgery

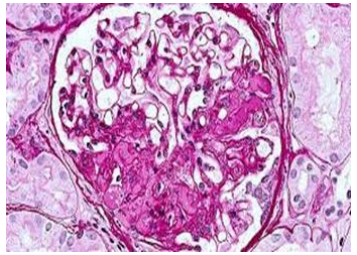
- The frequent occurrence of proteinuria within a few hours or days after transplantation suggests that podocyte injury is probably caused by a circulating permeability factor

Clinical Presentation of FSGS Recurrence



- The average time of onset of recurrence is 2 weeks in children and 7.5 months in adult patients
- in patients who have had recurrent FSGS in the first transplantation, the risk of recurrence in the second graft is exponentially greater

Risk Factors and Biomarkers of FSGS Recurrence

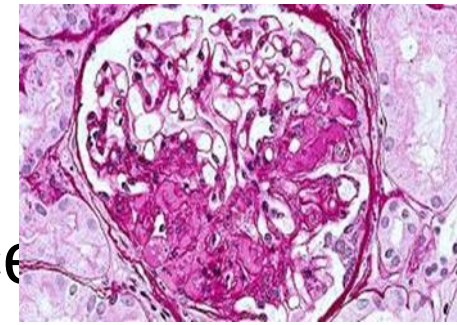


- younger age of the recipients
- Rapid progression to ESRD
- Mesangial proliferation in the native Kidney biopsy (reflecting a more severe form of disease) and steroid resistance
- Older donor
- Pre-transplant bilateral nephrectomy (native kidney seems to be absorber of permeability factors)
- and recurrence of FSGS in a previous allograft.
- Finally, ethnicity also influences the incidence of recurrence that is higher in white than in non-Caucasian patients

loss due to recurrent focal segmental glomerulosclerosis in renal transplant recipients in the United States.

Am. J. Kidney Dis. ***2001****, 37, 366–373*.

Risk Factors and Biomarkers of FSGS Recurrence



- The duration of dialysis and the type of post-transplant immunosuppression seem to be risk factors of recurrence
- The histologic type of FSGS seems not to provide correlation with the risk of recurrence
- Raafat et al. point out that use of anti-thymocyte globulin (ATG) is associated with a higher risk of recurrence

Raafat, R.; Travis, L.B.; Kalia, A.; Diven, S. Role of transplant induction therapy on recurrence rate of focal segmental glomerulosclerosis. Pediatr. Nephrol. ***2000****, 14, 189–194.*

Risk factors for recurrence

- Young age of native kidney disease occurence
- Rapid progression to ESRD (<3 years)
- Albuminemia <25g/l at onset
- Genetic background
- Loss of previous graft from recurrence
- Steroid sensitive more at risk as compared to steroid resistant

- Vinai, Pediatr Transplant, 2010
- Ponticelli, NDT 2010
- Koziell, JASN, 2014

Risk Factors and Biomarkers of FSGS Recurrence

- Several molecules may be biomarkers to define the risk of recurrence. Increased levels of Soluble Urokinase-type Plasminogen Activator Receptor (suPAR) before transplantation seem to be related with a higher risk of recurrence

- Delville et al. identify seven antibodies that may be related with recurrent FSGS: CD40 (correlated with a greater risk of recurrence), PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2

A circulating antibody panel for pretransplant prediction of FSGS recurrence after kidney transplantation. Sci. Transl. Med. ***2014****, 6, 256ra136*

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13:00 - 16:45

Kidney transplantation

Biomarkers = lack of consistency

- « permeability factor » remains unknown
- Inconsistent findings about suPAR (only association but poor specificity, and no effect on animal models)
- CD40 antibodies (but B7-1 blockade not efficient)
- Other biomarkers…

Treatment of Recurrent FSGS

- ACE-inhibitors and angiotensin-receptor blockers
- plasmapheresis or immunoadsorption with protein A(Best results seem to be achieved when plasmapheresis is started immediately when recurrence becomes clinically evident)
- In cases of plasmapheresis and Rituximab resistance, Abatacept was effective in reducing proteinuria

Management of recurrence

Plasma exchange

Ponticelli, NDT, 2010

Immunoadsorption : high rate of IA dependency

Jouve, Blood Purif 2020
Allard, NDT 2018

Corticosteroids

Intravenous ciclosporin

Rituximab

Cravedi, AJT 2013
Lanaret, AJT 2021

Abatacept: inconsistent

Ofatumumab

Colucci, Pediatr Nephrol 2020
Solomon, Pediatr Nephrol 2019

Membrano-Proliferative Glomerulonephritis (MPGN)

- DDD generally has the higher rate of recurrence after transplantation.
- Recurrent MPGN is seen in 27–65% cases of post-renal transplant resulting in graft loss in up to 50% of cases
- The recurrence rate of the second transplant seems to be even higher

- *Masani, N.; Jhaveri, K.D.; Fishbane, S. Update on membranoproliferative GN. Clin. J. Am. Soc. Nephrol.* ***2014****,*
- *9, 600–608.*

Risk factors for recurrence of C3 glomerulopathy after renal transplant

- the presence of monoclonal paraprotein
- lower serum complement level
- human leukocyte antigen B8, DR3, B49, and DR4
- higher proteinuria
- presence of crescents in the native kidney biopsy

Risk factors for recurrence of C3 glomerulopathy after renal transplant

instead C3NeFs levels seem to be **not** related to the risk of recurrence and the degree of disease activity

Clinical presentation of recurrent C3 glomerulopathy

- proteinuria, hematuria, and higher serum creatinine

DDD

- DDD usually recurs later than C3GN and presents clinically only with allograft dysfunction.
- Patients with DDD commonly have **low** serum levels of C3 and C3NeF in circulation

Strategies to prevent recurrence MPGN after transplantation

- Eculizumab?
- The use of Cyclophosphamide and Mycophenolate mofetil may be advantageous in native disease, but their efficacy in recurrence is restricted
- In patients with C3 glomerulopathy due to genetic mutations in CFH, chronic infusions of fresh frozen plasma to replace absent complement factors may be useful
- The use of plasmapheresis and/or Rituximab in the treatment of recurrence due to pathogenic antibodies is a controversial topic in literature

Hemolytic Uremic Syndrome (HUS)

- HUS is usually classified in typical and atypical forms.

- aHUS is characterized by a worse outcome than typical HUS.
- Rate of recurrent aHUS after renal transplantation is really significant, about 75–80%.
- The rate of recurrent aHUS after renal transplantation is closely related to the specific mutated factor, membrane-bound or circulating

patients with mutation of circulating factors, for example CFH and CFI, have a higher risk of developing recurrence leading to graft loss in 80–90% of cases.

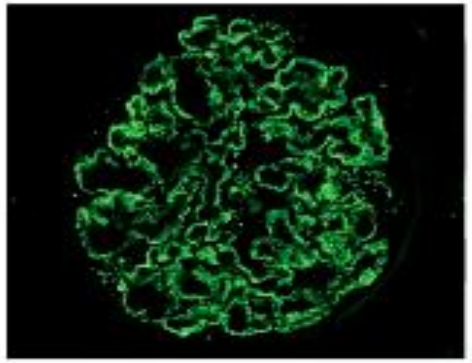
- These factors are mainly produced by the liver; thus these abnormalities persist after kidney transplantation predisposing to recurrence

Environmental factors may influence the recurrence of aHUS after renal transplantation:

- Infections including:
- Cytomegalovirus,
- Influenza virus,
- Parvovirus B19, BK virus;
- The use of immunosuppressive drugs such as CNI and less frequently mTORi,
- Rejection episodes

Prevention of post-transplant recurrence

- screening in the living-related donor to exclude genetic mutation
- Plasma therapy, including plasmapheresis, as a prophylactic treatment??
- prophylactic treatment with Eculizumab??
- In patients with genetic mutations of circulating factors, produced mainly from liver, combined liver-kidney transplant may reduce the rate of recurrence
- Treatment of post-transplant aHUS recurrence with Eculizumab seems to be effective both as a first line therapy and as second line therapy for recipient’s refractory to plasma therapy



Membranous nephropathy

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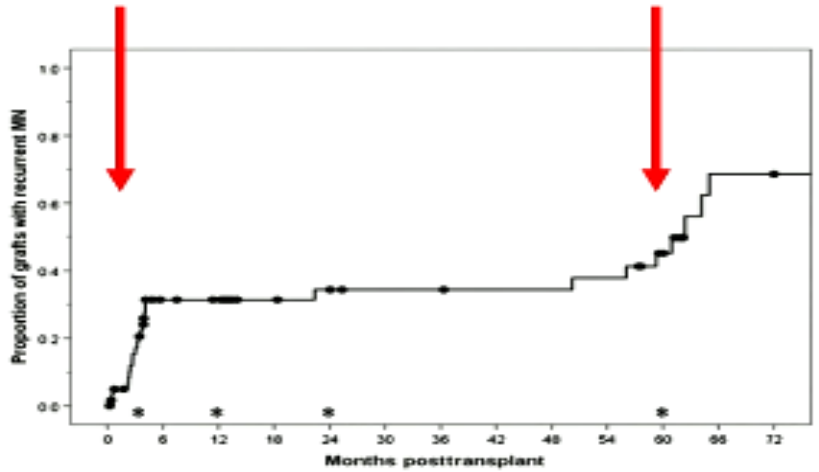
Recurrence of membranous nephropathy (MN)



Grupper, Transplantation 2015

Membranous Nephropathy (MN)

- The rate of recurrence in patients with idiopathic membranous GN following kidney transplantation is more than 40% and graft loss rates of over 10–15% at 10 years of follow-up have been reported, with a higher risk to recur in a second transplant

- Approximately 70% of patients with idiopathic membranous nephropathy have shown to have circulating anti-PLA2R antibodies, noticeably IgG4 type
- living related donors, HLA epitopes, and a more aggressive disease in native kidney are other risk factors for recurrence

Recurrent MN

- Clinically recurrent MN is characterized by proteinuria that can be in the nephrotic range
- Treatment of recurrence includes the use of corticosteroids, anti-proteinuric agents, alkylating agents, CNI, and Rituximab

Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J. Am. Soc. Nephrol. ***2017****, 28, 348–358.*

Increasing biomarkers

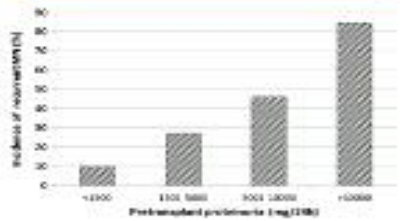
- ***Anti-PLA2R***
- *Anti-NEP*
- *Anti-THSD7A*
- ***Anti-NELL1***
- *Anti-semaphorin-3B*
- *Anti-PCDH7*
- *Anti-HTRA1*
- *Anti-EXT1 and EXT2*
- *Anti-NCAM*

Recurrence risk markers

Proteinuria at transplantation

Anti-PLA2R titer (in seropositive MN)

Living donor



Gupta, Clin Transplant 2016
Seitz-Polski NDT 2014
Kattah, AJT, 2015

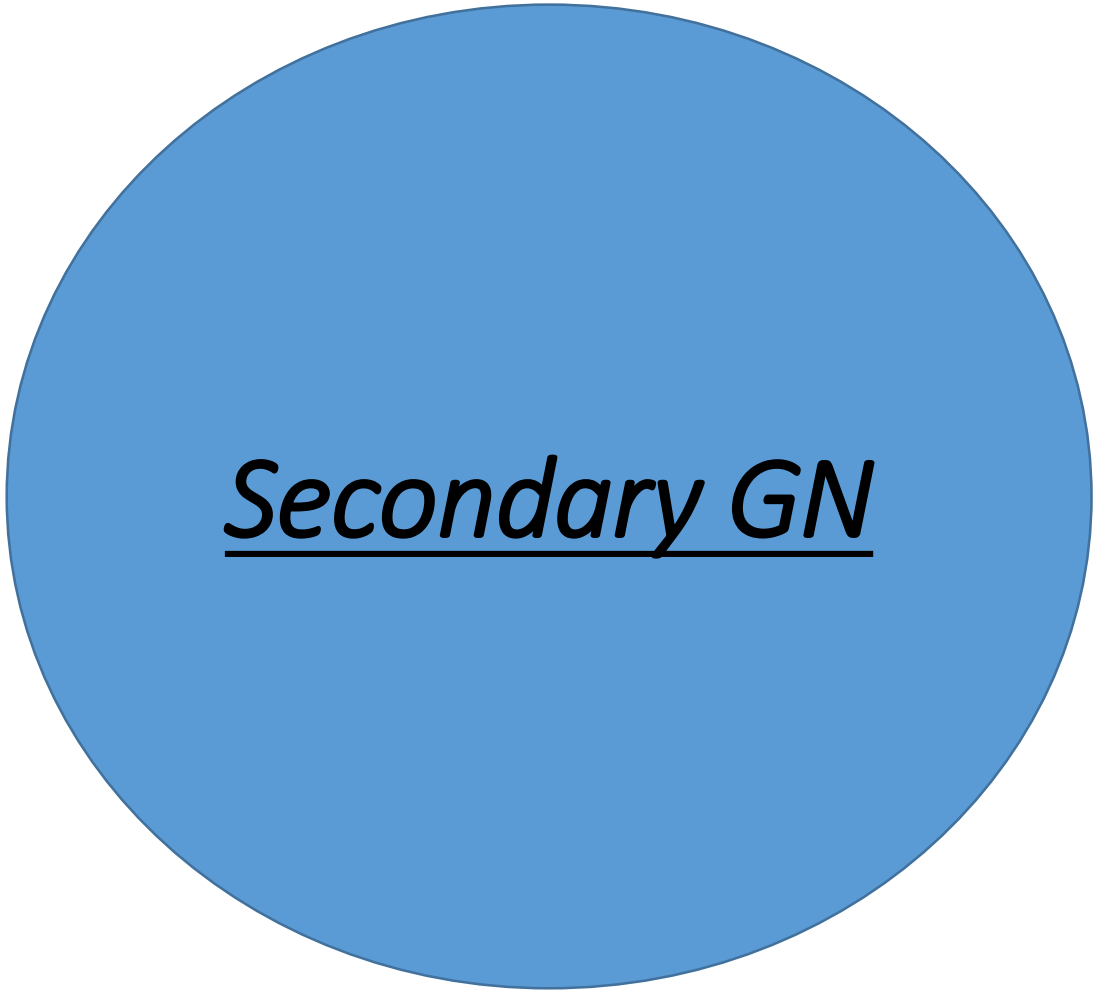
Management

- Rituximab is the best risk/benefit treatment for native disease

GEMRITUX, Dahan JASN 2017
MENTOR, Fervenza NEJM 2019
STARMEN, Fernandez Juarez, Kidney Int 2020
RI-CYCLO, Scolari, JASN 2020

- Rituximab ***could*** be efficient for prevention of PLA2R + (preconditioning) positive patients
- Rituximab ***could*** be efficient for management of MN recurrence after transplantation

Limited data based on small retrospective series with selection biases


Secondary GN

Secondary GN

- Secondary GN, such as Pauci-Immune Crescentic GN, SLE, anti-GBM may recur later after renal transplantation and rarely lead to allograft failure.

- Patients with ANCA associated vasculitis should be in clinical remission for at least 12 months, however, persistent ANCA positivity is not a contraindication to transplantation
- with Pauci-Immune Crescentic GN rate of recurrence is about 17% and incidence of allograft loss is about 7.7%

Secondary GN

- thanks to modern post-transplant immunosuppression therapy, such as mycophenolate-mofetil and tacrolimus, rate of recurrence of these diseases is low
- In both patients with native and transplanted kidney Rituximab may be a treatment of choice

sSLE

- In patients with SLE rate of recurrence is about 30% and allograft loss is uncommon
- Clinical manifestation of recurrent lupus nephritic (LN) is generally modest proteinuria, microhematuria, cutaneous rash, and arthralgias
- The risk factors associated with recurrent LN are black non-Hispanic ancestry, female gender, and young age.
- Patients with antiphospholipid (aPL) autoantibodies and those receiving the kidney from living donors also have a higher risk of recurrence
- In patients with LN recurrence generally **no** change of therapy is necessary compared to the treatment used for the maintenance of the transplant

*sSLE(*patients with clinical manifestations and severe histopathologic lesions)

- Patients with clinical manifestations and severe histopathologic lesions in the graft may require additional immunosuppressive treatment with bolus of steroid and higher doses

of mycophenolate mofetil or cyclophosphamide intravenously in case of rapid renal deterioration with crescentic lesions and severe extra renal disease such as pulmonary hemorrhage and central nervous

system involvement

- Review: Lupus nephritis: Pathologic features, epidemiology and a guide to therapeutic decisions. Lupus **2010**, 19, 557–574.

Anti-GBM

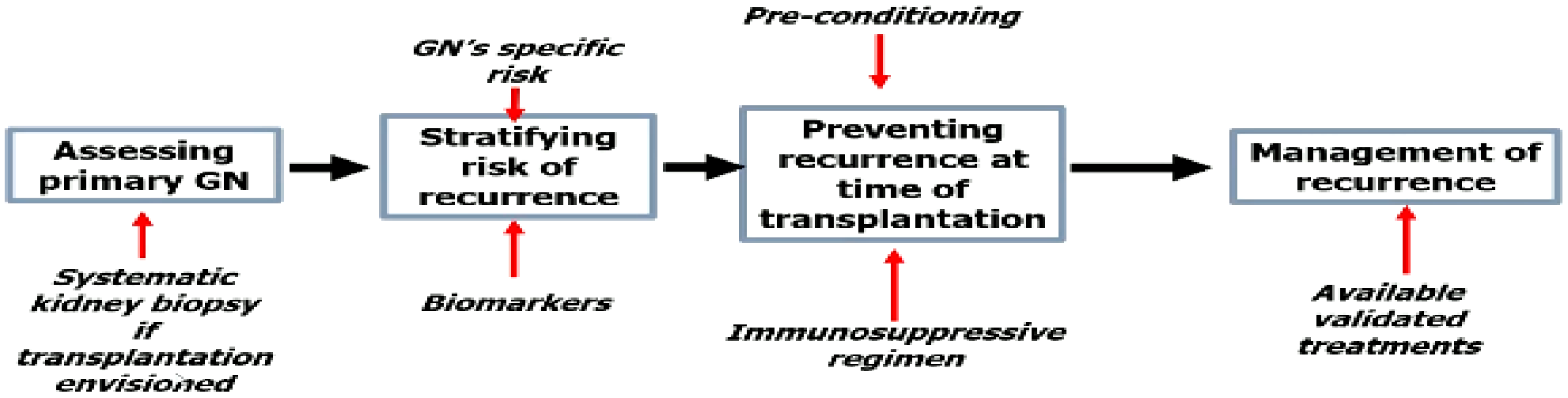
- In patients with anti-GBM rate of recurrence is about 50% when circulating antibodies are still present before transplantation, instead if these antibodies are absent for at least 12 months recurrence is rare, but still possible
- However, when anti-GBM recurs the graft loss is rapid.

- Recurrence of Goodpasture syndrome without circulating anti-glomerular basementmembrane antibodies after kidney transplant, a case report. BMCNephrol. 2019, 20, 6.

Conclusions

- a careful analysis of the pathogenesis and underlying bimolecular mechanisms of both native and transplanted kidney diseases allows an adjustment of the therapy for each patient, thus optimizing renal transplant outcome.

Global clinical management



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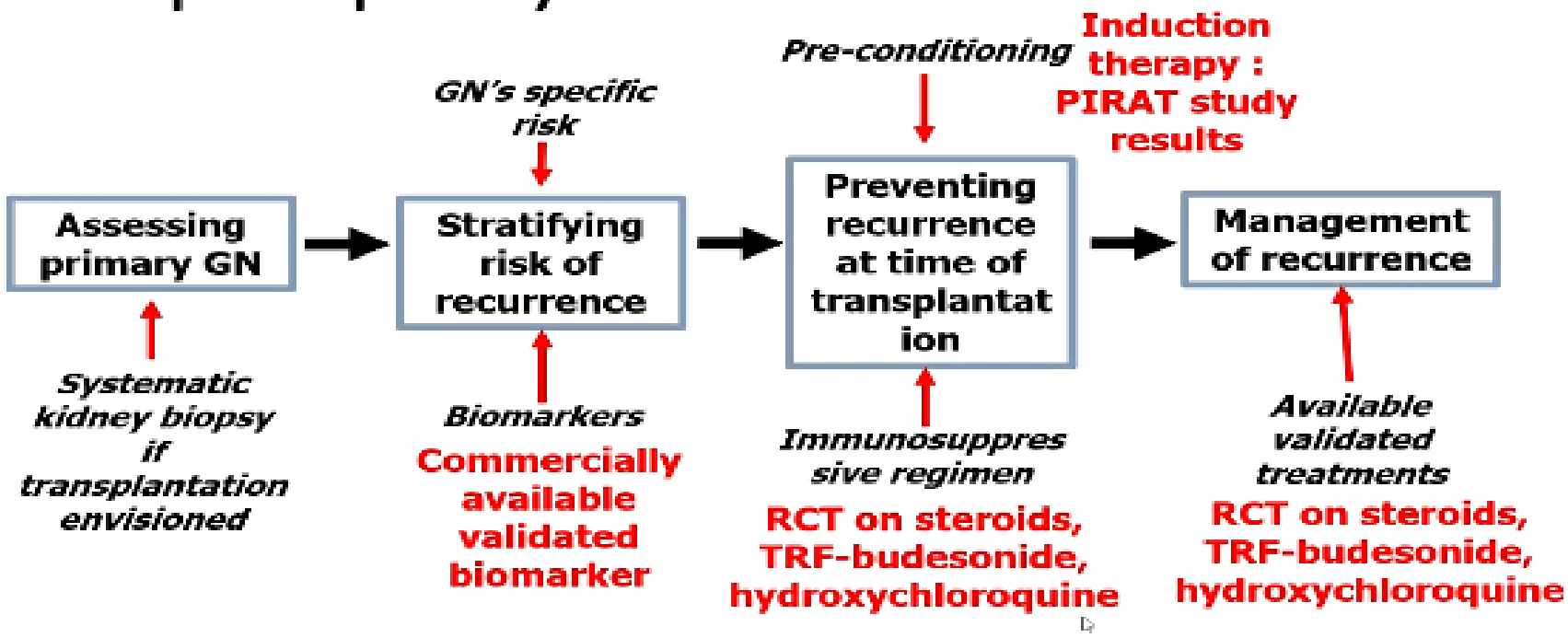
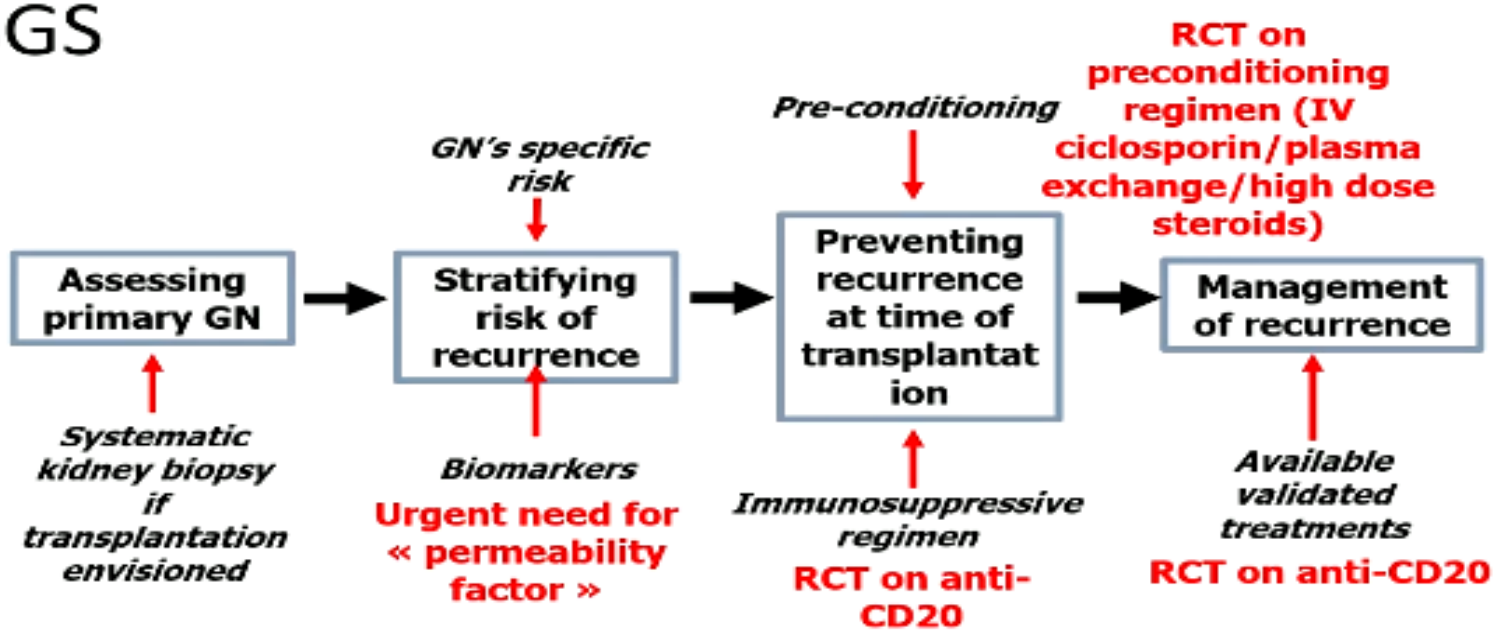
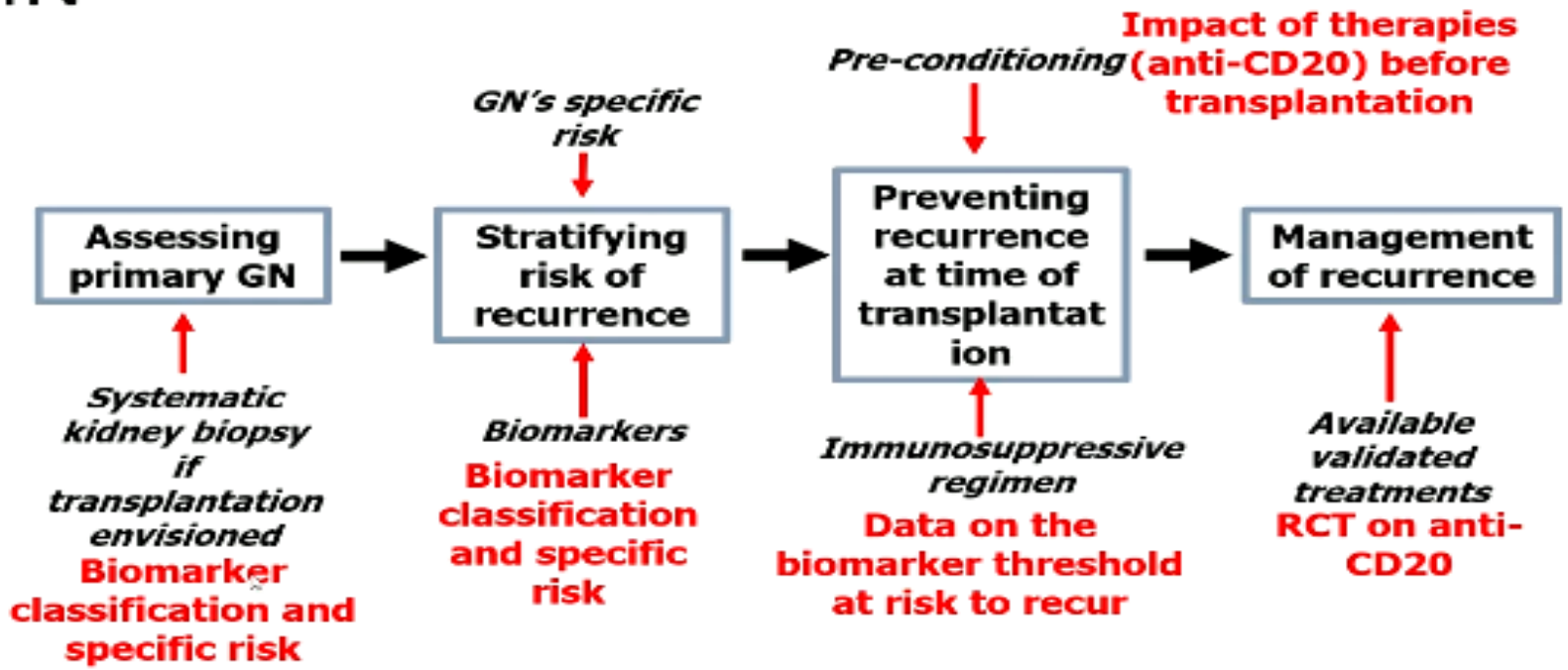
Studies needed IgA Nephropathy



Studies needed FSGS



Studies needed MN



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Review

Recurrent Glomerulonephritis after Renal Transplantation: The Clinical Problem

Barbara Infante [1,†], Michele Rossini [2,†], Serena Leo [1], Dario Troise [1], Giuseppe Stefano Netti [2], Elena Ranieri [2], Loreto Gesualdo [3], Giuseppe Castellano [1,*] and Giovanni Stallone [1]

1 Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Viale Pinto Luigi 251, 71122 Foggia, Italy; barbarinf@libero.it (B.I.); sereleo1989@libero.it (S.L.); dario.troise@gmail.com (D.T.); giovanni.stallone@unifg.it (G.S.)

2 Clinical Pathology Unit and Center of Molecular Medicine, Department of Medical and Surgical Sciences, University of Foggia, Viale Luigi Pinto, 71122 Foggia, Italy; michelerossini@libero.it (M.R.); giuseppestefano.netti@unifg.it (G.S.N.); elena.ranieri@unifg.it (E.R.)

3 Nephrology, Dialysis and Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, 70124 Bari, Italy; loreto.gesualdo@uniba.it

* Correspondence: giuseppe.castellano@unifg.it; Tel.: +39-0881732610; Fax: +39-0881736001

† These authors contributed equally to this work.

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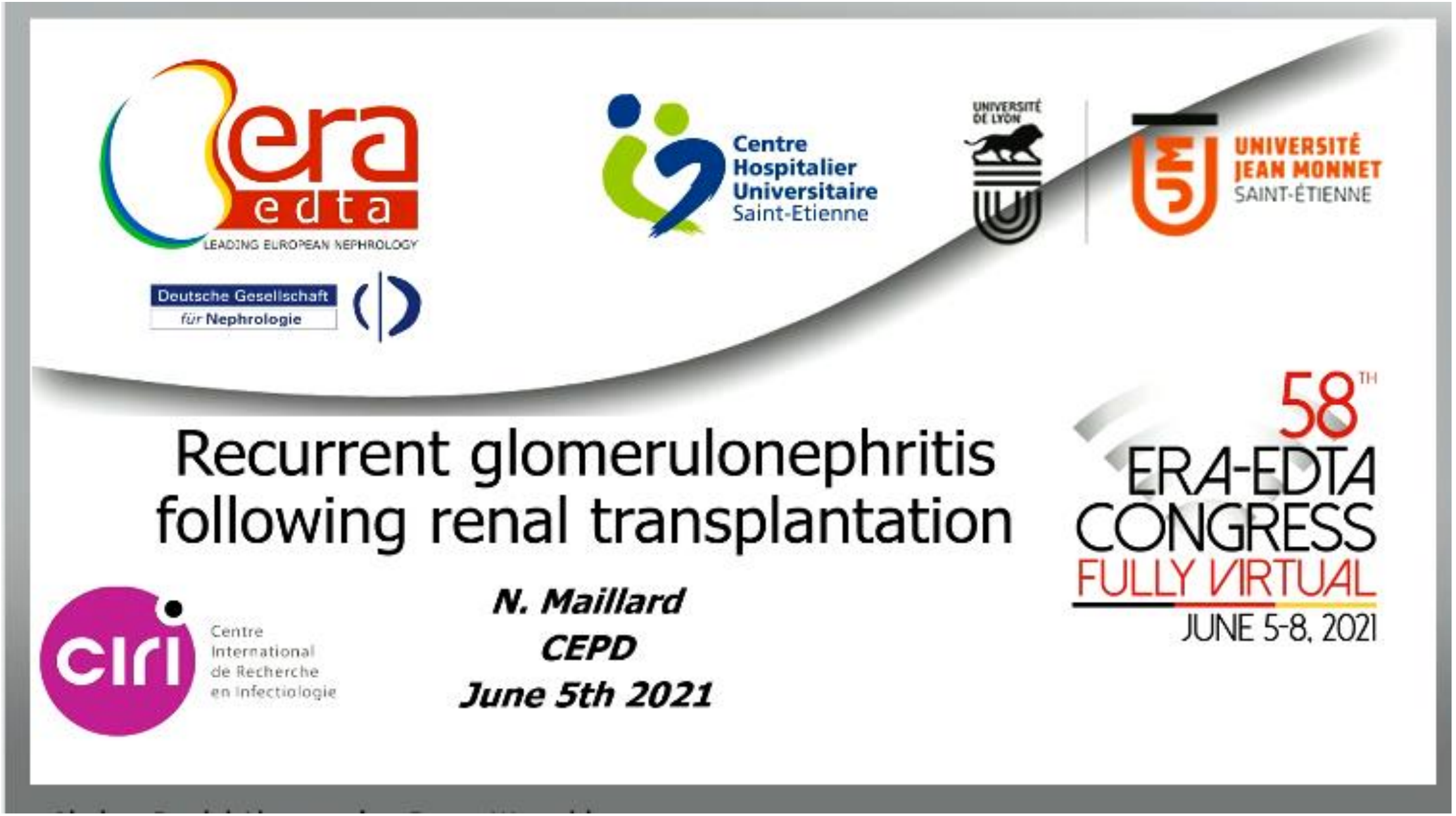
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UNIVERSITÉ JEAN MONNET SAINT-ÉTIENNE
Recurrent glomerulonephritis following renal transplantation
N. Maillard
CEPD
June 5th 2021
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Centre International de Recherche en Infectiologie
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