In The Name Of God

A Review of The Evaluation and Management of Candidates for Kidney Transplantation

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Introduction

Kidney transplantation is the preferred treatment option for patients with kidney failure.

It offers the best chance of improving both quality and quantity of life but requires careful consideration of the risks and benefits.

ACCESS TO TRANSPLANTATION

✓ All patients **with CKD G4-G5 (GFR < 30 ml/min/1.73 m2)** who are expected to reach ESKD should be informed of, educated about, and considered for kidney transplantation.

✓ Refer potential kidney transplant candidates for evaluation **at least 6 to 12 months before anticipated dialysis initiation** to facilitate identification/work-up of living donors and plan for possible pre-emptive transplantation.

✓ **Pre-emptive transplantation with a living kidney donor is the preferred treatment for transplant-eligible CKD patients.**

AGE

✓ **Do not exclude patients** from kidney transplantation **because of age alone** but rather consider the context of other comorbidities, including **frailty**, that may impact outcome when deciding about suitability for kidney transplantation.

frailty

- A state of reduced physiological reserve and is related to age and associated comorbidities .
- Prevalence of **10%-20%** among patients on the waitlist and transplant recipients.
- Increases with **age** and **dialysis vintage** and who are **female** (3.3-fold higher) ; and **African American**.
- **Post–kidney transplant frailty** is associated with **graft loss and mortality** in addition to higher rates of **delayed graft function and longer hospitalization**.
- Attempts to quantify frailty may prove useful by identifying patients who may benefit from strategies aimed at improving frailty scores.

Clin J Am Soc Nephrol. 2019;14(4): 576-582.

CLINICAL FRAILTY SCALE

1 **VERY FIT** — People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.

2 **FIT** — People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.

3 **MANAGING WELL** — People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.

4 **LIVING WITH VERY MILD FRAILTY** — Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.

5 **LIVING WITH MILD FRAILTY** — People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

6 **LIVING WITH MODERATE FRAILTY** — People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **LIVING WITH SEVERE FRAILTY** — **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8 **LIVING WITH VERY SEVERE FRAILTY** — Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.

9 **TERMINALLY ILL** — Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

DALHOUSIE

سوال ۱

آقای ۵۳ ساله Tobacco user 40 pack –years از یک سال قبل , کاندید پیوند کلیه می باشد .
آ یا برای اسکرین Occult lung cancer در بیمار **CT** درخواست می کنید؟

- ❑ بله
- ❑ خیر

TOBACCO

✓ All candidates **should avoid** tobacco products **before** and **indefinitely after** transplantation.

✓ **CT** for **current or former heavy tobacco users** (≥ 30 pack-years) to screen for **occult lung cancer** is suggested and chest radiograph for other candidates.

SURGICAL ISSUES

✓ Candidates **should not be excluded** from transplantation **solely** because of **obesity.**

✓ Patients with **BMI ≥ 35** kg/m2 **should be** considered for **interventions such as dietary counseling or bariatric surgery** prior to transplantation.
Those **with BMI ≥ 40** kg/m2 should be approached with **caution** since there is increased risk for post-operative complications (eg, delayed wound healing).

Obesity
(Clinical Utility)

- While obesity is associated with lower risk of death among patients on maintenance dialysis the impact of obesity on transplantation outcomes is complex.

- Despite a survival advantage of transplantation when compared with remaining on dialysis ,**obesity** also correlates with **poorer outcomes posttransplant**.

- Patients with obesity have a higher risk of **death, delayed graft function, rejection, wound complications , and prolonged hospitalization stays.**

- Thus, obesity remains an important issue for transplant candidates.

SURGICAL ISSUES …

✓ **Evaluate** native kidney size in patients with polycystic kidney disease.

Staged or simultaneous native nephrectomy and transplantation may be considered for candidates with a **painful, recurrently infected, or potentially malignant polycystic kidney, or if the patient has insufficient room for a transplant .**

✓ Candidates **should not be excluded** because of their need for **anticoagulation, antiplatelet therapy, or a history of heparin-induced thrombocytopenia.**

سوال ۲

در کدام گروه از بیماران زیر قبل از پیوند کلیه توصیه به انجام اکوکاردیوگرافی می کنید؟

الف. Asymptomatic candidates on dialysis for two years.
ب. portal hypertension
پ. connective tissue disease
ت. COPD
ه. All of the above

Pulmonary Hypertension

- PH prevalence increases with CKD stage and is highest among hemodialysis patients.
- With some studies reporting a prevalence of up to 70%.
- Several factors contribute to this increased prevalence, but, most commonly, it is related to **increased intravascular volume and elevated left sided heart pressures.**

Diagnosis and management of pulmonary hypertension in patients with CKD. Am J Kidney Dis. 2020

Pulmonary Hypertension…

- Patients with PH have increased risk of delayed graft function, inferior graft function, and higher mortality.
- Studies have also shown PH improves after successful kidney transplantation, along with improvement in patient-reported symptoms.
- Suggested that transplant should still be the favored strategy for PH patients with kidney failure.
- The KDOQI work group in general agrees with the KDIGO recommendation to **not exclude** patients from transplantation **purely** based on PASP criteria.

Am J Kidney Dis.2021

Pulmonary Hypertension…

- ✓ Suggested that **asymptomatic candidates** who have been on **dialysis for at least two years** or **have risk factors for pulmonary hypertension** (eg, **portal hypertension, connective tissue disease, congenital heart disease, chronic obstructive pulmonary disease) undergo echocardiography** (2D).

- ✓ Patients with an estimated pulmonary systolic pressure **greater than 45 mm** Hg by echocardiographic criteria **should be assessed by a cardiologist** (Not Graded).

- ✓ Recommend **not excluding** candidates with uncorrectable **Pasp greater than 60 mm Hg** (obtained from right heart catherization) from kidney transplantation; however, the risks of sudden deterioration or progression after transplantation should be a key consideration (1C).

Recurrent Glomerular Diseases:

- Focal Segmental Glomerulosclerosis
- Membranous Nephropathy
- Membranoproliferative Glomerulonephritis
- Hemolytic Uremic Syndrome

سوال۳

در کدامیک از موارد زیر توصیه به انجام پیوند کلیه ,مگر درصورت انجام اقدامات درمانی قبل پیوند; **<u>نشده است</u> ؟**

الف. aHUS with complement abnormality
ب.Prior graft loss due to MN
پ .Primary FSGS
ت.All of the above

FSGS

- Primary FSGS has a high risk of recurrence in the kidney allograft (**30%-50% with first transplant**) and high rates of **irreversible graft loss.**

- The risk of recurrence is higher, up to **80%**, in candidates who have **previously lost** a transplant due to FSGS recurrence.

- **Loss of a prior graft due to recurrent FSGS** indicates a high risk of recurrence upon subsequent transplantation and this factor **should be a major consideration** in determining candidacy (Not Graded).

Kidney Int. 2017;91(2):304-314.
Am J Kidney Dis.2021

FSGS

- Recommend **not excluding candidates with primary FSGS** from kidney transplantation however, the risk of recurrence should be considered and discussed with the candidate (1B).

- Suggested **genetic testing** (eg, for podocin and nephrin gene mutations) be performed in **children and young adults** with a **clinical course** consistent with **genetic FSGS** to inform the risk of recurrence (2C).

- **Suggested avoiding routine use of pre-transplant plasma exchange or rituximab to reduce the risk of recurrent FSGS (2D).**

Am J Kidney Dis.
77(6):833-856. March 18, 2021

Springer CEN Case Reports

CEN Case Rep. 2020 Aug; 9(3): 195–199.
Published online 2020 Jan 30. doi: 10.1007/s13730-020-00451-3

PMCID: PMC7320094
PMID: 31997159

Different effects of rituximab on a native kidney and a post-transplant kidney with recurrence of focal segmental glomerulosclerosis

Ayami Ino,✉ Segawa Kaori, Takashi Takei, and Kosaku Nitta

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Conclusion

Go to:

In this case, plasmapheresis and rituximab administration were ineffective on advanced stage of FSGS in the native kidney, but the same treatment was effective in achieving remission and maintenance on the recurrent FSGS in the transplanted kidney.

Membranous Nephropathy

- Clinical recurrence of MN is estimated to be around 10% and can go up to 50% with longer follow-up.

- **Autoantibodies to the PLA2R**, are seen in **60%-80%** of patients with primary/idiopathic MN.

- Since studies demonstrate an association between presence and strength of anti-PLA2R antibodies and post transplant recurrence, it may be reasonable to **monitor the levels** in those who are **positive for anti-PLA2R antibodies**.

N Engl J Med. 2019;381(1):36-46

Membranous Nephropathy

- The guideline does not specify how and when these antibodies should be measured pretransplantation.

- It is currently unclear if patients with high or increasing levels of anti-PLA2R antibodies should have a period of waiting time prior to kidney transplantation.

Transplantation. 2015;99(8):1709-1714.

Membranous Nephropathy…

- The higher rate of remission associated with rituximab and cyclosporine in the treatment of primary MN is well established, but similar data do not exist for the prevention and treatment of recurrent MN for transplant Recipients.

- **Graft loss associated with recurrent MN occurs in ~10%-13% of cases.**

- Counseling patients about disease recurrence is a valuable consideration.

Transplantation.
2015;99(8):1709-1714

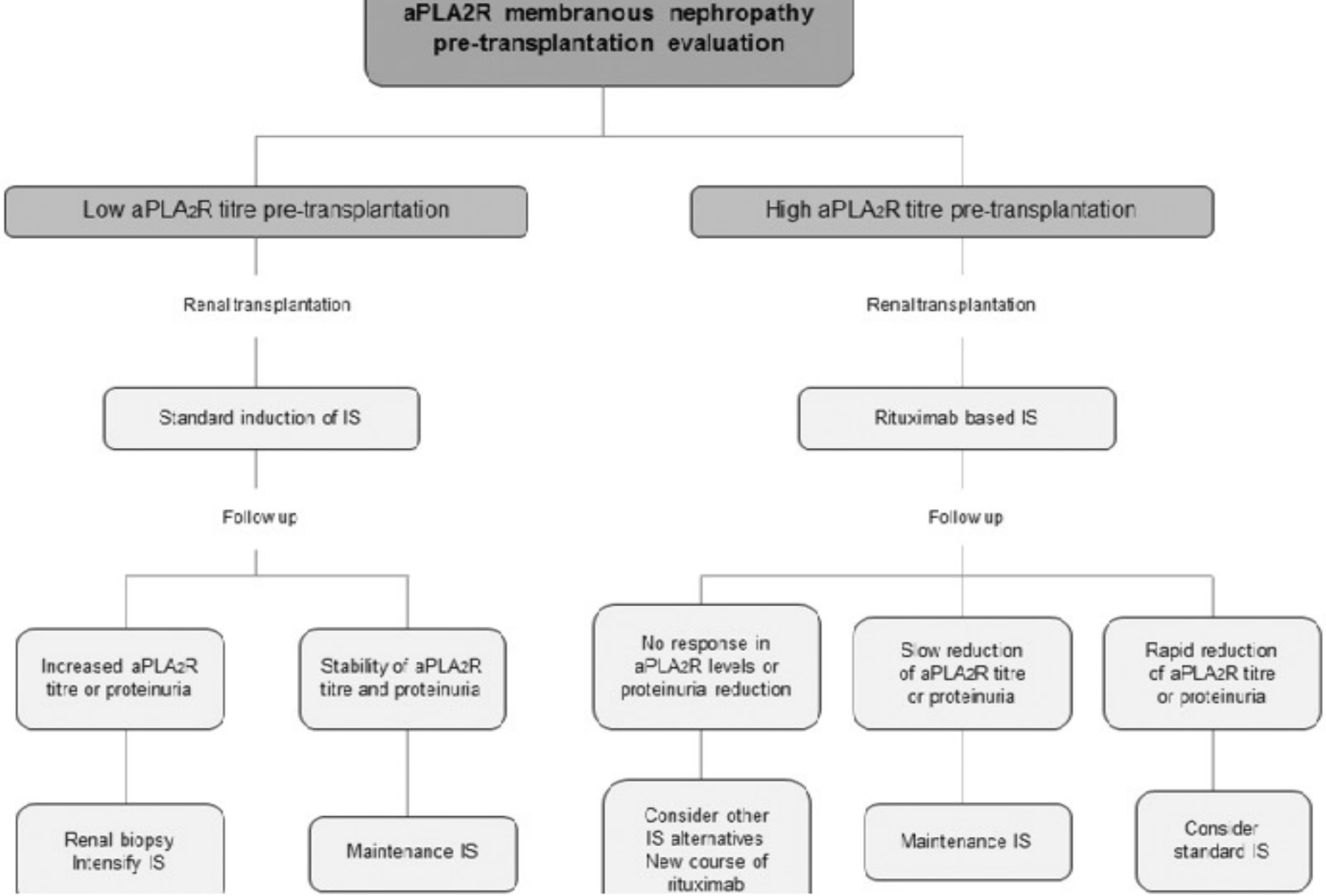
Membranous Nephropathy…

- Recommended not excluding candidates with MN from kidney transplantation (1B).

- Suggested **not excluding** candidates with **prior graft loss due to MN**; however, the risk of recurrence should be considered and discussed with the candidate (2D).

- Suggested that autoantibodies to PLA2R be measured pre-transplant to inform the risk of recurrence in patients with MN (2C).

- **Suggested not routinely using rituximab or alkylating agents to reduce the risk of recurrent MN** (2D).



Clin Kidney J. 2018 Jun; 11(3): 422–428

Usual dose of rituximab

The usual dose of rituximab consists of 375 mg/m^2 once weekly for 4 weeks or the alternative protocol of 1 g rituximab on days 1 and 15, with the regimen **repeated at 6 months if B cells are >15/ µL or elevated aPLA2R levels persist.**

Proteinuria may persist after the administration of rituximab, but this persistence **over months** should provoke a new course of treatment.

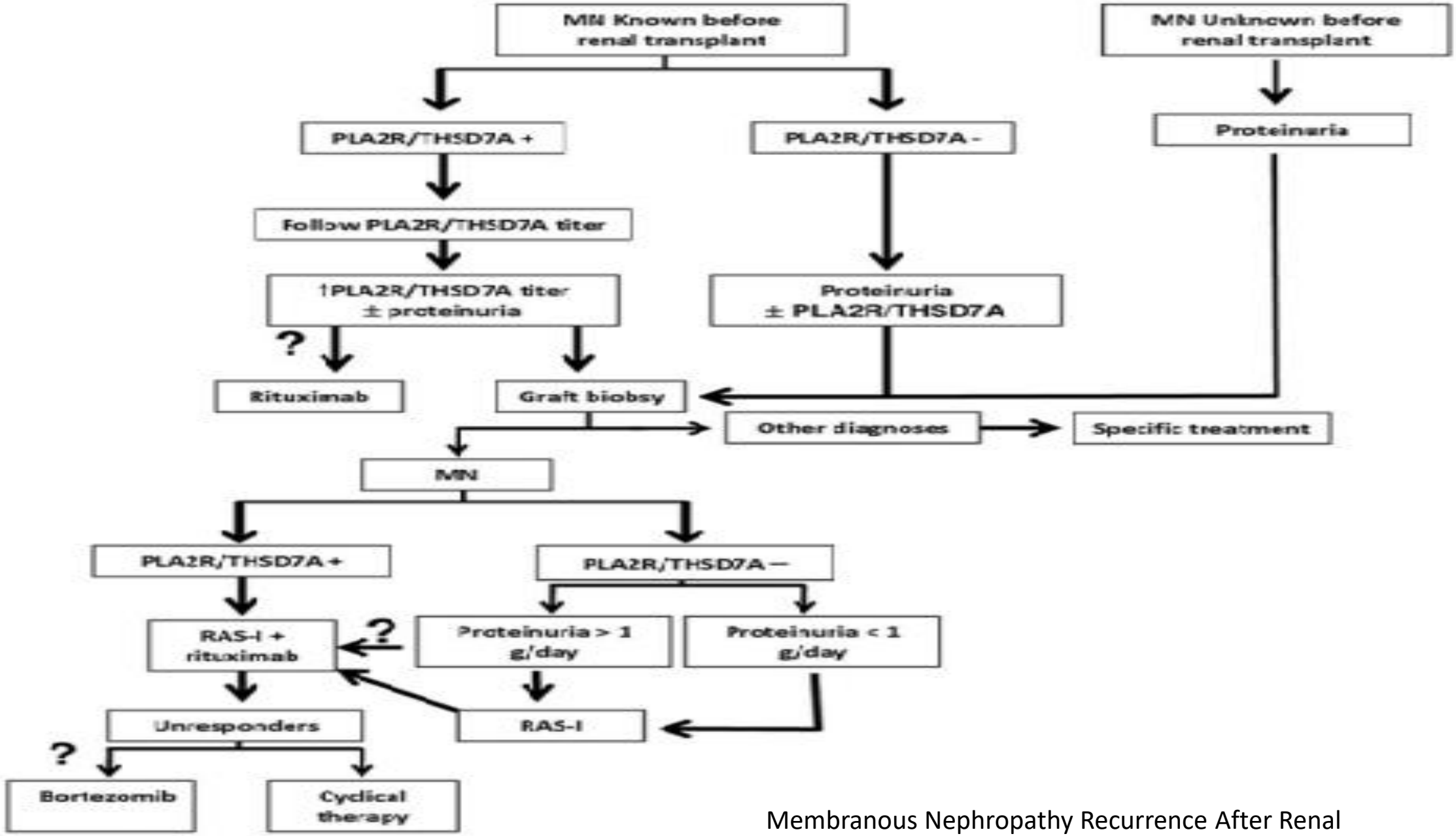
Clin Kidney J. 2018 Jun; 11(3): 422–428

aPLA2R…

•In transplant recipients, aPLA2R are a good indication for treatment initiation and for monitoring treatment response.

•MN may appear in the transplanted kidney as an allogenic manifestation of AMR. In these situations, aPLA2R may help to distinguish recurrent from *de novo* MN.

•Treatment with **rituximab may be considered** in patients with **high aPLA2R levels pre-transplantation, or when serial aPLA2R levels increase during the first year after transplantation**, **especially when proteinuria increases.**



Membranous Nephropathy Recurrence After Renal Transplantation

Frontiers in immunology 2019

Membranoproliferative Glomerulonephritis

- ❑ **IC-MPGN**
- ❑ **C3 glomerulopathy**

IC-MPGN

- ➢ Recommended **not excluding** candidates with **IC-MPGN** from kidney transplantation.

- ➢ Recommended investigation for an **infective, autoimmune, or paraprotein**-mediated cause of IC-MPGN prior to transplantation to guide treatment and inform risk of recurrence (1C).

- ➢ Suggested that, **when possible**, the cause of the **IC-MPGN be treated prior to transplantation** (2C).

Membranoproliferative Glomerulonephritis…

C3G: DDD and C3GN

- Recommended **not excluding** candidates with C3G from kidney transplantation(1B).

- Suggested that candidates with C3G be screened for **genetic or acquired causes** for the dysregulation of the complement alternative pathway to guide treatment and inform risk of recurrence (2C).

- **Loss of a prior graft due to recurrent C3G** indicates a high risk of recurrence upon subsequent transplantation and this factor **should be a major consideration in determining candidacy** (Not Graded).

Hemolytic Uremic Syndrome

- HUS secondary to Shiga toxin from Escherichia coli is a **rare cause of kidney failure without any recurrence after transplantation.**

- **Atypical HUS**, although rare, has **high rates of recurrence after kidney transplantation**.

- Candidates with no identified genetic mutation are presumed to have an intermediate risk of recurrence.

Disease penetrance even with identification of a pathogenic variant is approximately 50%, suggesting that an environmental factor like **infection, pregnancy, or transplantation** may be a necessary trigger

- **Recurrent aHUS can be a catastrophic event with a high rate of graft loss**. **The outcome**, though, can vary depending on the **complement abnormality**.

Semin Thromb Hemost. 2014;40(4):422-430.

Hemolytic Uremic Syndrome

- Recommend not excluding candidates with HUS due to infection with a Shiga-toxin producing organism, usually E. coli (STEC-HUS), from kidney transplantation (1A).

- Recommended assessment of candidates with suspected **aHUS** for a genetic or acquired defect in **complement regulation or other genetic causes of aHUS** to inform risk of recurrence (1B).

- **Recommend not excluding candidates with aHUS from kidney transplantation** (1B).

- Recommend that if the candidate has **an abnormality in complement regulation** placing them at **high risk of recurrence**, **kidney transplantation should not proceed unless a complement inhibitor can be administered or combined liver-kidney transplant can be performed** (1B).

سوال۴

درصورت نیاز به تجویز واکسن VZV ; پیوند کلیه چه مدت باید به تاخیر افتد ؟

الف. ۲ هفته
ب. ۴هفته
پ. ۶ هفته
ت. ۸هفته

Recipient Vaccination

- Suggested **not excluding** candidates who **do not complete an inactivated vaccine** series prior to kidney transplantation (2D).

- Recommend that the vaccination series be **completed** prior to kidney transplantation for **any live attenuated vaccines** (1B).

- Recommend a **4-week delay in kidney transplantation** if a **live vaccine** is administered (eg, MMR, VZV, shingles, yellow fever, oral typhoid, oral polio vaccine) (1B).

General principles about Inactivated vaccines (IVs)

- Vaccination status should be reviewed in all transplant candidates and recipients.
  - IVs are safe after SOT.
- Vaccination during active treatment for rejection should be avoided.
- IVs should be given at least 2 weeks prior to transplant
- In the post-transplant setting, IVs can be administered starting at 3-6 m post-transplant.

Cancer Screening

Recommend candidates undergo routine cancer screening, as per local guidelines for the general population (1D).

American Cancer Society. Survival Rates for Kidney Cancer.Accessed July 15, 2020,

Potential Kidney Transplant Candidates With Prior Cancer

Recommend that candidates with **active malignancy be excluded** from kidney transplantation **except for those with indolent and low-grade cancers such as :**

- **Prostate cancer (Gleason score ≤ 6)**
- **Superficial nonmelanoma skincancer**
- **Incidentally detected renal tumors (≤ 1 cm in maximum diameter) (1B).**

- Timing of kidney transplantation after potentially curative treatment for cancer is dependent on the **cancer type and stage** at initial diagnosis (Not Graded).

American Cancer Society. Survival Rates for Kidney Cancer.Accessed July 15, 2020,
KDOQI Commentary
AJKD 2021

Plasma Cell Dyscrasias, Monoclonal Gammopathy, and Multiple Myeloma

- **Multiple myeloma**
  - ✓ Suggested that candidates with multiple myeloma **be excluded** from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

- **Monoclonal immunoglobulin deposition disease (MIDD)**
  - ✓ Suggested that candidates with **LCDD** be **excluded** from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).
  - ✓ Suggested that candidates with **HCDD** be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

Plasma Cell Dyscrasias…

❖ AL amyloidosis

- Suggested that candidates with **AL amyloidosis be excluded** from kidney transplantation **unless**

  they have **minimal extrarenal** disease (eg, cardiac amyloid), have received a potentially curative treatment regimen and are in stable remission (2D).

❖ Monoclonal gammopathy of undetermined significance (MGUS)

- Suggested **not excluding** candidates with **MGUS** from kidney transplantation; however, a higher risk of post-transplant lymphoproliferative disease and other hematological malignancies should be considered and discussed with candidates (2D).

- Suggested **not excluding** candidates with **smoldering multiple myeloma** from kidney transplantation; however, a significant risk of transformation into multiple myeloma should be considered (2D).

Conclusion

- Recurrent disease remains an important problem for young transplant recipients who do not have diabetes or autosomal dominant polycystic kidney disease.

- Many patients present at a late stage of CKD with atrophic kidneys and thus lack a definite histologic diagnosis for the kidney disease.

- It is prudent that all such kidney transplant recipients be monitored very closely for proteinuria after transplantation with prompt renal histological diagnosis to characterize the type of recurrent disease.

- Benefits of kidney transplantation have been demonstrated even among patients considered as “high-risk” such as those who are elderly, those with obesity, and those with longstanding diabetes with vascular and coronary artery disease.

Thanks