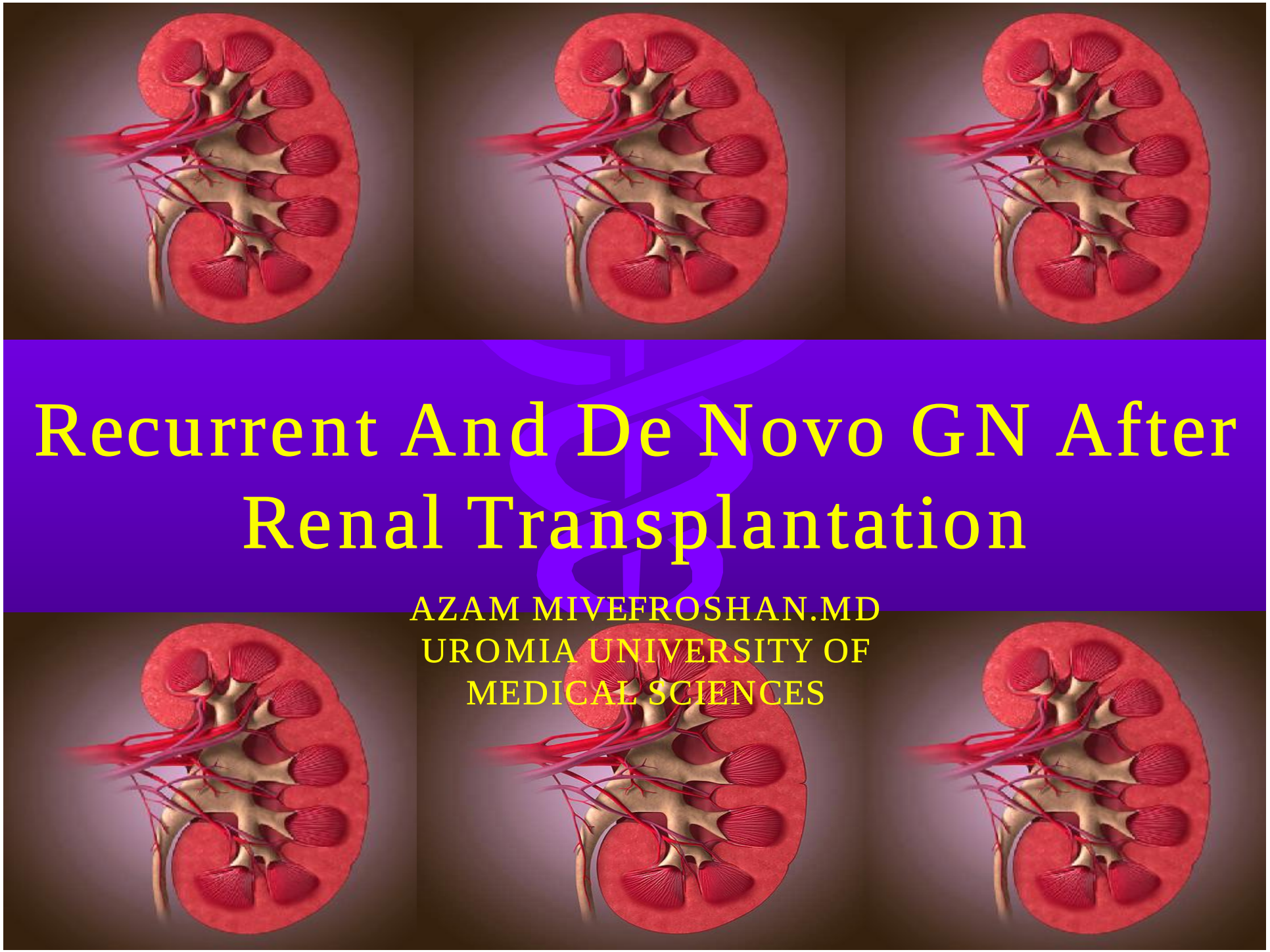

Recurrent And De Novo GN After Renal Transplantation

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Introduction

- The 1 year kidney allograft survival rate has improved dramatically during the last decade with the introduction of newer IS agents.

- Development and progression of recurrent and de novo disease does not seem to have been influenced by the use of those agents.

Introduction

- Clinically, recurrent GN manifests primarily as an increase in proteinuria in the allograft, usually associated with progressive loss of renal function or chronic kidney disease (CKD).

Introduction

- 30- 50 % of KT recipients have GN as the underlying cause of their ESRD

- Those patients are at risk of the recurrence of their original disease.

Introduction

- In patients who develop recurrent and de novo disease , there is a 190% increased risk of losing the graft compared with those without recurrent and de novo disease.

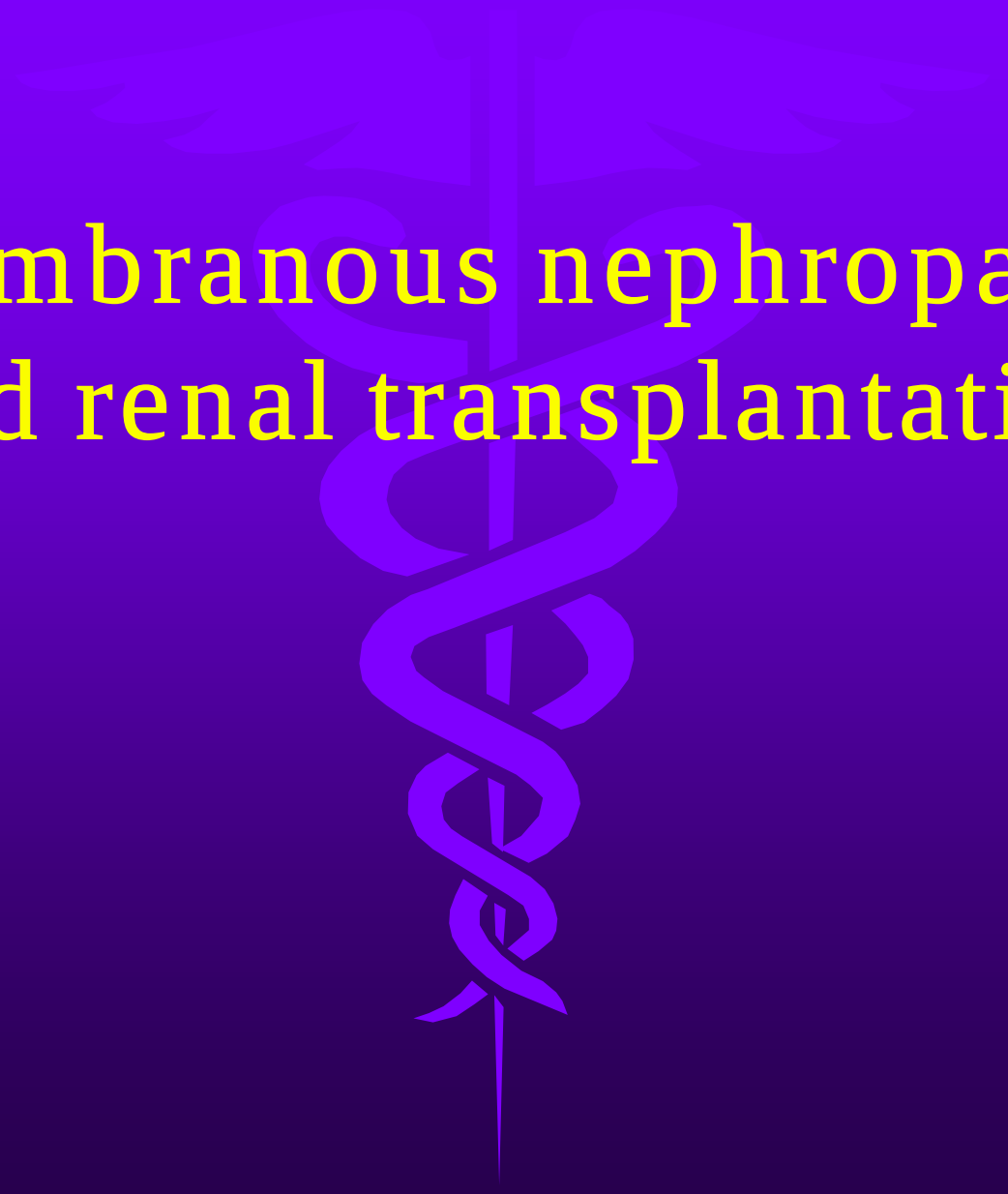
- Glomerulonephritis in the allograft is also associated with a reduction in long-term (5-year) survival

Table 2: Risk of recurrence and graft loss and treatment strategies for different types of glomerulonephritis

	Clinically relevant[1] recurrent risk[2]	Risk of graft loss due to recurrence 5–10 years post-transplant[2]	Prevention/treatment strategies
IgAN	13–46%	2–16%	ACEI and/or ARB for patients with proteinuria ± renal impairment due to recurrent IgAN (26,27
FSGS	20–50%	13–20%	Avoid living donors for patients with history of rapid graft loss from recurrence (38) Preemptive perioperative plasmapheresis (PP) fo 2 weeks for patients with high risk of recurren (39,40) Chronic PP with or without cyclophosphamide o cyclosporine for patients with relapse after init course of PP (29,30,35) ? Avoid omission of calcineurin inhibitors in sirolii based immunosuppressive regimen (24,42,43) ? Avoid induction therapy (47,48)
MPGN			
Type I	20–25%	~15%	No effective preventive or treatment measures
Type II	80–100%	15–30%	Exclude secondary causes
Membranous nephropathy	10–30%	10–15%	No effective preventive or treatment measures Exclude secondary causes
ANCA-associated glomerulonephritis	~17%	6–8%	Defer transplant till disease inactive (55) Cyclophosamide for recurrence (55,56) Combine therapy with PP, cyclophosphamide ± intravenous immunoglobulin for recurrence wi high titer of ANCA and cellular crescents in rer biopsies (57,58)
SLE	2–9%	2–4%	Defer transplant till disease inactive (60,61) Consider mycophenolate mofetil for recurrence (62,63)
Anti-GBM	Rare	Rare	Defer transplant till disease inactive Combine therapy with PP/immunoabsorption and cyclophosphamide for recurrence with high anti-GBM titer and cellular crescents in renal biopsies (57,65)

[1] Clinical relevant refer to patients with clinical symptoms of proteinuria/hematuria/renal impairment.
[2] % of transplanted patients.

Membranous nephropathy and renal transplantation



RECURRENT MN

- Incidence of recurrent MN is 10 - 45 %

- Clinical manifestations of recurrent MN are typically observed 13 to 15 months after transplantation although they may be observed much earlier (within weeks)

- Once the diagnosis of posttransplantation MN is made, it may be useful to distinguish idiopathic from secondary MN. Screening for HBV,HCV, lupus and malignancy should be considered.

Treatment

- Nonimmunosuppressive therapy
- Immunosuppressive therapy

Ø The standard doses of cyclosporine, tacrolimus, and mycophenolate mofetil used for IS after TX do not protect against or change the course of recurrent disease.

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Mild disease:

- Minimal protein excretion (less than 4 gr / day)
- Stable renal function
- Only histologic evidence of recurrent MN (as detected for example by protocol biopsy)

Nonimmunosuppressive therapies :

- Angiotensin inhibition
- Rigorous BP control
- Control of hyperlipidemia

Moderate to severe disease:

- Protein excretion greater than 4 gram / day
- Decreasing GFR

- Immunosuppressive therapy + nonimmunosuppressive therapy

Immunosuppressive therapy:

- Steroid Therapy:

Oral or IV high-dose steroid does not appear to be any consistent response to this treatment.

- Tacrolimus versus cyclosporine

- Antimetabolites (mycophenolate or azathioprine)

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- Rituximab:

The optimal dose of rituximab is not known.

ü Two doses of 1000 mg given two weeks or 4 weekly doses of 375 mg / m2

ü The response to rituximab generally occurs within a few weeks.

- All other immunosuppressive therapies that are used to prevent rejection are continued.

- A response is assessed by monitoring protein excretion and by measuring the percentage of CD19-B cells.

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Table 5 | Efficacy of rituximab in patients with idiopathic membranous glomerulonephritis

Study	Number of patients (number given prior therapies*)	Age (years)‡	Duration of disease‡	Follow-up (months)‡	Results	
					Outcomes	Decline in proteinuria from baseline
Bomback *et al.* (2009)[117,§]	69 (8)	NA	0.8–30 months	5–60	Complete response 23 Partial response 21 Relapse NA	48–99%
Segarra *et al.* (2009)[118,‖]	13 (13)	45 (26–71)	64 (35–96) months	35 (31–54)	Complete response 4 Partial response 9 Relapse 3	65.6% at 6 months; 71.8% at 12 months
Fervenza *et al.* (2010)[30]	20 (11)	48.6 (29–80)	29.7 (4–144) months	24	Complete response 4 Partial response 12 Relapse 1	8.5±6.6% per month for 24 months
Sprangers *et al.* (2010)[119,¶]	4 (4)	NA	3.4 (0.2–8) months	20–27	Complete response 1 Partial response 2 Relapse 0	NA
Sugiura *et al.* (2011)[61]	4 (3)	69 (54–74)	19 (7–25) years	6	Complete response 0 Partial response 2 Relapse 0	32.6%
Cravedi *et al.* (2011)[120,#]	22 (11)	50.1±12.3 vs 48.6±13.9	9 (6–17) vs 51 (26–55) months	24	Complete response 3 vs 2 Partial response 5 vs 5 Relapse 1 vs 1	69.4±40.4% vs 60.9±17.4%

Rituximab-resistant

- Cytotoxic agents, such as cyclophosphamide
- 2 mg/kg per day of cyclophosphamide
- Patients who are started on cyclophosphamide should discontinue any antimetabolites that they are on (such as mycophenolate or azathioprine), other antirejection medications, including CNI and glucocorticoids may be continued.

- Eculizumab
- IVIG

DE NOVO MN

- Incidence of is approximately 1.5 to 2%.

- The standard use of calcineurin inhibitors for immunosuppression post-transplantation has not changed the incidence of de novo MN.

- Protein excretion <4 g/d and stable renal function: increase in the maintenance dose of one or more components of the immunosuppressive regimen.

- Protein excretion that is ≥4 g/d or deteriorating renal function: Rituximab

Focal segmental glomerulosclerosis

- Recurrence rate of FSGS after the first allograft: 30% (in subsequent KT is 80–100%)
- Recurrence of FSGS usually occurs within hours to days after the transplant procedure.
- 5-year kidney graft survival is 57% in patients with recurrent FSGS versus 82% in patients without recurrence.

Table 1. Factors influencing the risk of recurrence of FSGS

Factors associated with increased risk of recurrence	Factors associated with low risk of recurrence
Second transplant after loss from recurrence	Familial FSGS
Childhood	Sporadic form with podocin mutation
Rapid progression to uraemia	Slow progression to uraemia
Mesangial proliferation in native kidneys	Non-nephronic proteinuria in the original disease
Living donation	
White race	
Elderly donor	

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- The rapidly of recurrence suggests the presence a circulating factor or the absence of a normally present factor in plasma, with either resulting in toxicity to the glomerular capillary wall.

- Screening:(with a spot urine protein / Cr ratio)

ü On the first postoperative day
ü The day of scheduled hospital discharge
ü Weekly for four weeks
ü Monthly for one year after TX.

Prevention of recurrent FSGS:

- Limited evidence suggests that some interventions may help prevent recurrent disease.
- Combined therapy with rituximab and pretransplant plasmapheresis
- FSGS, tended to be lower in patients who received thymoglobulin (polyclonal rabbit-antithymocyte globulin) compared with alemtuzumab and interleukin 2 receptor antagonists

TREATMENT:

- Protein adsorption and plasmapheresis(3 consecutive days followed by every other day for a total of 9 treatments)
- Plasmapheresis plus cyclophosphamide
- Plasmapheresis plus cyclosporine

- IVIG
- Cyclosporine : The role of cyclosporine in recurrent FSGS is uncertain. Although cyclosporine is often beneficial for the primary disease , it does not appear to prevent recurrence in the transplant when given as part of the initial immunosuppressive regimen.
- Corticosteroids
- Rituximab

Table 4 | Efficacy of rituximab in treatment and prevention* of recurrent FSGS

Characteristics	Tsagalis *et al.* (2010)[93]	Araya *et al.* (2011)[6]	Prytula *et al.* (2009)[54]
Patients (*n*)	4	39	15
Age (range)	32–57 years	5–48 years; 19 children (age not specified)	All children (age not specified)
Time to recurrence (range)	2–72 months	1–3, 513 days	NA
Pretransplant plasma exchange (patients)	None	9	NA
Post-transplant plasma exchange (patients); number of sessions or duration	4; 20–69 sessions	38; mean 21 sessions	10; NA
Rituximab regimen (375 mg/m^2 infusion, unless specified)	1 g; 2 doses every 2 weeks, repeated at 1 year	1–6 doses	1–4 doses every 1–2 weeks
Median interval between recurrence and rituximab therapy (range)	3 (1–12) weeks	149 (3–1,086) days	NA
Patients in remission (%)	Complete 2 Partial 2	Complete 17 (43.5%) Partial 8 (20.5%) No response 14 (35.9%)	Complete 6 (40%) Partial 3 (20%) No response 6 (40%)
Duration of follow-up	18–60 months	NA	5–84 months
Outcome at last follow-up	Complete remission 2 Partial remission 2	Complete remission 17 Partial remission 8	Complete or partial remission 5 Recurrence 3 NA 1

- Anti-TNF
- Retinoic acid and cyclin dependant kinase inhibitor
- Galactose
- Therapy with ACE inhibitors ARB + control of dyslipidemia with HMGCoA reductase inhibitors.

Leroy S,Transplant 2009;9(4):858-61.
He JC, et al. J Am Soc Nephrol 2007;18(1):93-102.

- Rapid recurrence: plasmapheresis

- late recurrence of FSGS (later than one year)

ü cyclophosphamide (100 mg orally daily) as replacement for the antimetabolite

ü If there is no response to this agent after 6 to 12 weeks : plasmapheresis

SECOND TRANSPLANTS

- Patients who develop recurrent disease in the first transplant are at very high risk (up to 75 %) for recurrence in subsequent allografts.
- Graft loss due to recurrent disease is seen in 10 - 80 % of these patients.
- Some clinicians have suggested that, if a first graft is lost to recurrent disease, a second transplant should be delayed for one to two years.

Pieving WF et al.AM J Nephrol 1985; 5:299

De novo FSGS

- Manifestation of chronic rejection
- Calcineurin inhibitor nephrotoxicity

- The hemodynamic factors associated with the glomerular hypertrophy.

- Viral-induced FSGS(HIV and parvovirus B19 infection , hepatitis C, EBV, and possibly CMV)

Post transplant Membranoproliferative glomerulonephritis

Recurrence after transplantation:

ØMPGN TYPE I :

- Rate of recurrent disease in MPGNI : 20 - 30 %
- Hypocomplementemia and presence of serum monoclonal proteins may be associated with recurrent disease.

SCREENING:

- In the first month to determine a baseline.
- Every 3 months during the first year
- Annually

Ø Allograft biopsy :

- New onset of proteinuria
- Unexplained proteinuria _3.0 g per gram creatinine or _3.0 g per 24 h.

TREATMENT OF RECURRENT MPGN TYPE I:

- There is no proven beneficial therapy for the treatment of recurrent idiopathic MPGN

- The combination of aspirin and dipyridamole may stabilize renal functionl

- In the setting of stable graft function, especially associated with non-nephrotic range proteinuria : conservative management (BP control, the use of ARB or ACE-inh) along with a statin.

- In the setting of rapidly worsening graft function or histologic findings suggestive of rapidly progressive disease : aggressive treatment using plasmapheresis and adjuvant immunosuppression.

- In the setting of active hepatitis C virus infection: the use of interferon gamma, is controversial; however, it should be considered in appropriate candidates .

MPGN TYPE II (DENSE DEPOSIT DISEASE)

- MPGN type II, tends to recur more frequently than MPGN type I, ranging from 50 to 100 %.
- Graft loss due to recurrent disease is occur in 30 to 50 %

- Diagnosis of MPGN II :

ü Screening for mutations in complement factor H (CFH)

ü Assays of complement activity

ü Testing for C3 nephritic factor (C3NeF)

TREATMENT OF MPGN TYPE II

- There is no known effective therapy
- Plasmapheresis (factor H deficiency , elevated c3NeF)
- Substitution of tacrolimus for cyclosporine
- Reduction in the dose or discontinuation of the calcineurin inhibitor, increase in the corticosteroid dose, or the administration of pulse metylprednisolone.

- Eculizumab

Ø MPGN TYPE III

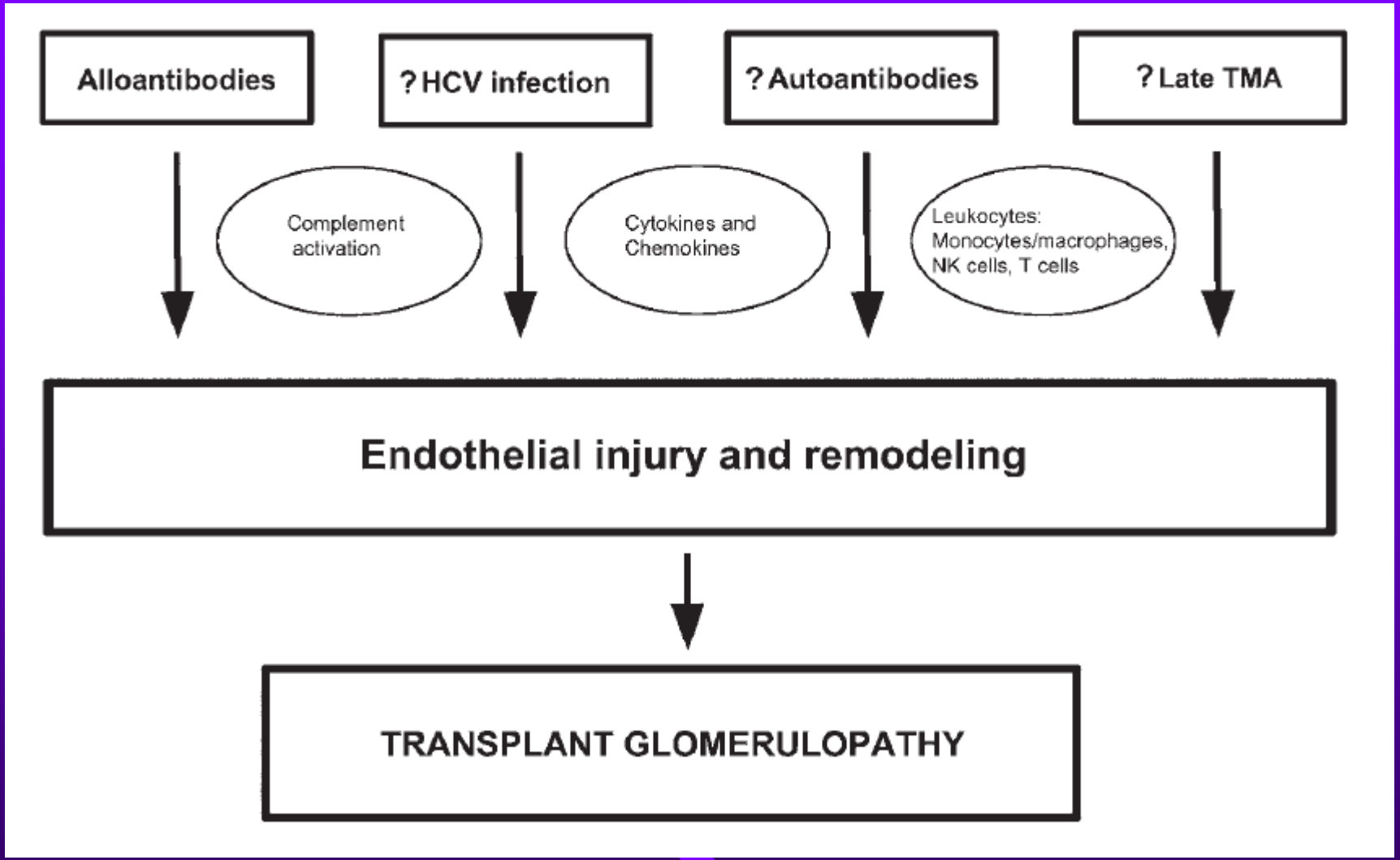
Ø DE NOVO MPGN:

- Rituximab may be useful in treating de novo MPGN in renal transplant recipients.

Transplant Glomerulopathy

Ø (TG) is a leading cause of posttransplantation proteinuria and graft loss. It constitutes a nonspecific glomerular response to at least a periodically persistent injury to the glomerular endothelium.

Ø TG is defined by duplication of glomerular basement membranes associated with cellular interposition into the subendothelial region of the glomerular capillaries.



Am J Kidney Dis. 2013;62(2):352-363

- Early detection of TG : (by EM)
- can be reversed with high-dose IVIG, plasmapheresis, and / or rituximab.

- Eculizumab (humanized anti-C5 antibody) and proteasome inhibition in plasma cells (bortezomib)

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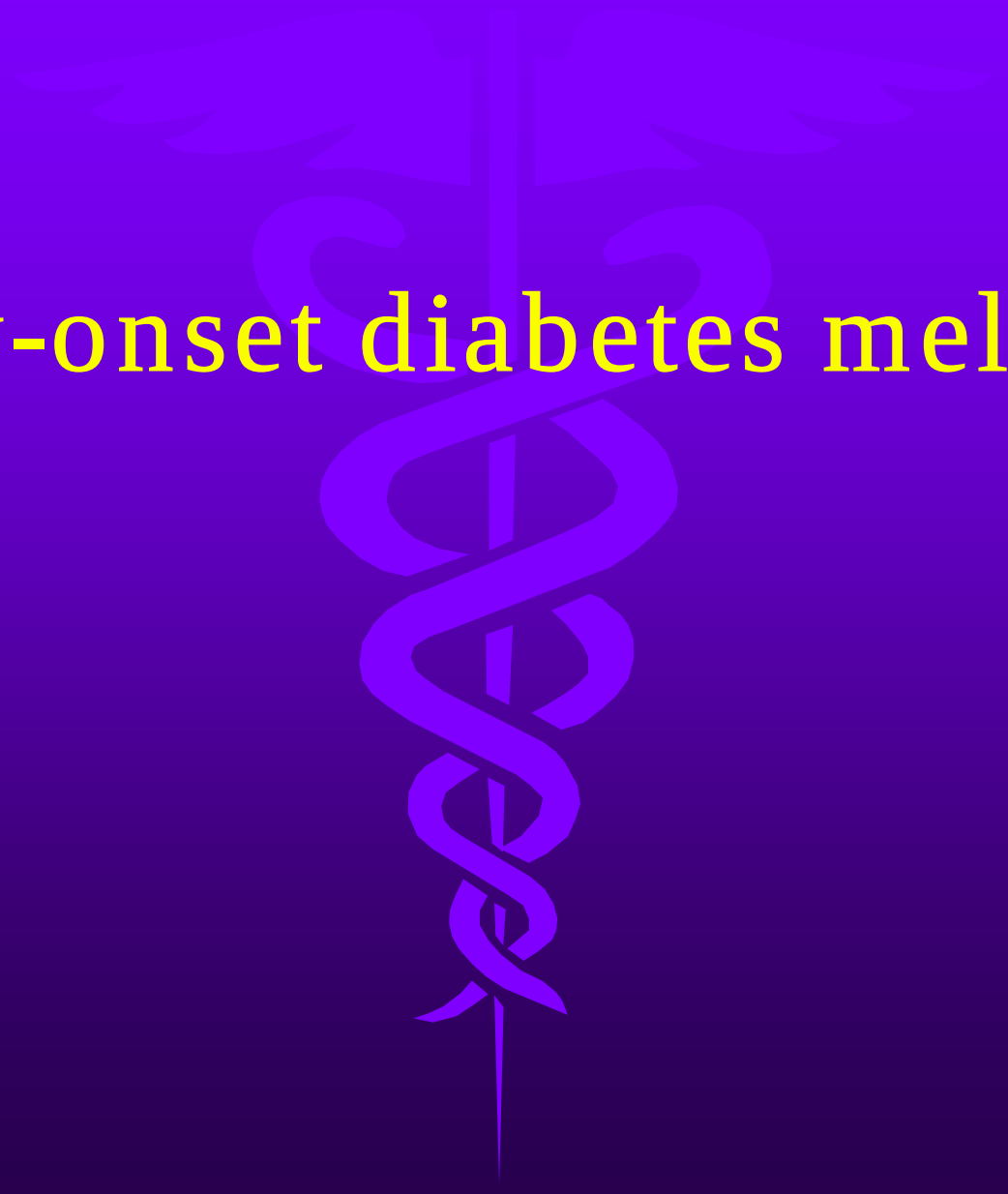
TREATMENT AND PREVENTION

- There is no effective treatment.

- Prevention in a sensitized patient also is difficult because current therapies cannot reduce donor specific antibody levels over a long period. Current therapies for desensitization and treating acute ABMR include IVIG, plasmapheresis, immunoadsorption, splenectomy, and rituximab.

New-onset diabetes mellitus



- PTDM was defined as the need for treatment with glucose-lowering agents post-transplantation for more than 30 days consecutively

- symptoms of diabetes plus casual:

ü plasma glucose (PG) concentrations ≥200 mg / dl (11.1 mol / l)

ü fasting plasma glucose (FPG) ≥126 mg / dl (7.0 mmol / l)

ü two-hour plasma glucose ≥200 mg / dl (11.1 mmol / l) during an oral glucose tolerance test (OGTT).

Etiology:

- Prednisolone
- CsA andTac
- Sirolimus
- use of basiliximab(a chimeric anti IL-2 receptor monoclonal antibody) in induction therapy

Figure 1. *Pre-transplantation screening and prevention of NODAT*

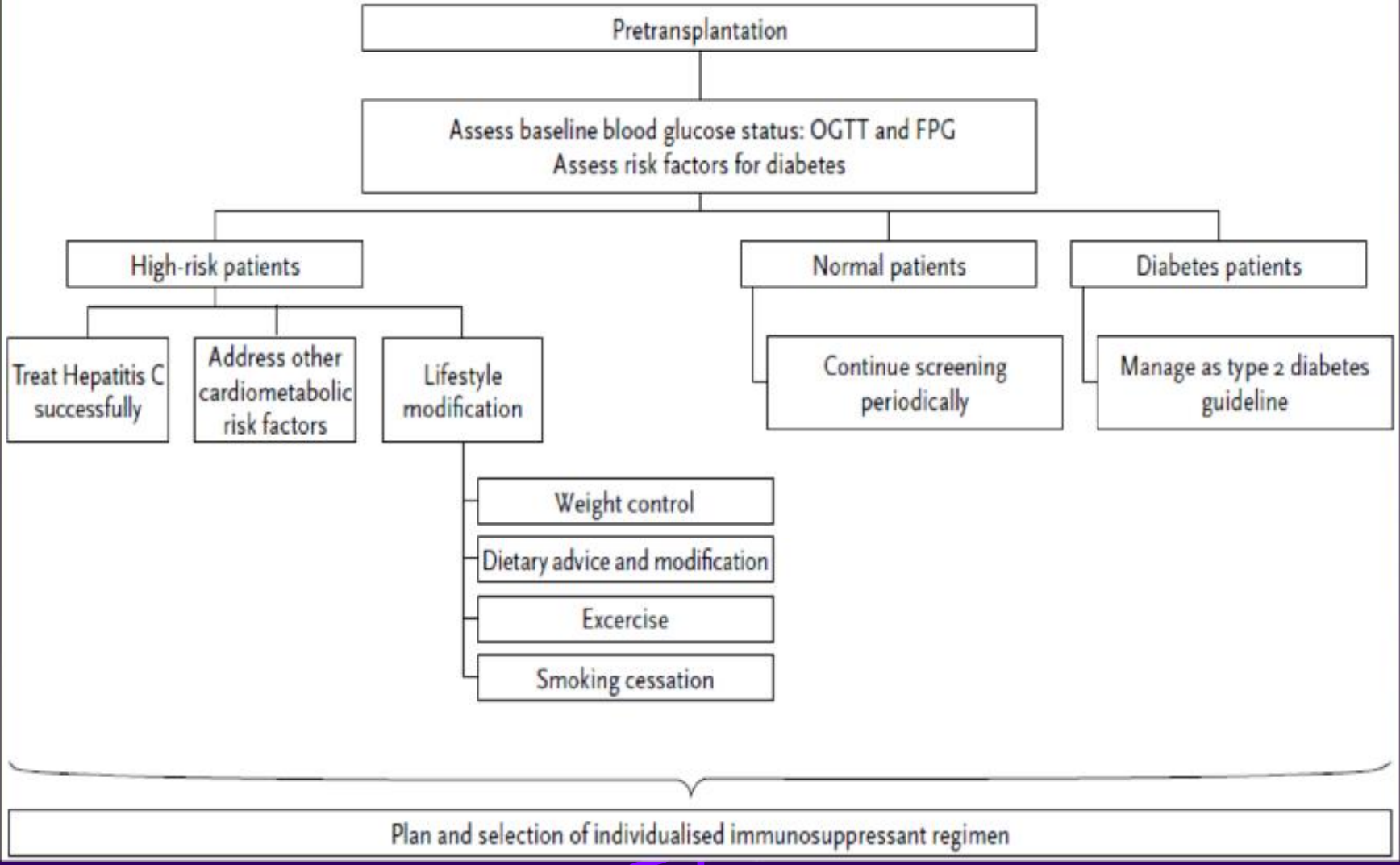


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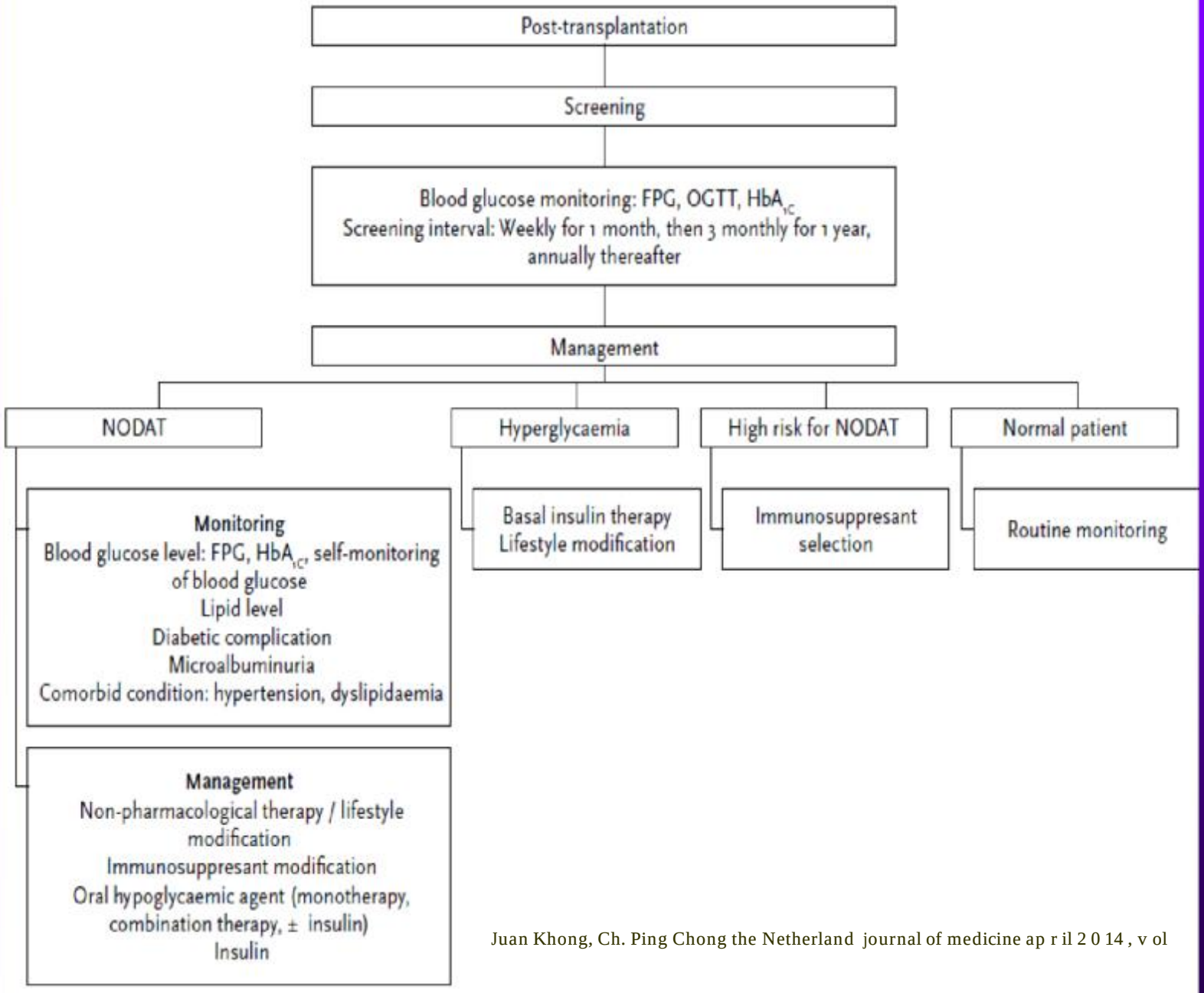
Figure 2. *Post-transplantation screening and management*



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- Lifestyle modification

- Modification of the immunosuppressive

1. Reducing the dose of Tac, CsA or corticosteroids
2. Discontinuing Tac, CsA or corticosteroids;
3. Replacing Tac with CsA, MMF or AZA;
4. Replacing CsA with either MMF or AZA

- Combination of CNI and mTORi therapy and switching from Tac to Sir is not recommended

- Steroid-sparing strategy

- Oral glucose-lowering agents :

ü first-line : sulfonylurea (glipizide) and meglitinides (repaglinide and nateglinide).

ü Metformin

ü Thiazolidinedione

- Insulin therapy

Diabetic nephropathy

- 80 to 100 %of diabetic transplant recipients develop histological changes of recurrent diabetic nephropathy (DN).

- The time of development of nephropathy may be as little as six years post-transplantation.
- The incidence of DN as a cause of graft failure is poorly studied and has been thought to be rare.

- Recurrent disease in the allograft theoretically can be prevented by optimal glycemic control.