
Namaste
مرحبا
Willkommen
Bem Vindo
Selamat Datang
Welcome
Bienvenidos
Benvenuti
Welkom
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Croeso
أهلا وسهلا
Bienvenidos
Selamat Datang
Welcome
Willkommen
добре дошъл
Καλώς ήλθατε
Benvenuti
Bem Vindo

- **Proteinuria**
- **Hypertension**

} ***the main risk factors for progression of native kidney diseases***

## Classification of chronic kidney disease using GFR and ACR categories

| GFR and ACR categories and risk of adverse outcomes | | | ACR categories (mg/mmol), description and range | | |
|---|---|---|---|---|---|
| | | | <3 Normal to mildly increased | 3–30 Moderately increased | >30 Severely increased |
| | | | A1 | A2 | A3 |
| GFR categories (ml/min/1.73 m$^2$), description and range | ≥90 Normal and high | G1 | No CKD in the absence of markers of kidney damage | | |
| | 60–89 Mild reduction related to normal range for a young adult | G2 | | | |
| | 45–59 Mild–moderate reduction | G3a[1] | | | |
| | 30–44 Moderate–severe reduction | G3b | | | |
| | 15–29 Severe reduction | G4 | | | |
| | <15 Kidney failure | G5 | | | |

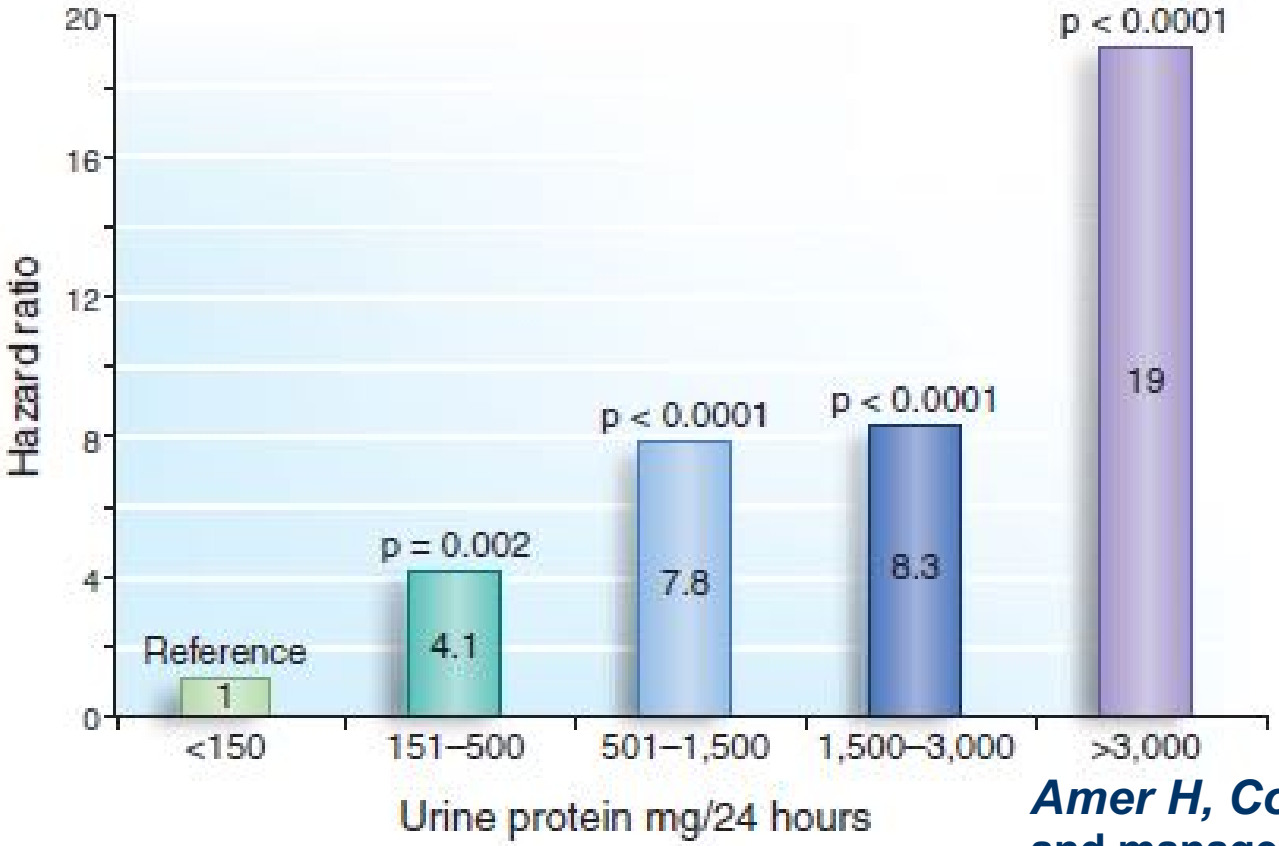
Increasing risk

Increasing risk

**KDIGO 2012**

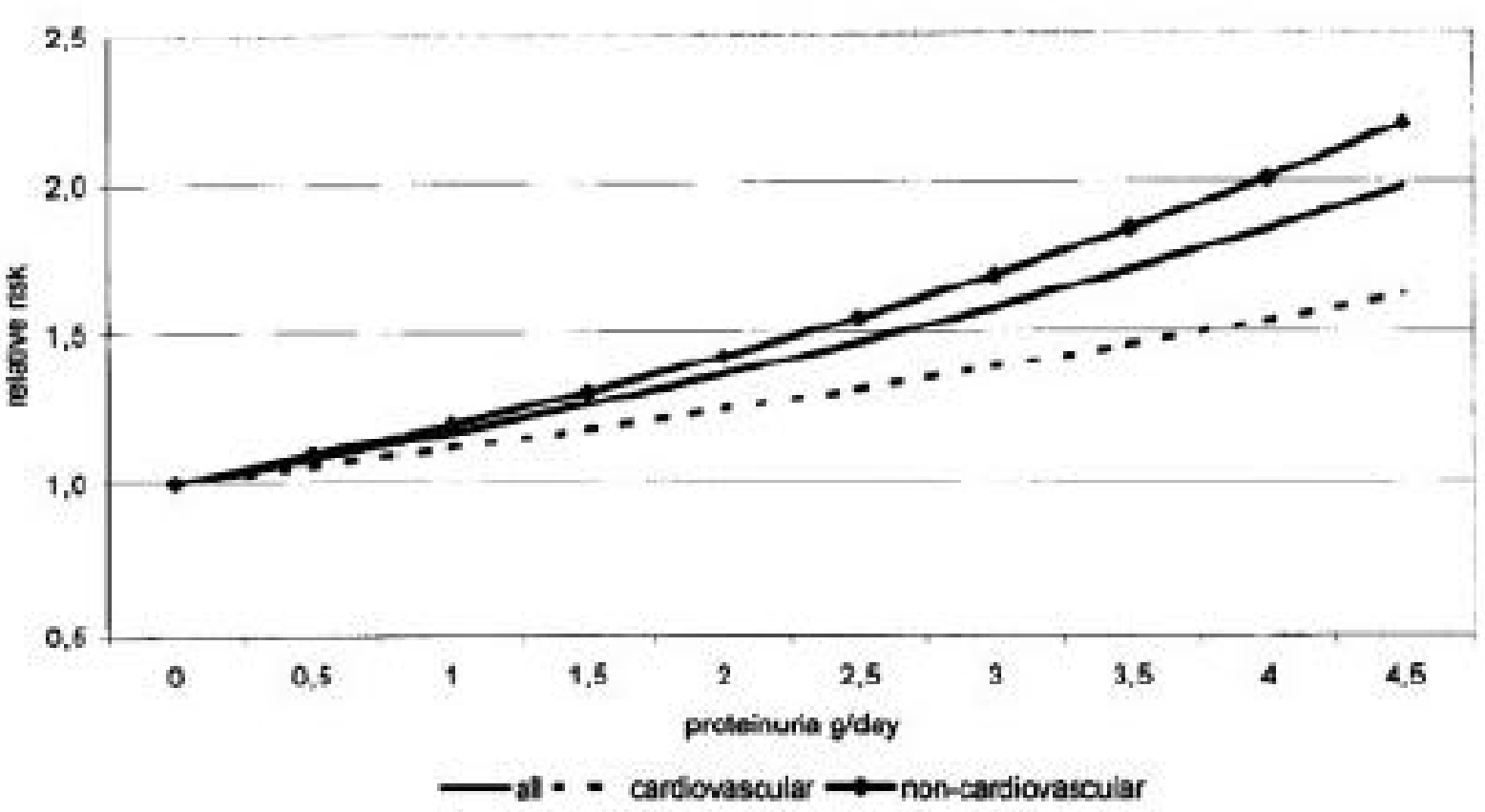
**Part of both definition & classification of CKD**

# Proteinuria 1 year post-tx is associated with ↑ graft loss (after median follow-up 46 Mo)

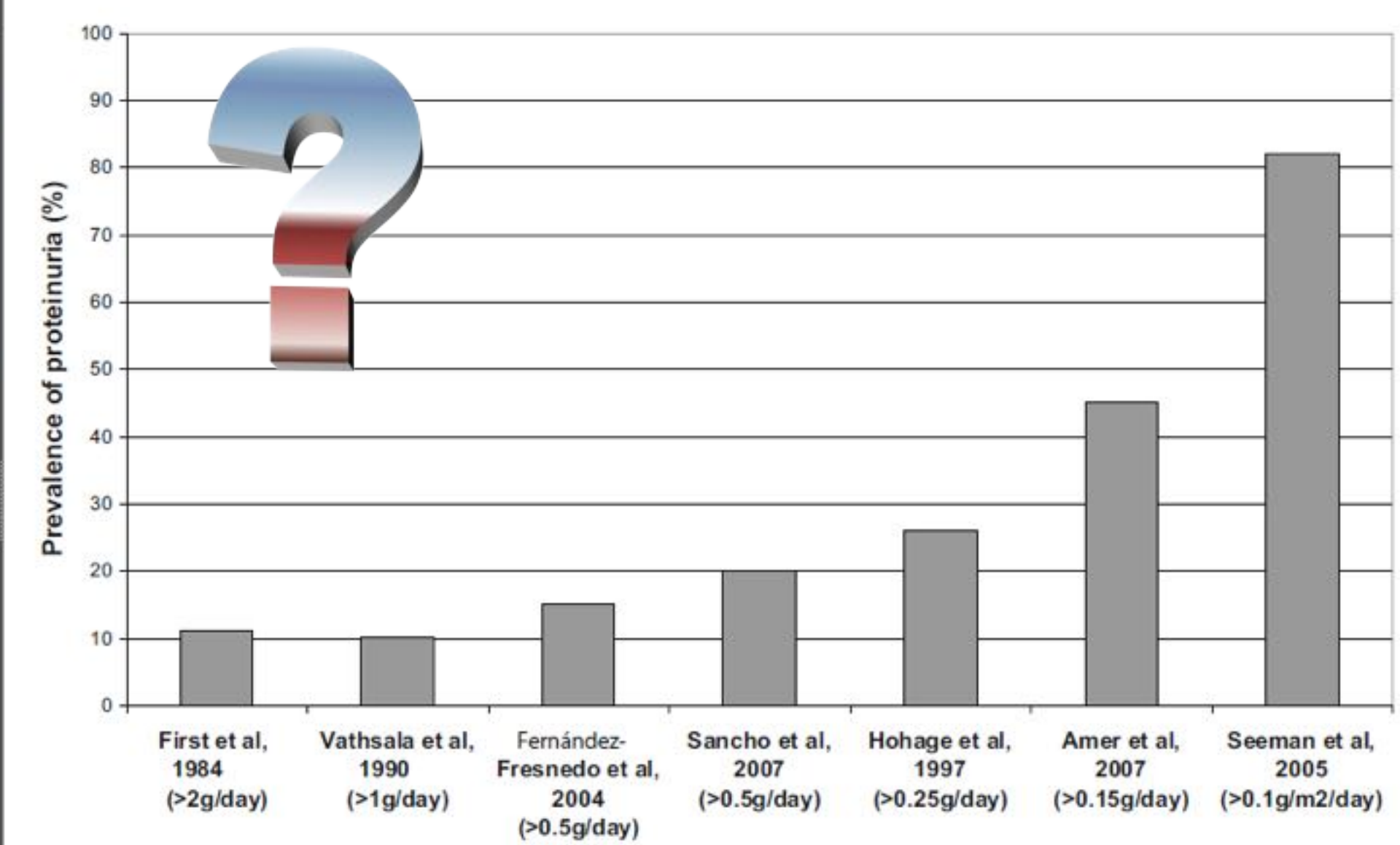



***Amer H, Cosio FG (2009)*** **Significance and management of proteinuria in kidney transplant recipients.** ***J Am Soc Nephrol***

# Proteinuria is associated with ↑ both cardiac & non-cardiac deaths




*Roodnat et al (2001) Proteinuria after renal transplantation affects not only graft survival but also patient survival. Transplantation*




Prevalence of post-transplant proteinuria according the threshold used for definition of proteinuria

***Tomáš Seeman (2015) Management of proteinuria in the transplanted patient. Pediatr Nephrol.***

- **Heavy proteinuria**

  ***>2-3g/d or >0.960 g/m2/day***

  **~10-15% in children & adults**
- **Low-grade proteinuria may be more common in children (40-80%)**
- **Proteinuria from native kidneys falls rapidly after renal transplantation (~4-10wks)**

  ***Persistent or worsening proteinuria is usually indicative of allograft pathology.***

# Post-transplantation proteinuria

- **Common**
- **Serious**

  ***Graft loss, CV events & death***

- **Even low levels of proteinuria are associated with decreased graft survival and as such warrant attention**
- **Later (3 Mo+) & persistent (>3Mo) ➔ poor outcome**

# KDIGO; 2009

**Suggests measuring proteinuria at least**

- **once within the first month**
- **q3 months in the first year**
- **Annually after >1yr**

***-Patients with proteinuria should be monitored more frequently (every 1–3 months)***

***-Idiopathic FSGS should be monitored daily for 2-4 wks & every OP visit in the first yr***

# What constitutes proteinuria?

| Parameter | Collection method | Threshold for pathological finding |
|---|---|---|
| Proteinuria (total) | Spot urine | >20 mg/mmol creatinine, i.e. >200 mg/g creatinine<br>Nephrotic range: >220 mg/mmol creatinine, i.e. >2,200 mg/g creatinine |
| | 24-h urine collection (children) | >96 mg/m$^2$/day<br>Nephrotic range: >960 mg/m$^2$/day |
| | 24-h urine collection (adults) | >150 mg/day<br>Nephrotic range: >2,200 mg/day |
| Albuminuria | Spot urine | >3 mg/mmol creatinine; i.e. >30 mg/g creatinine |
| Alpha-1-microglobulinuria; beta-2-microglobulinuria | Spot urine | >0.55 mg/mmol creatinine |
| | Spot urine | >0.04 mg/mmol creatinine |

***Excretion rate (timed collection)***
***Normalized for body size***

KDIGO

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***Creatinine Normalization ➔ SPOT urine***

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***Protein or Albumin ?***

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***PCR > 200mg/g, ACR > 30mg/g (micro) -300mg/g***

# Glomerular or tubular

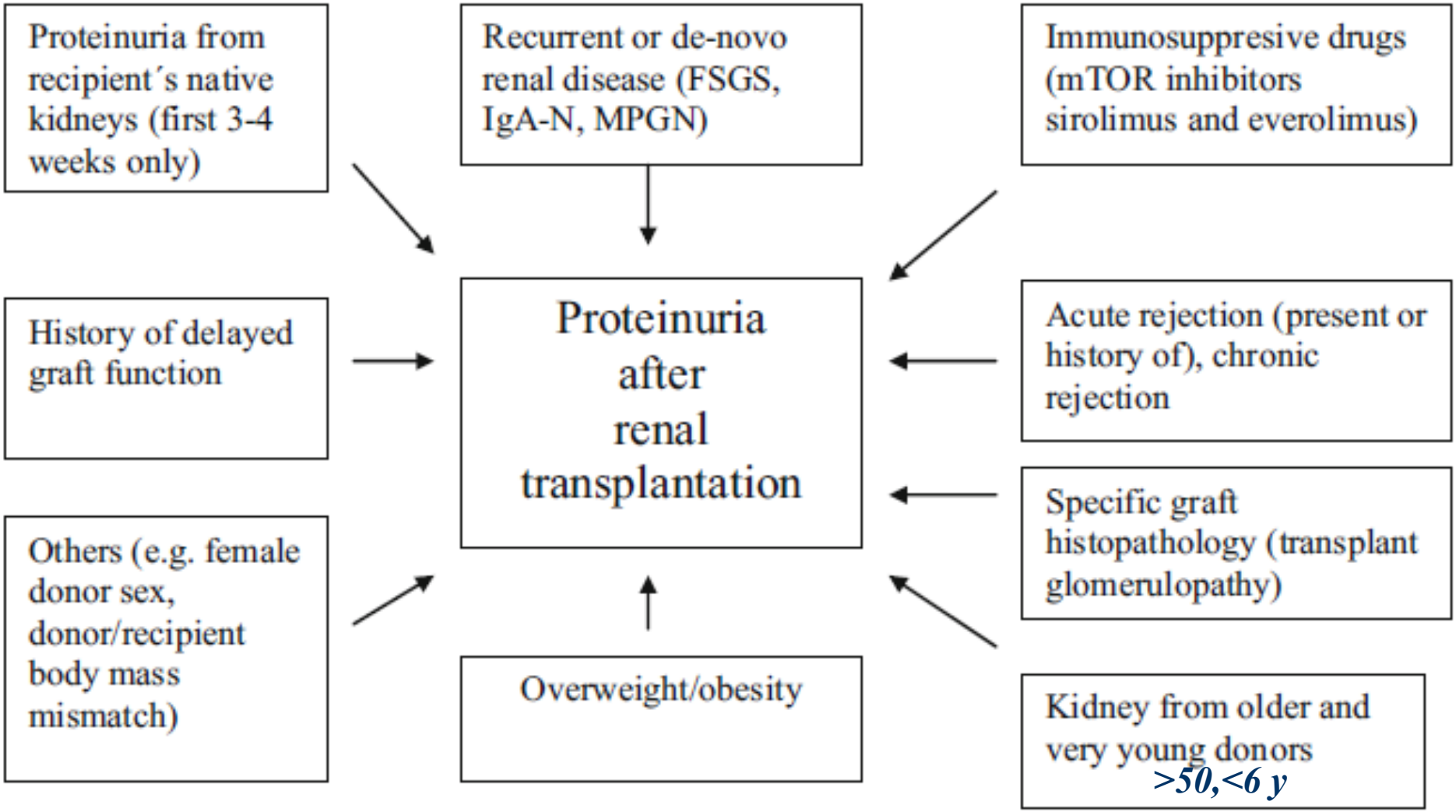
- Glomerular pathology associated with heavy albuminuria in adult studies
- Glomerular: T.glomerulopathy, recurrent/ de-novo glomerulopathy, Hypertension, IF/TA
- Tubular is common (~80%)
- Both associated with impaired graft survival
- Both may have the potential as biomarkers of early AR (controversial)

# POST-TRANSPLANT PROTEINURIA

- What?
- Why?
- Etiology
- Approach
- Antiproteinuric therapy

*Tomáš Seeman (2015) Management of proteinuria in the transplanted patient. Pediatr Nephrol.*

# Causes/ risk factors



# Take Care !!

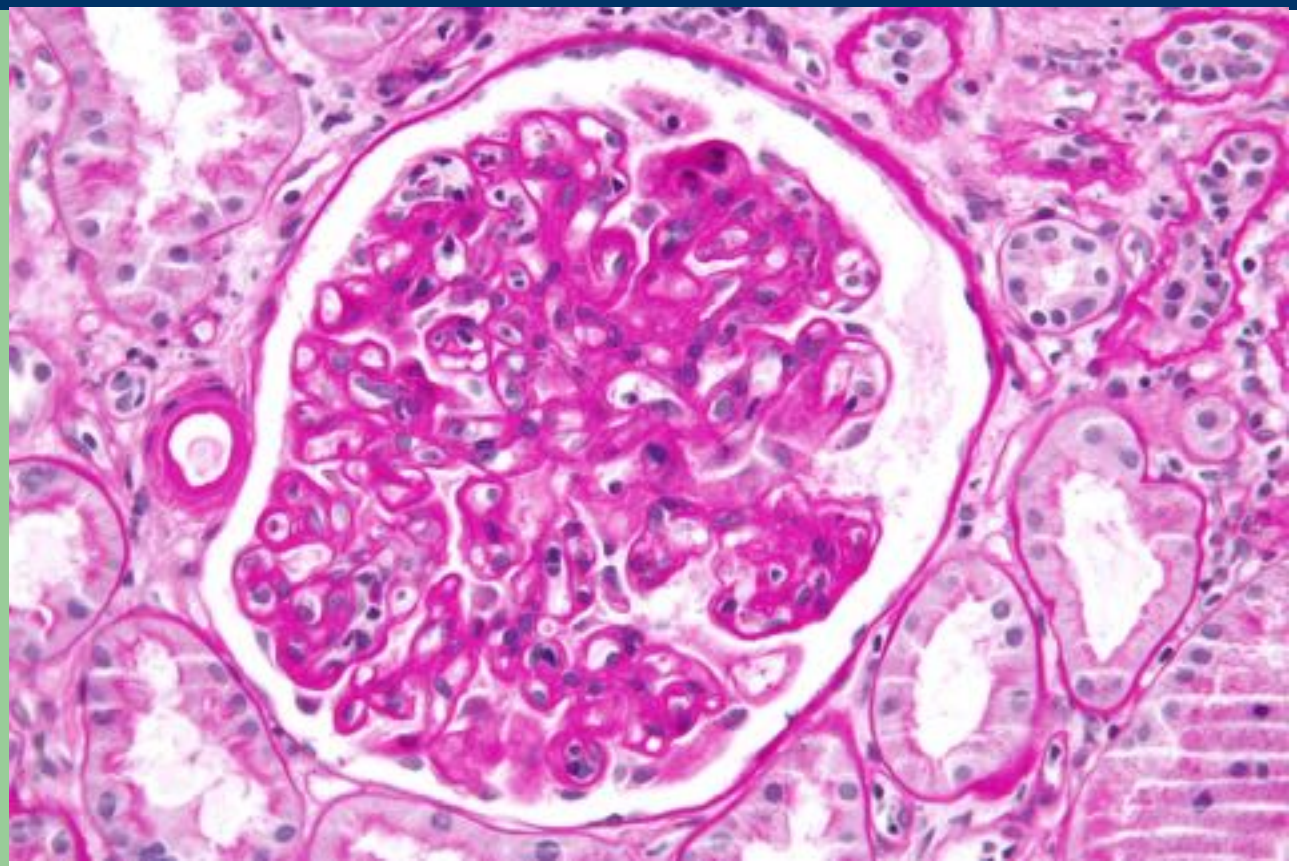
**Identifying the cause & its specific treatment can be both difficult & rewarding**

- ***Cause may be progressive***
- ***Opportunity for specific treatment***

# The common … think of

- Acute-onset proteinuria & ↑ creatinine
  - ➔ AR
- Sporadic FSGS
  - ➔ Recurrence
- Mild persistent or slowly progressive
  - ➔ IFTA, HTN
- mTORi

# Transplant glomerulopathy



***-GBM thickening***
***-Mesangial expansion***
***-Glomerulo sclerosis***

https://commons.wikimedia.org/w/index.php?curid=19497580

# Proteinuria & Rejection

- Glomerular & tubular proteinurias have been proposed as markers of early AR, few days before rising creatinine

  *Results not consistent*
- Specific proteins in urine

**Urine: the fluid biopsy of the kidney**

***(Prof. Ramzi El Baroudi)***

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v5.i4.251

World J Transplant 2015 December 24; 5(4): 251-260
ISSN 2220-3230 (online)


MINIREVIEWS

# Role for urinary biomarkers in diagnosis of acute rejection in the transplanted kidney

Basma Merhi, George Bayliss, Reginald Y Gohh

perforin and granzyme B mRNAs, FOXP3 mRNA, CXCL9/CXCL10 and miRNAs.

# Mining the human urine proteome for monitoring renal transplant injury

Tara K. Sigdel , Yuqian Gao , Jintang He , Anyou Wang , Carrie D. Nicora , Thomas L. Fillmore , Tujin Shi , Bobbie-Jo Webb-Robertson , Richard D. Smith , Wei-Jun Qian , Oscar Salvatierra , David G. Camp II and Minnie M. Sarwal

Kid Int, 2016

**35 proteins were identified for their ability to segregate the 3 clinical groups:**

- 11 urinary peptides for acute rejection (AUC93%)
- 12 for chronic allograft nephropathy (AUC99%)
- 12 for BK virus nephritis (AUC83%).

# Proteinuria & recurrence

- FSGS
- Others

# Proteinuria & mTORi

- Known to be associated with proteinuria
- Low dose with CNI→ less proteinuria
- Proteinuria at initiation related to success of therapy (conversion)

# Proteinuria & mTORi

- Known to be associated with proteinuria
- No specific histological pattern
- Various mechanisms hypothesized:
  - antiproliferative & proapoptotic effects on tubular cells
  - ↓↓ expression of nephrin, podocin and other slit diaphragm proteins

# Hypertension & Obesity

- Both are well established in adults
- Hypertension, esp by ABP monitoring, has been associated with increased proteinuria in children
- Both are MODIFIABLE risk factors
- Both have many other complications

# POST-TRANSPLANT PROTEINURIA

- What?
- Why?
- Etiology
- Approach
- Antiproteinuric therapy

# APPROACH

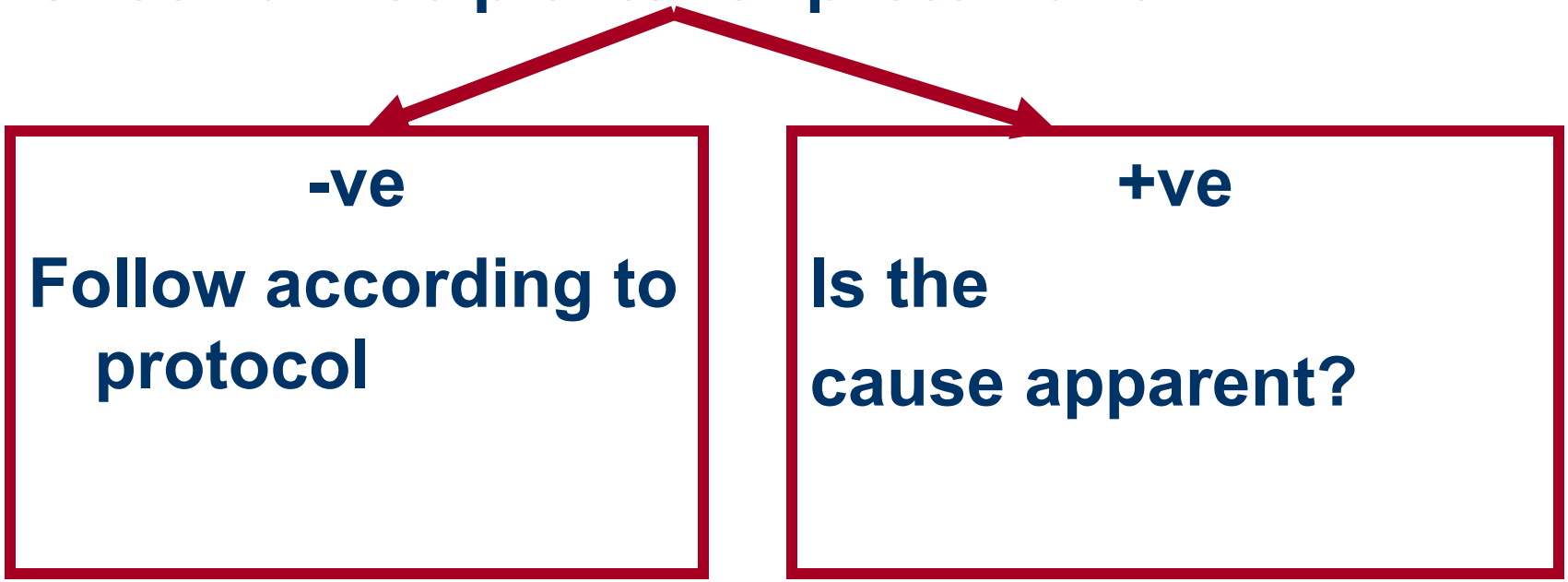
**Check all recipients for proteinuria**

## THRESHOLD

- **Any persistent pathological proteinuria (>150mg/d, >96 mg/m2/d or PCR >200 mg/g)**
- **Nephrotic range proteinuria (any duration)**

# APPROACH

**Check all recipients for proteinuria**



+ve

Is the cause apparent?

# APPROACH

- acute with ↑ creatinine (?AR) ➔ Biopsy
- pt with FSGS ➔ acute neph-range proteinuria (recurrence, Bx NOT necessary)
- mTORi
- Hypertension
- …..

| | n = 34 (%) | Time of onset of proteinuria Median (range) (month) | Proteinuria level at onset Median (range) (mg/m$^2$/h) |
|---|---|---|---|
| Acute rejection | 7 (20) | 24 (2-98) | 14 (7-57) |
| Uncontrolled hypertension* | 6 (17,6) | 4 (1-34) | 14.5 (5-49) |
| Infection-related | 3 (8.8) | | |
| BKV infection | 2 | 3 (2-4) | 10.5 (9.7-11.4) |
| Severe pneumonia | 1 | 52 | 7.9 |
| FSGS recurrence | 2 (5.8) | 1 | 145 (111-179) |
| De novo amyloidosis | 1 (2.9) | 36 | 94 |
| Tubulopathy | 1 (2.9) | 3 | 30 |
| Hyperoxaluria | 1 (2.9) | 1 | 30 |
| Unknown | 13 (38.2) | 1 (1-37) | 10 (6-24) |

*One of the patients also had obesity.

***Yılmaz et al. (2018). Proteinuria in pediatric renal transplant recipients. Pediatr Transplant.***

| | n = 34 (%) | Time of onset of proteinuria Median (range) (month) | Proteinuria level at onset Median (range) (mg/m$^2$/h) | | | |
|---|---|---|---|---|---|---|
| Acute rejection | 7 (20) | 24 (2-98) | 14 (7-57) | 5 | 1 | 1 |
| Uncontrolled hypertension* | 6 (17,6) | 4 (1-34) | 14.5 (5-49) | 3 | 3 | |
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| Hyperoxaluria | 1 (2.9) | 1 | 30 | | | |
| Unknown | 13 (38.2) | 1 (1-37) | 10 (6-24) | 9 | 2 | 2 |

**Outcome: 3 graft losses** remission improvement on-going

*One of the patients also had obesity.

*Yılmaz et al. (2018). Proteinuria in pediatric renal transplant recipients. Pediatr Transplant.*

# APPROACH

Check all recipients for proteinuria

**-ve**

Follow according to protocol

**+ve**

Is the cause apparent?

NO ➔ Unexplained

Follow

Transient/ persistent

# APPROACH

## *GRAFT BIOPSY*

- **Evaluation of unexplained persistent proteinuria, particularly:**
  - ***New-onset***
  - ***Acute deterioration***
  - ***Nephrotic-range***

**Transplant-specific diagnoses:**

**-T.glomerulopathy**

**-Ch. Rejection**

**-De novo GN**

# Treatable causes

Rejection, recurrent FSGS, HTN, drug-associated, infection-associated, ..

# POST-TRANSPLANT PROTEINURIA

- What?
- Why?
- Etiology
- Approach
- **Antiproteinuric therapy**

# Antiproteinuric therapy: ACEi

- **Reduce proteinuria in adults & children**
  - ↓ intraglomerular P
  - Podocyte slit diaphragm preservation
  - Antiproliferative antifibrotic effects
- **Recommended by KDIGO for hypertension in CKD**
- **Can ↓ proteinuria in normotensive patients**

| Class of drugs | Generic name | Recommended daily dose (mg/kg/day, if not indicated otherwise) | Number of daily doses |
|---|---|---|---|
| Angiotensin-converting enzyme inhibitors | Enalapril[a] | 0.08–0.6 | 2× |
| | Ramipril[a] | 1.5–6 (mg/m$^2$/day) | 1× |
| | Fosinopril | 0.1–0.6 | 1× |
| | Lisinopril | 0.08–0.6 | 1× |
| Angiotensin receptor blockers | Losartan[a] | 0.7–1.4 | 1× |
| | Irbesartan[a] | 6–12 years of age: 75–150 mg/day;≥13 years of age: 150–300 mg/day | 1× |
| | Valsartan | 1–2 | 1× |
| | Candesartan[a] | 0.16–0.5 | 1× |

[a] Drugs used in the clinical setting in children after renal transplantation, based on published studies

# ACEi + ARBs

- Combination has additional 30-40% benefit in NON-TRANSPLANTED children on maximal ACEi
- Cautions with ARBs
- K & GFR

# Control of hypertension

**Control of BP to <75$^{th}$ percentile recommended for**

- **Adult transplant recipients (KDIGO)**
- **Non-transplant children with CKD (Eur Society of HTN)**

# Role of vitamin D?

- Suggested to reduce proteinuria in CKD
- Not studied in transplanted children

# Treatment targets

- No direct evidence
- No published data

But there ARE DATA to support than low grade proteinuria affects outcome

- Attempt to reach NORMAL

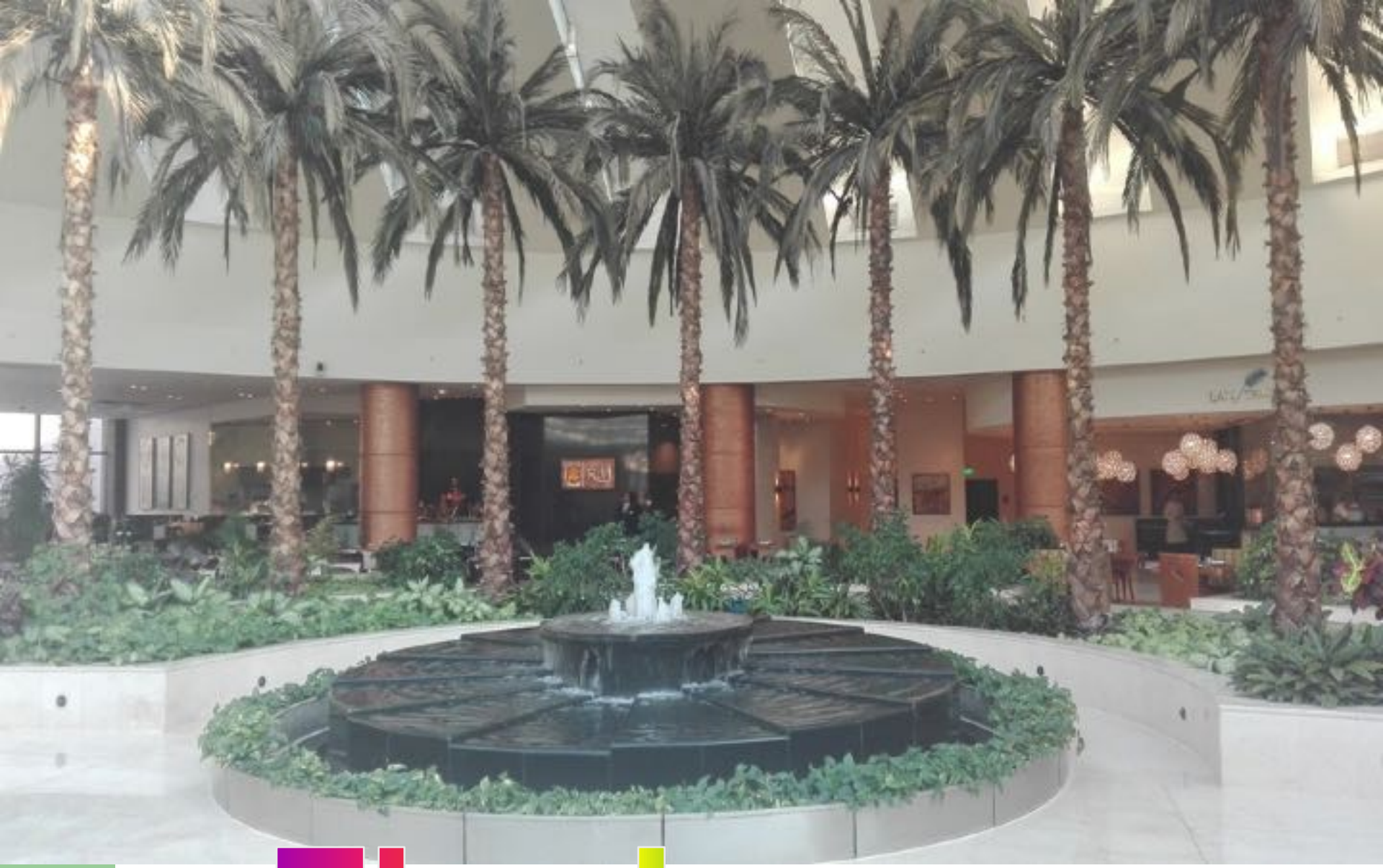
***<20 mg/mmol or <200mg/g creatinine***

# Remaining questions

- Validation of PCR in those with reduced GFR
- Role of urinary proteomics
- Direct evidence for intervention thresholds & treatment targets for proteinuria & HTN
- Direct evidence for long-term benefit (vs risk?) of antiproteinuric therapies

# Conclusions

- Proteinuria after transplantation is common
- It adversely affects graft outcome
- Patients should be monitored for proteinuria
- Apparent causes include rejection, mTORi, recurrent/ de novo glomerulopathies & HTN
- Biopsy may be needed
- Antiproteinuric therapy has a role
- HTN & obesity must be controlled



# Thank you

1

## Pathological proteinuria is associated with a urinary protein/ creatinine ratio more than

A 2g/g

B 500mg/g

C 200mg/g

D 30mg/g

2

# Proteinuria is most characteristically associated with the following drug

A Captopril

B Tacrolimus

C Sirolimus

D Mycophenolate

3

# Of the following conditions, acute onset of post-transplant proteinuria associated with increasing creatinine is suggestive of

A acute rejection

B de novo FSGS

C interstitial fibrosis/ tubular atrophy

D end-stage graft failure