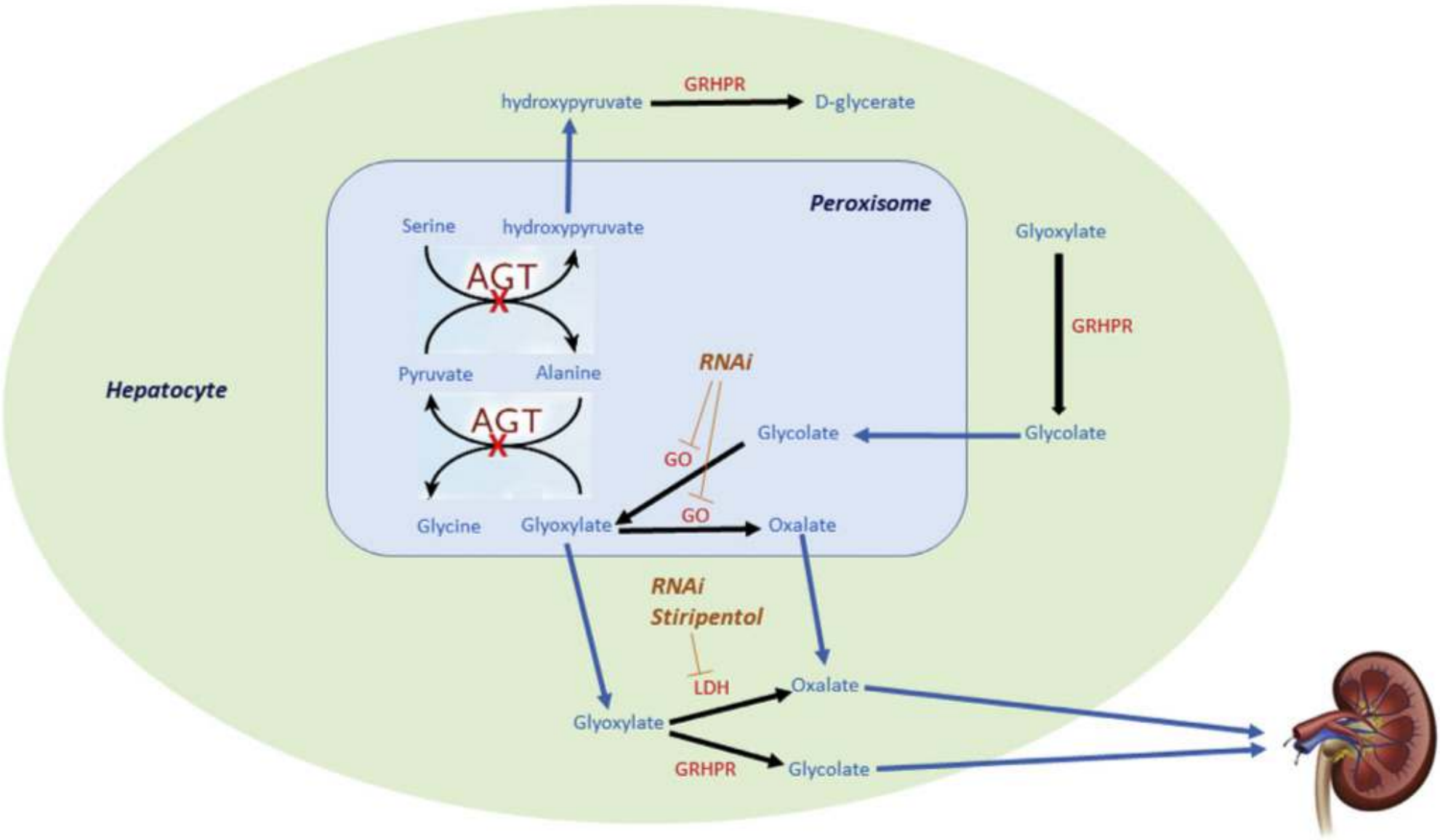
- Primary hyperoxalurias are a rare AR inborn errors of glyoxylate metabolism that characterized by the overproduction of oxalate, which lead to accumulation of oxalate within the body
- The kidney is the prime target for oxalate deposition, as it can not be metabolized and excreted in the urine
- Hyperoxaluria is the hallmark of any kind of PH

Oxalate Metabolism

- Oxalate is a poorly soluble end-product of the metabolism of a number of amino acids, particularly glycine, and of other compounds such as sugars and ascorbic acid
- The immediate precursors of oxalate are glyoxylate and glycolate
- The main site of synthesis of glyoxylate and oxalate is the liver peroxisome



AGT: alanine:glyoxlate transaminase
LDH: lactic acid dehydrogenase
GO: glycolate oxidase

PRIMARY HYPEROXALURIA TYPE 1

- PH1 was first described in the literature by a French physician Lepoutre in 1925
- But the significant research on the disease did not begin until 1950s and the molecular genetic basis was not determined until the cloning of the AGXT gene in 1990 by Danpure and his colleagues

Prevalence

- PH1 is the most common form of PH (1:60,000 to 1:120,000 live births) .
- The prevalence of PH1 ranges from 1-3/M depending on the population studied and methods of ascertainment
- It is responsible for less than 0.5% of ESRD in children in Europe versus ~10% in MENA (reflecting high rates of consanguinity)

Alfadhel ,Alhasan ,Ped Neph 2023
Danpure Am J Nephrol. 2005
Al-Eisa Transplant proc

Genetics:

- Human liver AGT gene and genomic DNA have been cloned and sequenced; the normal AGT gene is a single copy gene that is located on chromosome 2q37.3

- More than 150 mutations have been identified in the AGXT gene
- These mutations result in three different expressions of AGT protein and its activity:

1. Absence of both immunoreactive AGT protein and AGT catalytic activity, which occurs in about 40% of patients.
2. Presence of immunoreactivety and absence of AGT catalytic activity, which occurs in about 15% of patients.
3. Presence of both immunoreactivety and catalytic activity but at levels that are 50% below normal values. (mistargeting phenotype)

Genotype/phenotype correlation

- PH1 is a heterogeneous disease with variable expression in patients and even in family members with the same genotype.
- There has been speculation that environmental factors or modifier genes are responsible for the range of phenotypes within a single pedigree.

Therapeutics and Clinical Risk Management

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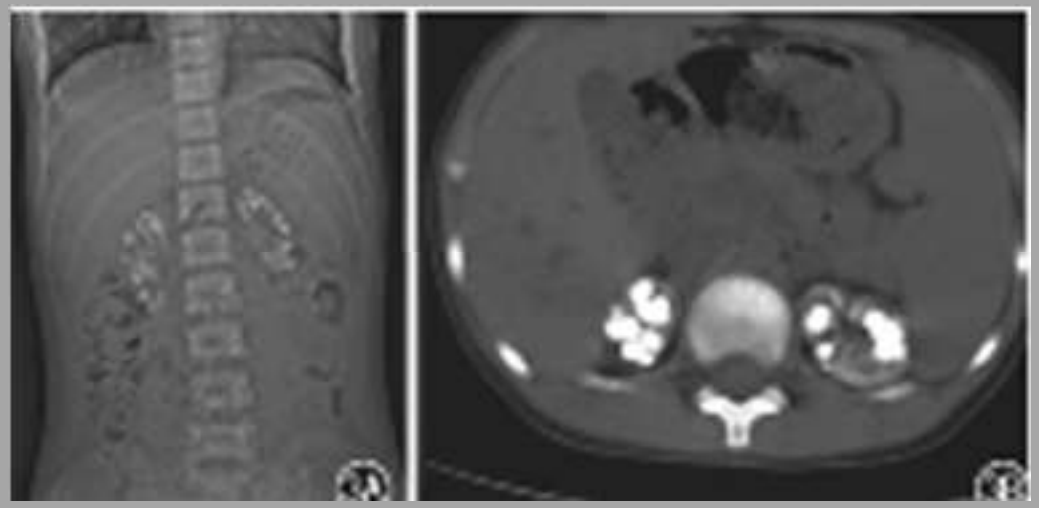
CASE REPORT

Extreme intrafamilial variability of Saudi brothers with primary hyperoxaluria type 1



- There appears to be some correlation between genotype and phenotype for specific mutations of the AGXT gene
- Patients with c.508G>A and c.454T>A mutations have significant pyridoxine responsiveness resulting in better long-term outcomes

Clinical Kidney Journal, 2022, vol. 15
Kidney Int. 2010;77(5):443

Pediatric Nephrology (2023) 38:1801–1810
https://doi.org/10.1007/s00467-022-05784-y

ORIGINAL ARTICLE

Check for updates

Clinical and molecular characterization of a large primary hyperoxaluria cohort from Saudi Arabia: a retrospective study

Majid Alfadhel[1,2] · Muhammad Umair[2] · Malak A. Alghamdi[3] · Khalid Al Fakeeh[4] · Abdullah T. Al Qahtani[4] · Afrah Farahat[5] · Mohamed A. Shalaby[6] · Jameela A. Kari[6] · Rupesh Raina[7] · Pierre Cochat[8] · Khalid A. Alhasan[9,10]

- Consanguinity was present in 88%
- Missense variants were the most commonly observed variants (48%), followed by frame-shift duplication variants (28%).
- AGXT gene variants [c.33dup; p.(Lys12GlnfsX156), c.187G > C; p.(Gly63Arg)] were observed in 14 cases (56%)

Clinical Manifestations

- PH1 has five general clinical presentations:
  1. A rare infantile oxalosis: Infants generally present before six months of age with nephrocalcinosis and renal impairment
  2. A rare late-onset form with occasional stone passage in late adulthood
  3. A rare condition where PH1 is diagnosed after failed isolated renal transplantation

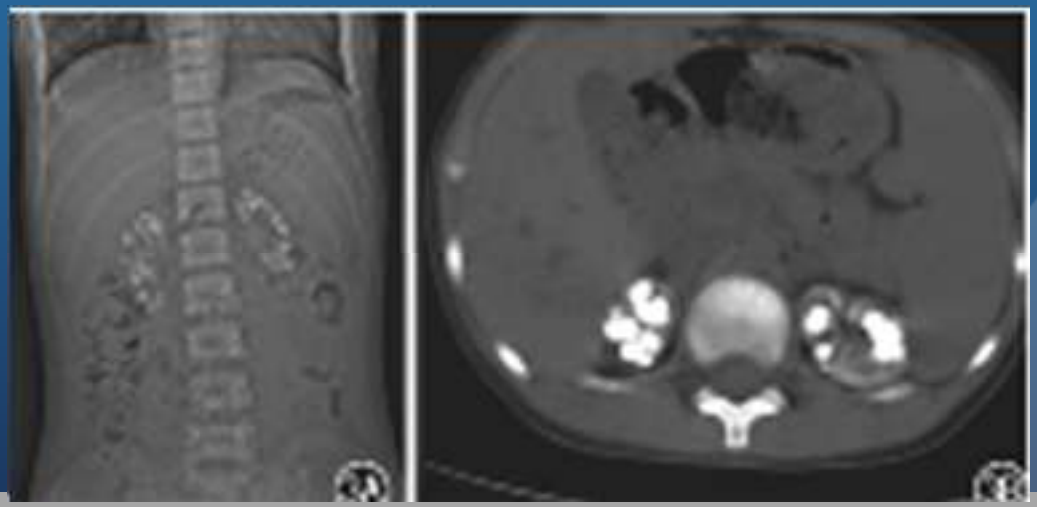
4. A symptomatic diagnosed after family screening
5. The most common form with recurrent urolithiasis and progressive renal failure leading to a diagnosis of PH1 in childhood or adolescence

1-Renal Involvement

- PH1 presents with symptoms referable to the urinary tract :

  loin pain, hematuria, UTI, passage of stones, uremia, metabolic acidosis, growth delay, anemia.

- Nephrocalcinosis, urolithiasis ,multiple, bilateral, and radiopaque-are composed of calcium oxalate.

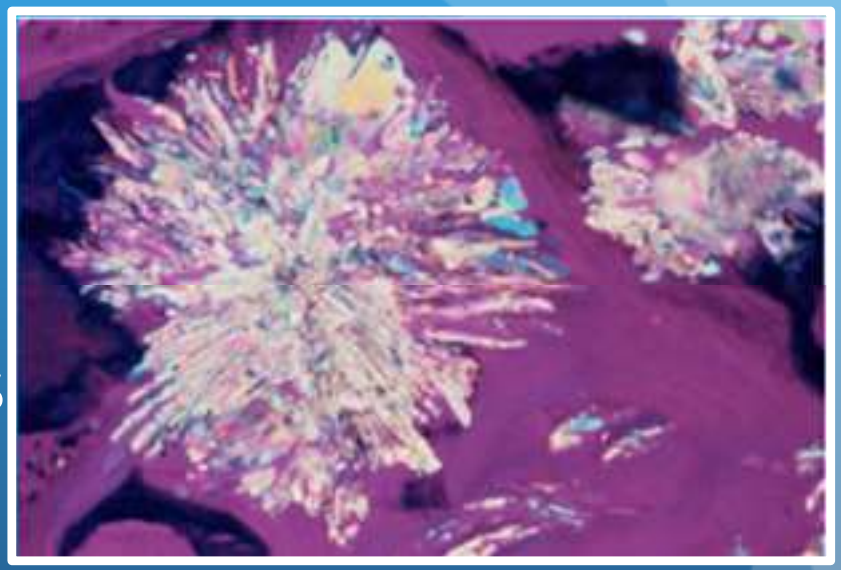


- The Median age at presentation is 5 years,ESRF is reached by 25 years in 50% of patients .
- The infantile form often presents as a life-threatening condition because of rapid progression to ESRF due to both early oxalate load and immature GFR & 80% develop ESRF by 3 years

2-Extrarenal Involvement

- When GFR falls to below 40 to 50 mL/min per 1.73 m^2, a critical staturation point for plasma oxalate (Pox > 30 to 50 µmol/L) (N < 7 µmol/L). Oxalate deposition occurs in many organs .
- Bone is the major compartment of the insoluble oxalate pool.
- Bone oxalate content 15- 910 µmol /g bony tissue
  In ESRD pt. without PH1 2-9 µmol/g

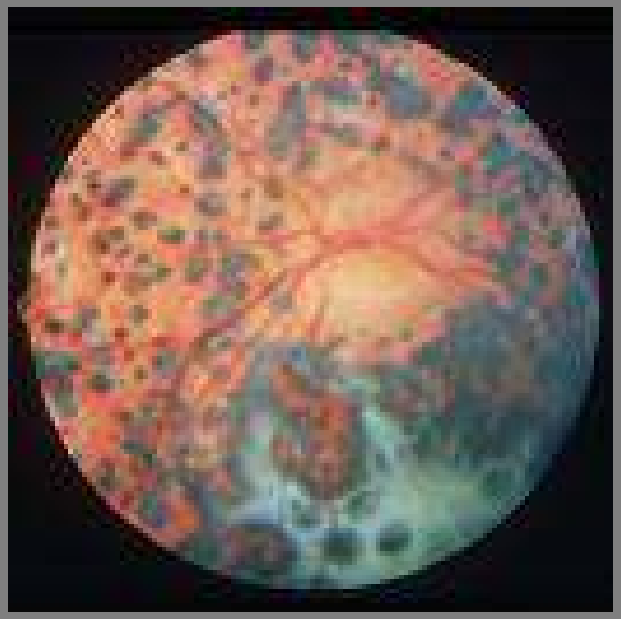
- Calcium oxalate deposition in the bone cause oxalate osteopathy that leads to pain, erythropoietin-resistant anemia, and spontaneous fractures.

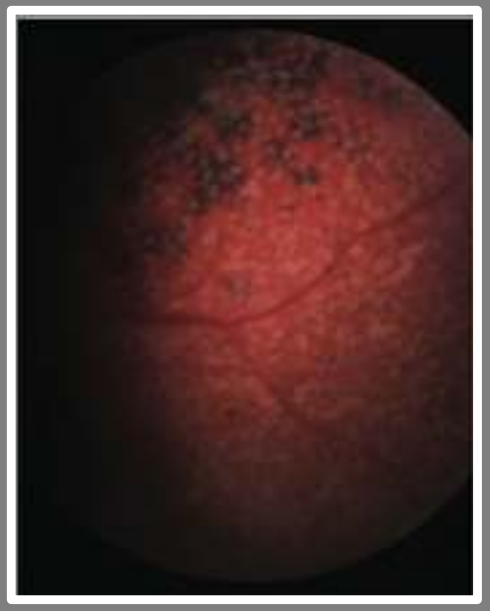


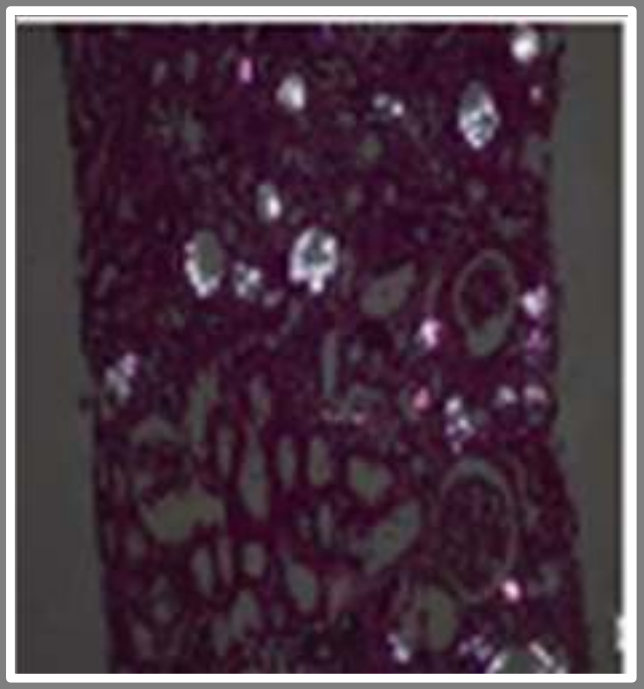
Bone biopsy examined under polarized light shows calcium oxalate crystals

Systemic involvement includes also many other organs because of progressive vascular lesions:

Tissue	Clinical Symptomes
Heart	**cardiomyopathy,arrhythmias**
Joints	**synovitis, chondrocalcinosis**
Skin	**calcinosis cuties, livedo reticularis**
Soft tissues	**peripheral gangrene**
Retina	**flecked retinopathy**
Other Visceral lesions	**hypothyroidism**







Numerous oxalate crystals deposited in dilated tubular lumens using a polarized filter

Ajzensztejn, Arch Dis Child 2007
Chang Chin Med J 2009

Diagnosis

- The diagnosis of PH should be suspected in children with any of the following findings:
  - Recurrent stones formation, especially in a patient with oxalate crystals in the urine sediment
  - Nephrocalcinosis
  - Marked hyperoxaluria in the absence of GI disease, ingestion of mega dose vitamin C
  - Family history

- Hoppe B :a survey of American nephrologists, a delay in the recognition of PH was noted in over 40% of patients ,30 % of the patients had ESRD at the time of diagnosis

- The diagnosis of PH type 1 is made in the following step-wise approach:
  - A clinical diagnosis based on findings suggestive of PH
  - Metabolic screening that demonstrates markedly increased urinary oxalate and glycolate excretion is strongly supportive of the diagnosis of PH1

- In patients with GFR <30 ml/min/1.73m2 or on dialysis , the biochemical assessment may include plasma oxalate or glycolate to creatinine ratio, and oxalate or glycolate measurement in dialysate
- The plasma oxalate levels are much higher in patients with PH1 compared to those with other causes of ESRD (100 -200 versus 40s micromol/L)

- The diagnosis is confirmed by molecular genetic testing
- The diagnosis can also be confirmed by a liver biopsy demonstrating absent or significantly reduced AGT activity

- Family history
- 24 hours urinary oxalate (UOx)
- Pox levels in ESKD
- Genetic testing

Prenatal diagnosis

- Prenatal diagnosis can be performed from DNA obtained from chorionic villi or amniocytes
- It allows the identification of normal, affected and carrier fetuses.

Cochate P Ped. Nephrol 2006

CURRENT MANAGEMENT AND TRANSPLANT STRATEGIES
(before RNAi era, widely used)

A-Supportive Treatment

- The aims are to decrease oxalate production and to increase the urinary solubility of calcium oxalate.
- The risk of stone formation is increased when urine oxalate exceeds 0.4 to 0.6 mmol/L, especially if urine calcium exceeds 4 mmol/L.

1) Maintaining a high fluid intake:

> 2-3 L/m^2/day, sometimes requiring a NGT or gastrostomy in infants

2) Calcium-oxalate crystallization inhibitors:

K Citrate , Mg citrate/oxide
(keeping urine pH ≥ 7)

3) Pyridoxine (cofactor of AGT):

- The dose increased up with stepwise to10 - 20 mg/kg
- Pyridoxine sensitivity can be detected by monitoring of both oxalate and glycolate
- Large doses of pyridoxine might induce sensory neuropathy.

4) Restriction of dietary oxalate intake:

- ERKNet and OxalEurope : Recommend that patients with PH receive a balanced diet, avoiding only foods that contain extremely high levels of oxalate

Nature Reviews Nephrology |March 2023

B-Stone Management:

- Management of stones in patients with PH is challenging
- The treatment of stones should avoid open surgery because further renal lesions will alter GFR
- It is suggested to do PCNL and ureteroscopy instead of ESWL as intervention to remove stones in PH

C-Renal Replacement Therapy

1) Dialysis

- With advancing CKD, urinary clearance of oxalate decreases and POx levels rise.
- Calcium oxalate supersaturation (ßCaOx) is reached when POx levels exceed 30–45 µmol/L; thereafter, significant systemic oxalate deposition occurs, resulting in oxalosis

- Dialysis is most often used as a bridge to liver–kidney transplantation.
- It may be required post-operatively to protect the newly transplanted kidney from systemic stores that can cause hyperoxaluria, nephrolithiasis and nephrocalcinosis

- Dialysis should commence at this point to maintain POx at levels less than the βCaOx, even if the GFR exceeds levels for typical dialysis initiation
- Conventional dialysis is unsuitable in patients who have reached ESRF ?????

- In such patients, Pox levels range between 100 and 200 µmol/L (normal is less than 7 µmol/L)
- End. Oxalate generation 4-7 mmol/1.73 m2/d
  Conv. HD removal 1- 4 mmol/1.73 m2/d

Nature Reviews Nephrology |March 2023
Kidney International Reports (2020)

- The challenge is to keep pre-dialysis Pox below 50 µmol/l in order to limit the progression of systemic oxalosis
- The lower clearance of POx with PD versus HD (7.14 versus 115.6 mL/min/1.73 m2) necessitates the use of the latter as a primary dialysis modality.
- Daily hemodialysis (4 hours per session) using high-flux membranes would be required.
- Sometimes in combination HD with PD is required

Clinical Kidney Journal, 2022
Am J Nephrol. 2014

- It is recommended using a maximal blood flow (>150–200 cm3/min/m2 BSA)
- It is recommended to personalizing the dialysis regimen based on clinical observations of oxalosis and POx values, aiming to keep POx in the range of values for patients with kidney failure without PH (50–70 μmol/l)
- Note: reference values for patients on dialysis without PH may vary between laboratories, and residual diuresis should be taken into account

- In a study (Illies, F. et al) , found that administration of six, 4.5 h sessions of HD per week with a high-flux filter achieved the removal of 24 mmol/1.73 m2 per week, which approaches estimates of weekly oxalate production (28-37.7 mmol per week)

Kidney Int. 70,1642–1648

D-Organ Transplantation

- PH1 is one of the most challenging issues for both adult and pediatric nephrologists worldwide.

Three different transplant options are available.

- CLKT/SLKT
- Isolated liver transplantation
- Isolated renal transplantation

The optimal transplantation strategy for patients with PH type 1 remains uncertain

Kidney Transplantation

- Isolated elective kidney transplantation is no longer recommended in pyridoxine-unresponsive patients because, the experience of renal transplantation alone in PH had been relatively disappointing
- May be an option in patients who respond to pyridoxine and have minimal oxalate deposition

J Scheinman Ped Neph 2010
Bergstralh AJT 2010
Niaudet P Uptodate 2011

There are number of manipulations have improved subsequent outcome of isolate renal transplantation:

- Aggressive preoperative dialysis (as often as six days per week) to reduce urinary and systemic oxalate levels
- Consideration of early transplantation once the GFR falls 30 mL/min to minimize systemic oxalate accumulation
- Aggressive medical management post-transplant
- Administration of pyridoxine

Cochate P. Current. Opin.OT 2010
Niaudet P Uptodate 2011

Isolated Liver Transplantation

- **Isolated liver transplant might be the considered initial therapy in selected patients before advanced renal failure has occurred GFR 60 - 40 mL/min/1.73 m^2**
- It has Strong biochemical rationale, but raises ethical controversies, especially when the GFR is superior to 60ml/min/1.73m2

- The native liver need to be remove ;exposing the patient to the known risk factors associated with liver transplantation and removal of the native liver, which is totally normal except for the absence or reduction in AGT activity

Combined liver-kidney transplantation

- Combined L KTx has increasingly become the treatment used in children with PH1 with progressive renal disease
- Simultaneous Tx : Immunological benefit
- Sequential Tx (LTx followed by KTX): Biochemical benefit

Am J Nephrol 2005

- Combined transplantation should be planned when the GFR ranges between 20 to 40 mL/min/1.73 m^2 because, at this level, oxalate retention increases rapidly.

- PH1 is one of the most frequent indications for CLKT, both in adults and children
- The results are encouraging, report from the US Renal Data System showing 3- and 5-year death-censored graft survivals after CLKT of 95% and 78%, respectively

- In CKD stage 5 or chronic dialysis, when systemic oxalosis is more intense, sequential transplantation can be another option: first the liver followed by hemodialysis to decrease systemic oxalate storage and then the kidney
- Choosing between combined and sequential liver- kidney transplantation remains controversial

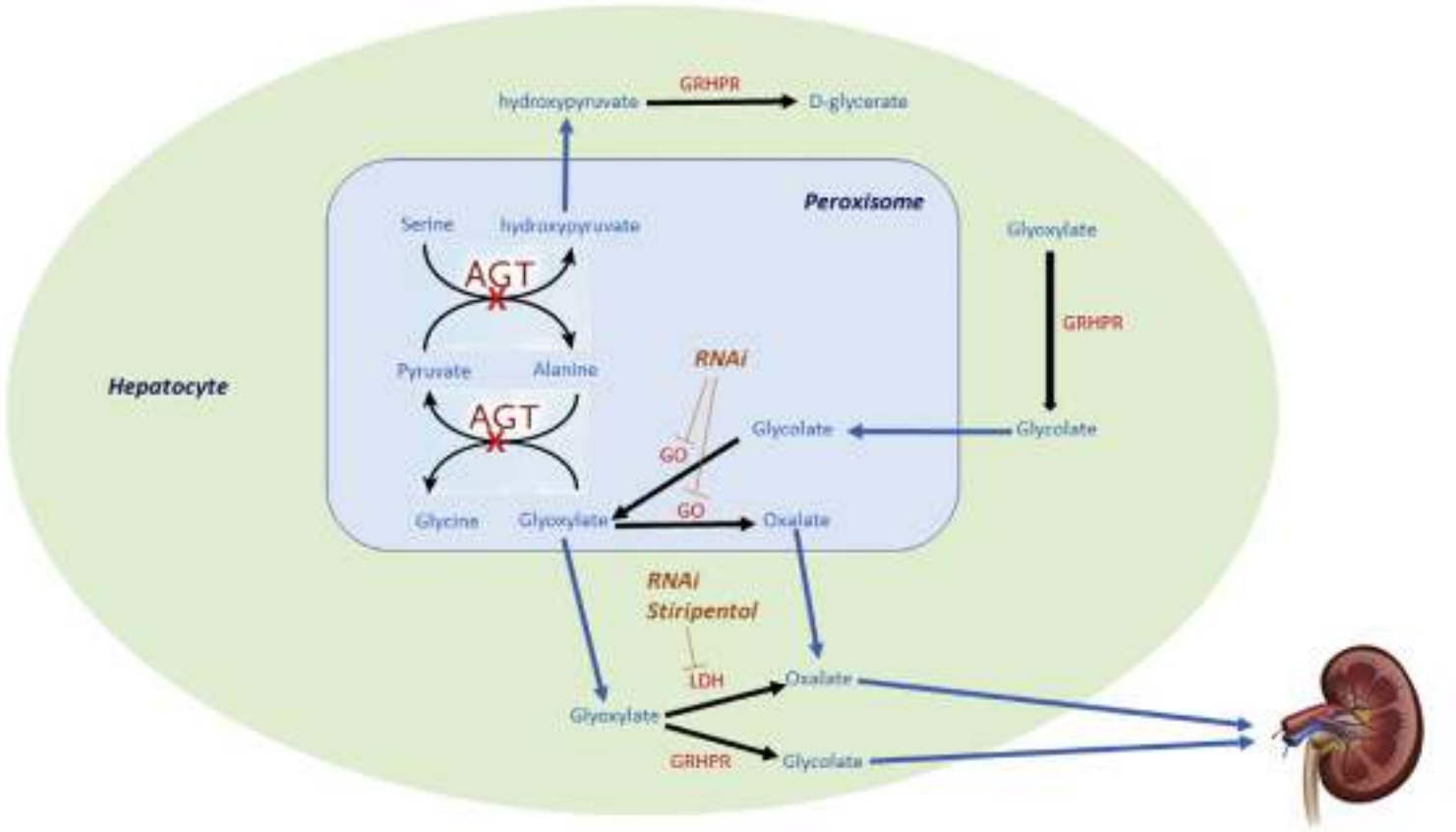
LIMITATIONS OF CURRENT STRATEGIES:

- The main issue is the need for liver transplantation, which until now was the only way to cure the liver metabolic defect.
- Liver transplantation is associated with many risk in addition to worldwide organ shortage

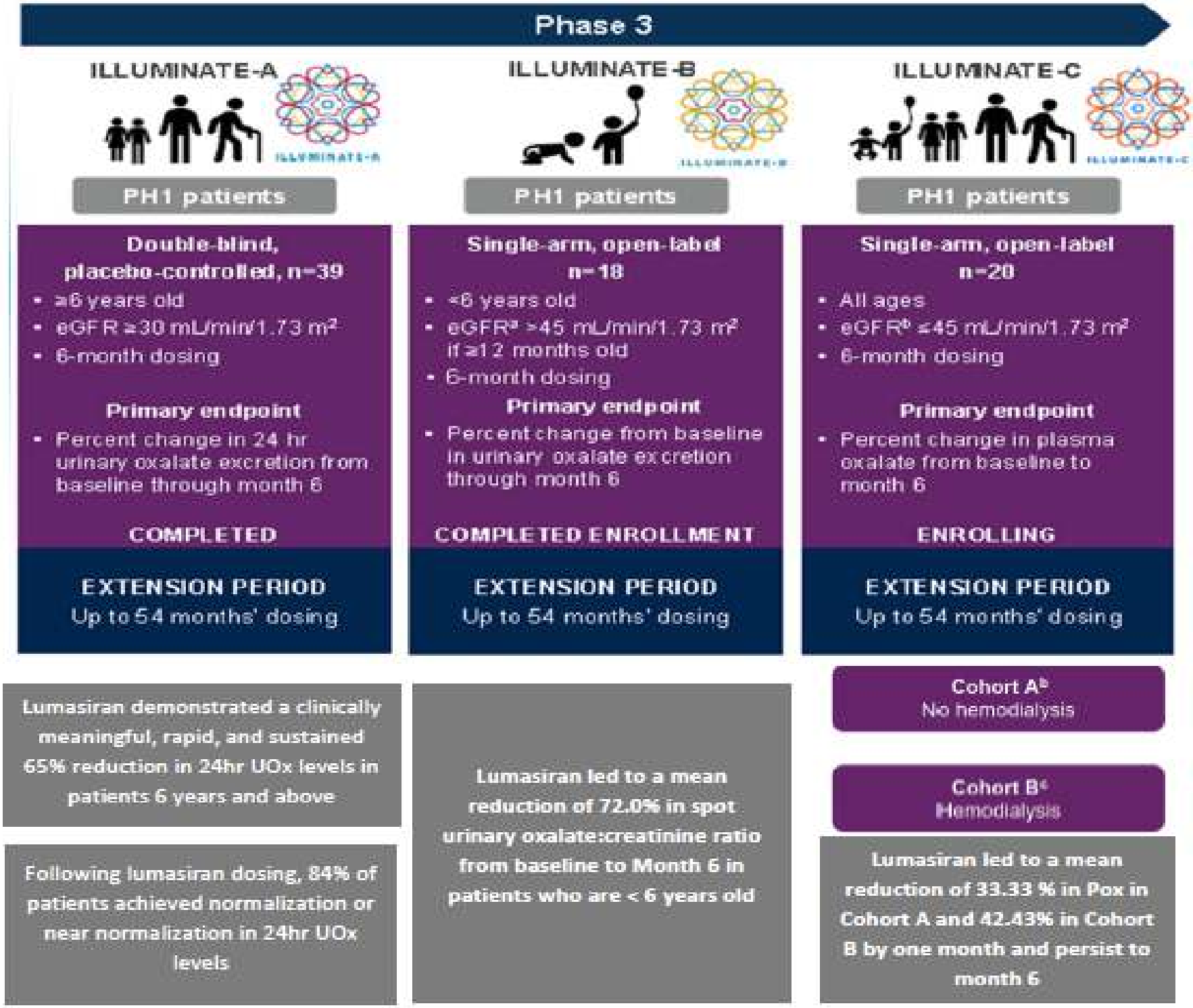
MANAGEMENT IN THE ERA OF RNAi Therapy

- Until very recently, treatment of PH1 was supportive, burdensome to patients and only partly effective
- New therapies, particularly those based on RNAi, have shown promise in reducing oxalate production in patients with PH1, at least in the short term.

- Emerging data that demonstrate clinical efficacy suggest that these drugs may indeed revolutionize the management of PH1 in the near future.
- Two RNAi therapies are now available for patients with PH1
- Lumasiran (Oxlumo; Alnylam) has approved by the EMA and FDA

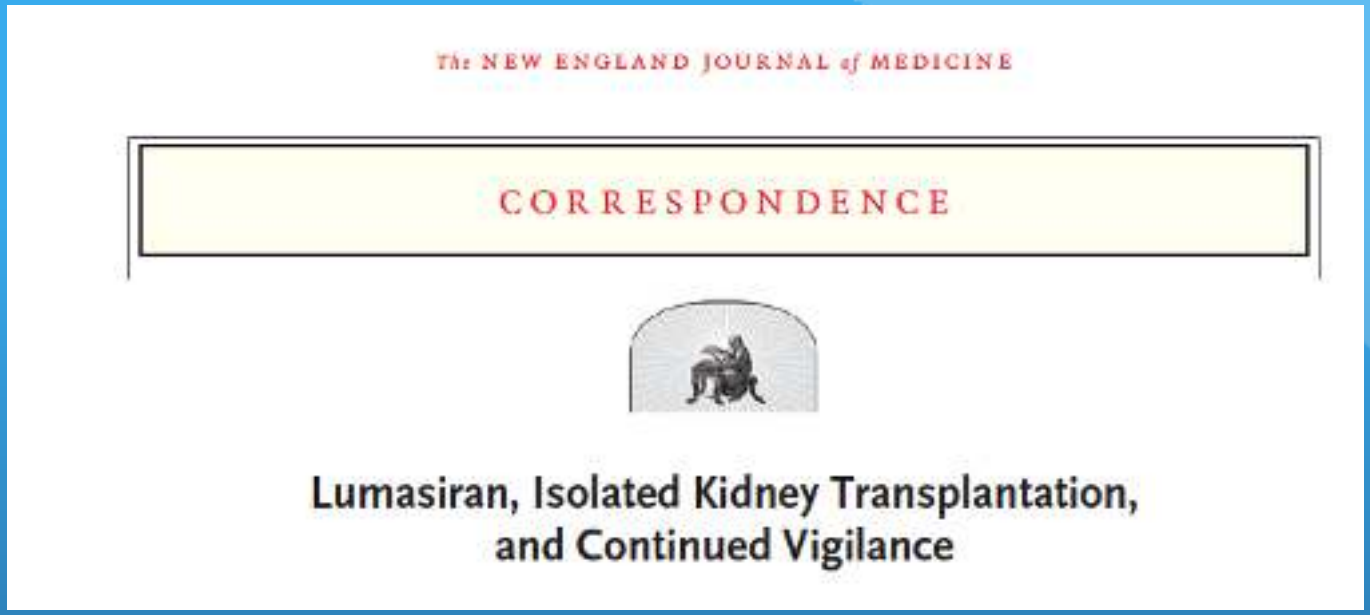


- Lumasiran is designed to silence the gene that encodes the enzyme glycolate oxidase, which catalyses the conversion of glycolate into glyoxylate.


Phase 3
ILLUMINATE-A
PH1 patients
Double-blind, placebo-controlled, n=39
• ≥6 years old
• eGFR ≥ 30 mL/min/1.73 m²
• 6-month dosing
Primary endpoint
• Percent change in 24 hr urinary oxalate excretion from baseline through month 6
COMPLETED
EXTENSION PERIOD
Up to 54 months' dosing
Lumasiran demonstrated a clinically meaningful, rapid, and sustained 65% reduction in 24hr UOx levels in patients 6 years and above
Following lumasiran dosing, 84% of patients achieved normalization or near normalization in 24hr UOx levels
ILLUMINATE-B
PH1 patients
Single-arm, open-label n=18
• <6 years old
• eGFR[a] >45 mL/min/1.73 m² if ≥12 months old
• 6-month dosing
Primary endpoint
• Percent change from baseline in urinary oxalate excretion through month 6
COMPLETED ENROLLMENT
EXTENSION PERIOD
Up to 54 months' dosing
Lumasiran led to a mean reduction of 72.0% in spot urinary oxalate:creatinine ratio from baseline to Month 6 in patients who are < 6 years old
ILLUMINATE-C
PH1 patients
Single-arm, open-label n=20
• All ages
• eGFR[b] ≤45 mL/min/1.73 m²
• 6-month dosing
Primary endpoint
• Percent change in plasma oxalate from baseline to month 6
ENROLLING
EXTENSION PERIOD
Up to 54 months' dosing
Cohort A[b]
No hemodialysis
Cohort B[c]
Hemodialysis
Lumasiran led to a mean reduction of 33.33 % in Pox in Cohort A and 42.43% in Cohort B by one month and persist to month 6

- Nedosiran (Dicerna/Novo Nordisk) is another RNAi drug, which is designed to inhibit the production of l-lactate dehydrogenase A (LDHA), which is essential for the cytosolic conversion of glyoxylate into oxalate.

- CLKT is recommended in patients with PH1 and advanced disease (eGFR <30 ml/min/1.73 m2) who do not respond to pyridoxine and have no access to RNAi therapy
- It is recommended to monitoring urinary and plasma oxalate levels at least every 6 months after kidney transplantation for patients receiving pyridoxine or/and RNAi therapy until levels normalize, and thereafter at least once per year



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Lumasiran, Isolated Kidney Transplantation, and Continued Vigilance

- Bacchetta et al , recently reported five successful cases of isolated kidney transplantation in patients with PH1 who received lumasiran and proactive management during the immediate postoperative period.
- Then report data from at least 23 months of follow-up for each patient

- All the grafts continued to function at the time of their report.
- None of the patients had nephrocalcinosis, and the urinary oxalate: creatinine ratio had normalized or almost normalized in four of the patients.
- It took 21 months for the urinary oxalate level to become nearly normalized in the only patient with infantile oxalosis

RNAi therapy recommended under the following conditions:

A. PH1 is genetically established in patients of any age AND

B. Patients are biochemically unresponsive to pyridoxine OR have a mutation consistent with pyridoxine unresponsiveness AND

C. Urine oxalate excretion is >1.5 times the upper reference limit AND

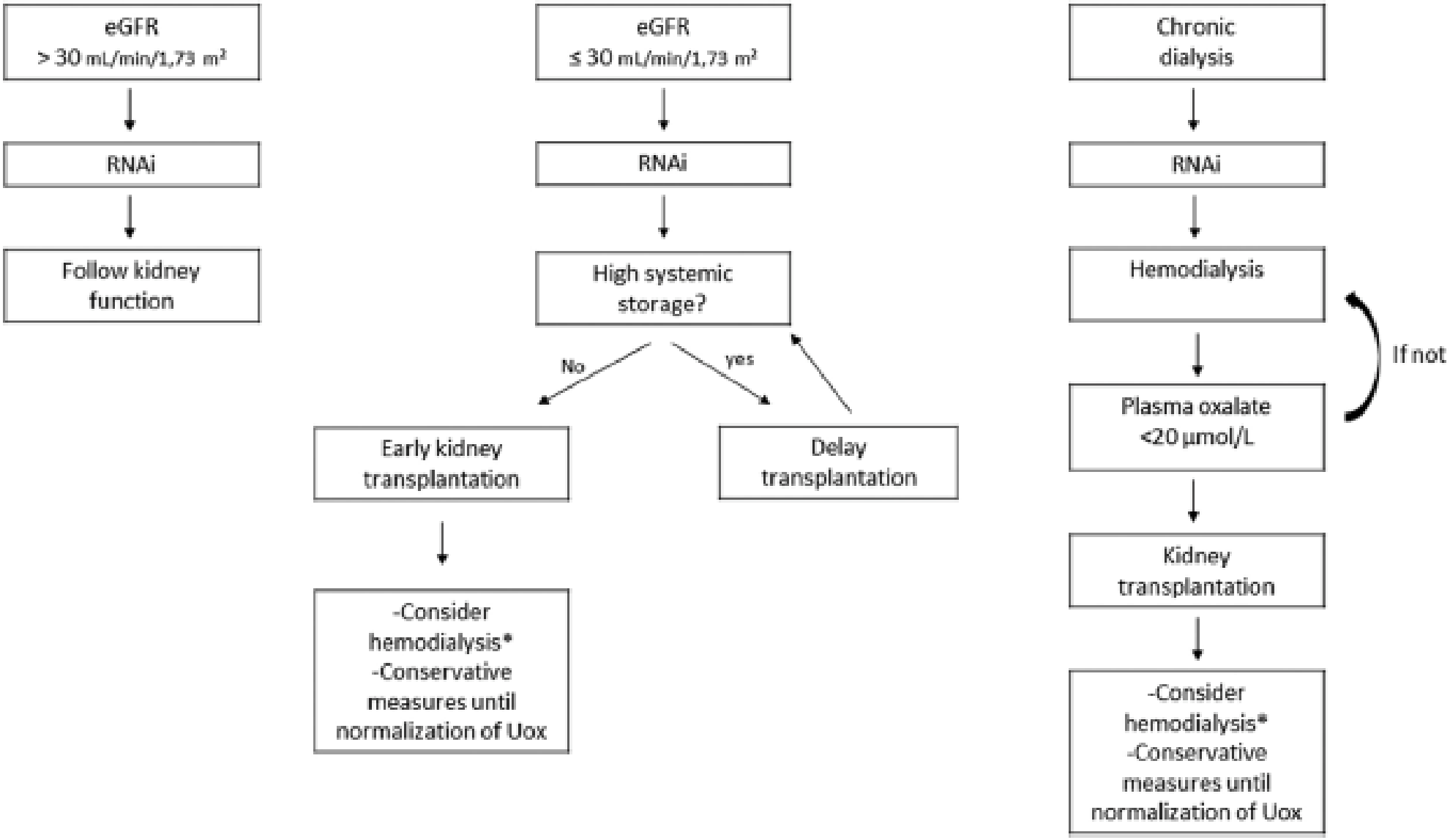
D. Patients demonstrate a clinical phenotype of PH1, characterized by active stone disease AND/OR

E. Nephrocalcinosis AND/OR renal impairment

Nature Reviews Nephrology |March 2023

Group[a]	Start	Cessation criteria after 6 months of therapy	Six-monthly analyses for 5 years and cessation criteria
Group A (VB6⁻, eGFR >30)	We recommend starting therapy	Uox >1.5 UL or less than a 30% reduction in Uox[b] or a deterioration of the clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group B (VB6⁺, eGFR >30)	We suggest starting therapy, based on patient characteristics (not fully VB6 responsive, severe disease)	Uox >1.5 UL or <30% reduction Uox[b]; or deterioration of clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group C (VB6⁻, eGFR <30)	We recommend starting therapy	Decrease in Pox <20% from baseline or deterioration of clinical condition or evidence of a SAE[c]	Stop if decrease in Pox is <20%[d,e] from baseline: discuss options if the decrease in Pox is <30% from baseline[d,e]. Also stop treatment if there is evidence of an SAE OR deterioration in clinical condition related to RNAi therapy[c]
Group D (VB6⁺, eGFR <30)	We suggest starting therapy based on patient characteristics (not fully VB6 sensitive, rapidly deteriorating kidney function in case of eGFR 20–30)	Decrease in Pox <20% from baseline[d,f] or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	Stop therapy if the decrease in Pox is <20%[2,4]; discuss options if the decrease in Pox is <30%[d,f]. Also stop treatment if there is evidence of a SAE or deterioration in clinical condition related to RNAi therapy[c]
Group E (no genetic diagnosis, eGFR <30)	We recommend starting therapy with monthly monitoring of Pox levels	Decrease Pox <20% of baseline or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]. Also stop therapy if the suspected PH diagnosis is not confirmed genetically	Not applicable
Group F (no ongoing clinical disease)	We suggest starting therapy in adults and recommend starting therapy in children	Uox >1.5 UL or <30% reduction Uox of baseline; or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group G (full VB6⁺)	We do not recommend starting therapy	Not applicable	Not applicable

Nature Reviews Nephrology |March 2023



Kidney International Reports , 2136–2145

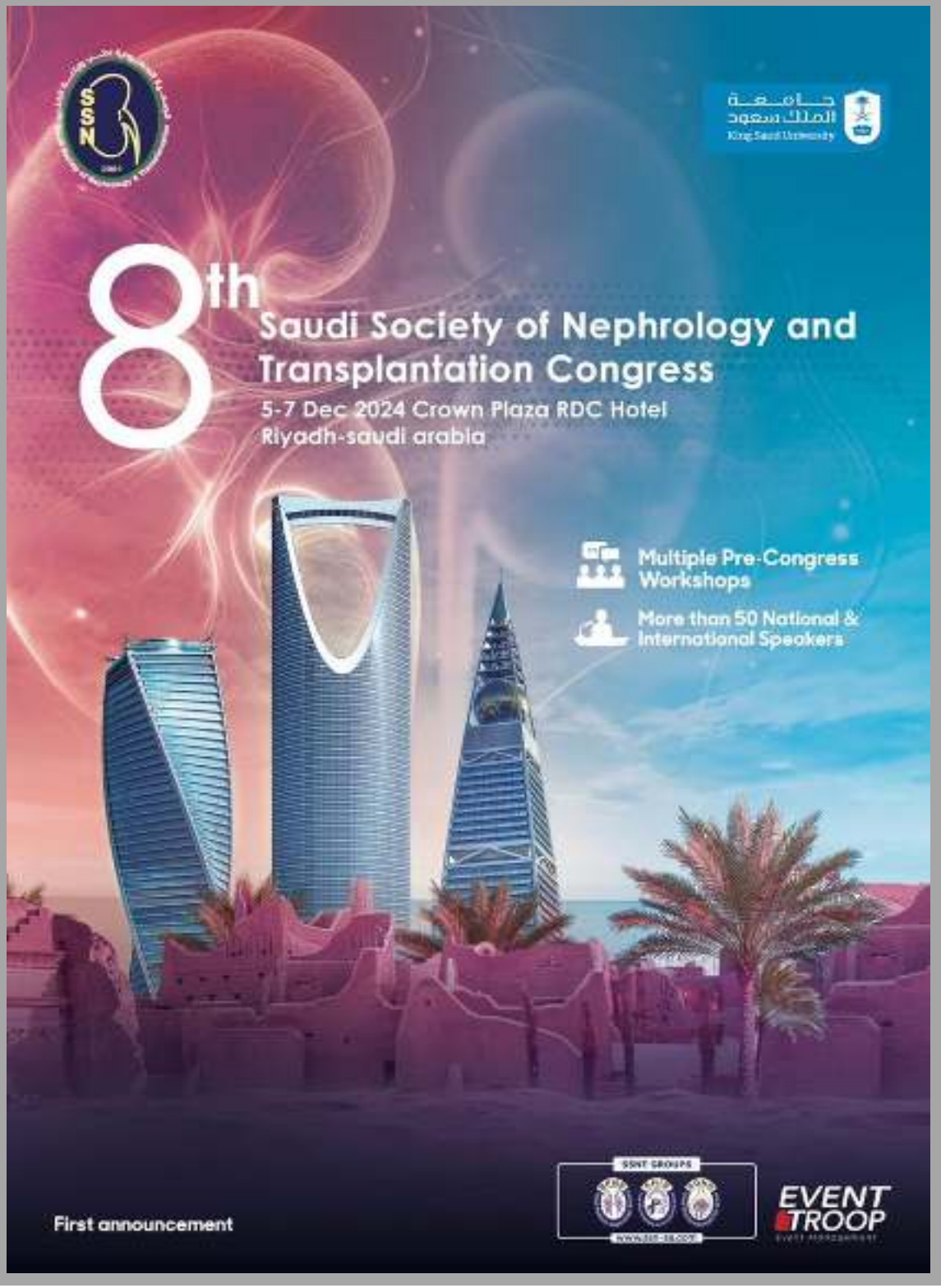
Future Therapy

- Recently, it has been shown to be possible to reprogram mature somatic cells to generate induced pluripotent stem cells (iPSCs).
- These iPSCs can further differentiate in many cell types, including liver cells

- Recently, Estève et al.were able to generate in vitro transgene-free iPSCs after reprogramming dermal fibroblasts from a PH1 patient. PH1-iPSCs could further be differentiated into hepatocyte-like cells that displayed a low residual AGT expression
- Although gene therapy has been advocated, many years of research will be required before its potential may be actualized.

Home message

- The ultimate goal before kidney transplantation is to limit as much as possible the systemic storage of oxalate to prevent oxalate precipitation in the allograft.
- To reach this goal, early initiation of a treatment (e.g. RNAi drugs) that corrects the metabolic defect seems logical.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King Saud University
8th
Saudi Society of Nephrology and Transplantation Congress
5-7 Dec 2024 Crown Plaza RDC Hotel
Riyadh-saudi arabia
Multiple Pre-Congress Workshops
More than 50 National & International Speakers
SSNT GROUPS
EVENT TROOP
First announcement

Spectrum of Steroid-Resistant and Congenital Nephrotic Syndrome in Children: The PodoNet Registry Cohort

Bassam Saeed

Chairman Farah Association in Syria

Deputy Chair ISN ME Regional Board

16th ASNRT & 22nd JSNRT Congress. Amman 05-08 June 2024

Introduction

- SRNS is a rare kidney disease involving either immune-mediated or genetic alterations of podocyte structure and function*
- 12%–15% of children with idiopathic NS do not respond to oral steroid therapy
- SRNS is a challenging clinical condition with highly variable outcomes
- 50% of children with SRNS progress to ESRD within 15 years**

*Kim JS, et al. Kidney Int 68:1275–1281, 2005
**Cochat P. Pediatr Nephrol 24: 1525–1532, 2009

Histopathology vs Genetics

- Historically, diagnostic evaluation and prognostic classification relied largely on histopathologic assessment.

- In recent years, abnormalities in a growing number of genes essential for podocyte development have been identified in patients with congenital NS and SRNS

Changing Understanding of SRNS

- In childhood-onset SRNS, the ongoing discovery of genetic podocytopathies is about to redefine:
  - **The physiopathologic understanding**
  - **Diagnostic assessment**
  - **Prognostic judgment**
  - **Therapeutic approaches**

Low incidence of SRNS

- However, the development of evidence-based management algorithms of SRNS has been hampered by the low incidence of SRNS, which is estimated at 2–4 per million person/year

McKinney PA. Pediatr Nephrol 16: 1040–1044, 2001

PodoNet Consortium

- **To overcome the limitations imposed by:**
  - ✓**The rarity** of SRNS and CNS
  - ✓**Slow evolution** of SRNS and CNS

  →**The PodoNet Consortium** has created an international registry for CNS and childhood-onset SRNS.

Registry Description

- The PodoNet Consortium was formed in 2008 by **research groups** from Heidelberg, Paris, Rome, Bergamo, Genova, and Ankara.

- **The PodoNet project** (www.podonet.org) encompasses clinical, genetic, and experimental research into hereditary podocyte disorders.

- The clinical activities encompass a **web-based** international clinical registry and a **central biobank for SRNS**.

Design

- Since Aug. of 2009 to Oct. 2021, clinical, biochemical, genetic, and histopathologic information was collected both retrospectively and prospectively from **2671 patients** with childhood-onset (Age ≤20years old) SRNS, congenital NS, or persistent sub-nephrotic proteinuria of likely genetic origin at **81 centers** in **32 countries** through an online portal.

PodoNet: Home www.podonet.org

Acknowledgments

We acknowledge the continued support of patient families and medical staff at all participating centers.

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PodoNet Consortium

- **The PodoNet Registry cohort represents, by far, the largest collection of clinico-pathologic and genetic information assembled to date.**

Genetic Screening

- DNA samples are collected from all available & consenting patients and any affected relatives.

- **Central genetic screening has been offered for free** for patients with lacking or incomplete screening results.

Ethically Approved Project

- The registry study protocol was approved by the local institutional review boards/ethics committees, and written informed consent is obtained from the families.

- Data protection is ensured by pseudonymized data input.

Definitions

- **SRNS:** Persistent proteinuria after 4weeks of oral steroid therapy (prednisone at 60 mg/m2 per day).

- **Sub-nephrotic proteinuria:**
  - 24-hour protein >100 mg but <1 g/m2/day
  - UPCr of 0.6 to 2 mg/mg if age < 2 years
    0.2 to 2 mg/mg if age > 2years
  - or dipstick proteinuria of 1+.

- **Nephrotic-range proteinuria:**

24-hour protein excretion ≥1g/m2 per day

UPCr ≥2 mg/mg, or dipstick ≥2+

Definitions

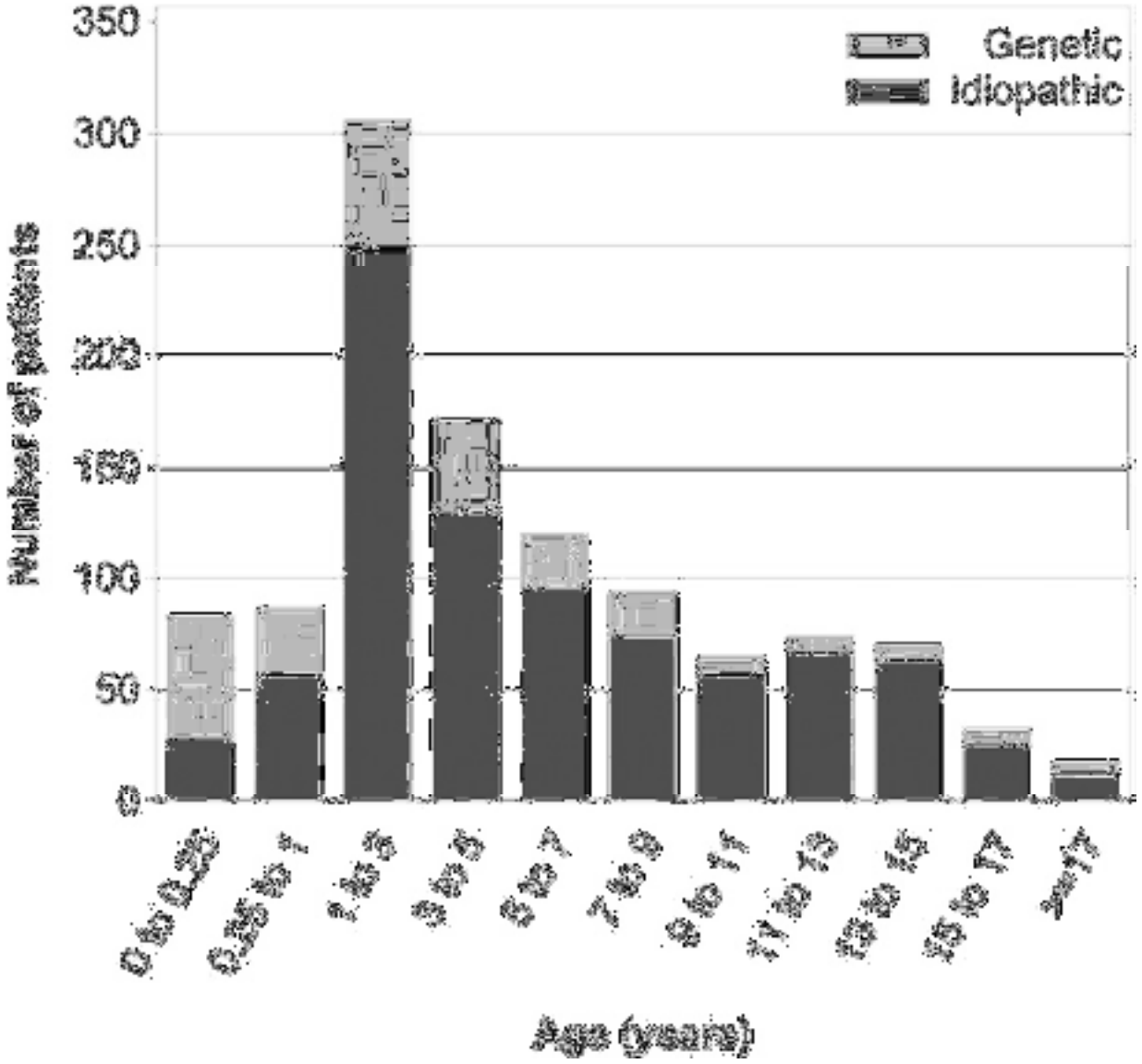
- **Complete remission:**
  - 24-hour protein: <100 mg/m2/day
  - UPCr <0.2 mg/mg
  - dipstick of 0 or (+)
  - s albu >3.5 g/dl (In absence of proteinuria information)
- **Partial remission:**
  - 24-hour protein excretion of 0.1–1 g/m2/day
  - UPCr=0.2–2 mg/mg
  - dipstick of 1+ and s. albu >3.0 g/dl
  - S. albu of 3.0–3.5 g/dl. (in absence of proteinuria information)

Results

Parental Consanguinity

- **Parental Consanguinity** Reported in 28.6%
- **Familial disease occurrence** was reported in 25.6%
- **Consanguinity and familial disease occurrence** were most common in the Middle Eastern countries (Syria, Lebanon, UAE).

Age at first disease manifestation in children with and without an identified genetic cause of SRNS



Trautmann et al. PodoNet Registry Cohort. Clin J Am Soc Nephrol. Vol 10 April, 2015

First Disease Manifestation

1–11 years of age	**75%**
Congenital	**6%**
3-12 months **Early infantile**	**7%**
>12 years **Adolescent-onset NS**	**16%**

→**SRNS** manifested in the first 5 years of life in 64% of the patients

→**Congenital NS** accounted for 6% of all patients.

Genetic Disease Detection Rate Versus Age at First Manifestation

- **Genetic Disease Detection Rate Markedly Higher in CNS**
  - 66% in patients with CNS
  - 16% in children first presenting at age ≥ 6 years old

- **Hypoalbuminemia**:
  - More common in CNS
  - Nephrotic-range proteinuria: not yet present in 8.7% of the children at the time of diagnosis

- **Hypertension**: more prevalent in adolescents

Follow-Up Information

- After a median duration of follow up of 3.7 years.

  - **61.3% were still without RRT**
  - **11.7% required dialysis**
  - **14.2% had received kidney allografts**
  - **2.3% were deceased**
  - **10.6%were lost of follow-up**

Follow-Up Information

- **Among the patients without RRT:**
  - 33% were in full remission
  - 22.5% were in partial remission

- **Among the patients with full or partial remission:**
  - 66.9% had normal kidney function
  - 26.4% were in CKD stage 2
  - 5.1% in CKD stage 3
  - 1.6% in CKD stages 4 or 5

Histopathologic Findings

- **The most common histopathologic diagnosis**
  - **FSGS:** 56.0%
  - **MCN:** 21.1%
  - **MesPGN**: 12.4%
  - **Diffuse mesangial sclerosis** 2.9%

- **Repeat biopsies**
  - Performed in 12.5% of patients
  - At a median of 31 months after the initial biopsy.
  - The diagnosis changed in 54% of patients:
    Mostly MCN → FSGS and MesPGN → FSGS

Extrarenal Symptoms

Type of Extrarenal Abnormality	*N*	%
Patients without reported extrarenal abnormalities	1368	82.7
Mental retardation	65	3.9
Anomalies of central nervous system	42	2.5
Microcephaly	17	1.0
Visual impairment	32	1.9
Hearing disorder	25	1.5
Anomalies of peripheral nervous system	7	0.4
Myopathy	13	0.8
Cardiomyopathy	6	0.4
Urogenital abnormalities	33	2.0
Impaired sex differentiation	16	1.0
Short stature	84	5.1
Facial dysmorphism	37	2.2
Spondyloepiphyseal dysplasia	8	0.5
Polydactyly	5	0.3
Nail patella syndrome	2	0.1
Cardiac structural disorder	36	2.2
Malignant disorder	21	1.3
Hematologic disorders	7	0.4
Diabetes mellitus	7	0.4
Other endocrine abnormalities	23	1.4
Skin abnormalities	13	0.8
Abnormalities of the gastrointestinal tract	5	0.3
Autoimmune disorder	9	0.5
Connatal cytomegaly virus	9	0.5
Hepatitis B	6	0.4
Hepatitis C	10	0.6

Extrarenal Symptoms

- **In 17.3% of the patients**
  - ❑ **CNS abnormalities:** 5.3% of all patients, the most common
    - ➢ Brain anomaly
    - ➢ Microcephaly
    - ➢ Mental retardation
  - ❑ **WT1 disease** (sex reversal/urogenital abnormalities & cancer)
  - ❑ **Impaired mitochondrial energy metabolism** (myopathy, cardiomyopathy, and impaired hearing),
  - ❑ **Pierson syndrome**
- **SRNS occurred as an isolated kidney disease in 83% of the patients in the cohort.**

Mutation Screening Results

- **A total of 3037 individual gene screens were performed** in 1174 of 1655 study participants (70.9%)
- The extent of genetic screening varied among countries.
- Among 11 countries contributing at least 30 patients:
  - Screening prevalence was highest in Chile (91% of patients), Syria (84%), and Germany (80%)
  - Screening prevalence was lowest in Colombia (26%) & Iran (21%)
- The most commonly screened genes were NPHS2(93%) and WT1 (77%) of screened patients

Mutation Screening Results

- Other podocyte genes were screened selectively guided by:
  - Age
  - Histopathology
  - Syndromic features
  - As part of joint research projects

- **More recently, patients undergo comprehensive screening using a next generation sequencing panel of 31 podocyte genes**

Mutation Screening Results

- **Genetic diagnoses were established in 277 out of 1174 (23.6%) screened patients:**
  - Mutations in **NPHS2**: 49.8% of patients
  - Mutations in **WT1**: 17.3% of patients
  - Mutations in **NPHS1**: 14.8% of patients
  - Mutations in **SMARCAL1**: 4.3% of patients
  - Mutations in **PLCE1:** 3.6% of patients.
  - The remaining 10% of patients were attributable to variants in nine different genes

Mutation Screening Results

Table 4. Results of genetic screening studies

Gene	Patients Screened	Patients with Causative Mutation	Screened Positive (%)
NPHS2	1088	138	12.7
WT1	902	48	5.3
NPHS1	208	41	19.7
SMARCAL1	68	12	17.6
PLCE1	75	10	13.3
PTPRO	45	6	13.3
LAMB2	84	5	6.0
INF2	112	4	3.6
COQ6	30	3	10.0
MYO1E	48	2	4.2
TRPC6	96	1	1.0
COQ2	56	1	1.8
LMX1B	27	1	3.7
ADCK4	27	1	3.7
PDSS2	56	0	0.0
ACTN4	59	0	0.0
CD2AP	56	0	0.0
All	1174	277	23.6

Pharmacologic Therapy

- **Steroid:** 42.6% of patients
- **Cyclophosphamide pulse therapy**: 3.5%
- **Oral cyclophosphamide:** 21.2%
- **Cyclosporine A:** 66.3%
- **Tacrolimus:** 12.2%
- **MMF:** 24.9%
- **Rituximab:** 6.6%
- **RAS antagonists:** 76.1%

Response Rate to Pharmacologic Therapy

- **CNI–based therapy showed the highest response rates:**
  - Two thirds of patients achieving partial or complete proteinuria remission.
- **A few patients with genetic diagnoses exhibited responsiveness to intensified immunosuppressive therapy**
- **Steroid pulse therapy and cyclophosphamid-based protocols showed poor efficacy**
  - Did not achieve better results than antiproteinuric treatment with RAS inhibitors
- **The initial histopathologic diagnosis did not predict responsiveness to IS treatment.**

Late Outcomes

- Children with **CNS and early infantile NS** were more likely to develop ESRD than older children.
- Patients with **DMS and global glomerulosclerosis** had the highest likelihood of ESRD.
- Patients with **FSGS** were more likely to progress than those with MCN.

Post-Transplant Disease Recurrence

- **Post-Tx disease recurrence is a diagnostic and prognostic relevant feature of SRNS**

- **Recurrence Rate:**
  - 15.2% of all transplanted patients
  - 28.5% of patients without a genetic diagnosis
  - **4.5% (4) of patients with genetic disease.**
    - ✓All had NPHS2 mutations
    - ✓These peculiar cases **deserve a detailed analysis** of the nature of the genetic abnormalities diagnosed

- **The risk of disease recurrence** increased with age at first disease manifestation

Post-Transplant Disease Recurrence

- **The histopathologic diagnoses of native kidney Biopsy:**
  - **FSGS in 68.8% of patients**
  - **MesPGN** 12.5%
  - **GGS** 6.3%
  - **MCN** 6.3%
  - **MPGN** 3.1%
  - **DMS** 3.1%

Is There Any Association Between:

Genetic Disease Causes & Histopathologic Diagnoses ?

Genetic Abnormalities & Histopathology

- **Genetic abnormalities were found:**
  - 22% of patients with **FSGS**
  - 19% of patients with **MesPGN**
  - 12% of patients with **MCN**

- Close associations with specific genetic disorders were limited to:
  - **DMS** (WT1 and PLCE1 nephropathies)
  - **CNS** (NPHS1 disease)

Genetic Abnormalities & Histopathology

- **A noteworthy aspect of this study is:**

→The limited value of kidney biopsies in distinguishing genetic from nongenetic disease etiologies.

The Complexity of SRNS Management

- **The wide range of reported monotherapies and combined therapies**
- **Frequent medication changes** because of lack of efficiency or observed or anticipated adverse effects
- **Significant variation regarding first- and second-line drug choices** across the centers and countries
- **Treatment preferences seemed to change with time.**

Proteinuria Response Patterns in SRNS

Main Findings

1. **Steroid pulses and cyclophosphamide** are of very limited, if any, efficacy in children with SRNS.

2. **CNI:** 40%–50% of patients with SRNS seem to respond to CNI by achieving complete remission of proteinuria

3. **Rituximab** may be an equally effective option as CNI.

4. **MMF** may be less efficacious than CNI and rituximab in SRNS

5. **Nonspecific antiproteinuric therapy by RAS inhibition** is associated with complete remission of proteinuria in 25% and partial remission in another 20% of patients with SRNS

1. Proteinuria was multidrug resistant in the vast majority of genetic cases

Conclusions

- A genetic disease cause was identified in 23.6% of the screened patients and the most commonly identified abnormalities were NPHS2, WT1, and NPHS1.
- The proportion of patients with a genetic disease cause decreased with increasing manifestation age from 66% in CNS to 15%–16% in schoolchildren and adolescents
- 40%–45% of SRNS patients treated with CNI or Rituximab achieved complete remission.
- Post-transplant disease recurrence was noted in 28.5% of patients without a genetic diagnosis and 4.5% of patients with a genetic diagnosis.

Conclusions

- Establishing a genetic diagnosis is far superior to histopathologic disease classification in predicting IS therapy responsiveness and post-transplant disease recurrence in patients with SRNS

- Because hereditary forms of SRNS encompass a large number of genes, we recommend the routine use of the next-generation sequencing technologies for simultaneous assessment of all known podocytopathy genes

Thank You

Renal vasculitis in children

Dr. Doaa Al-Qaoud

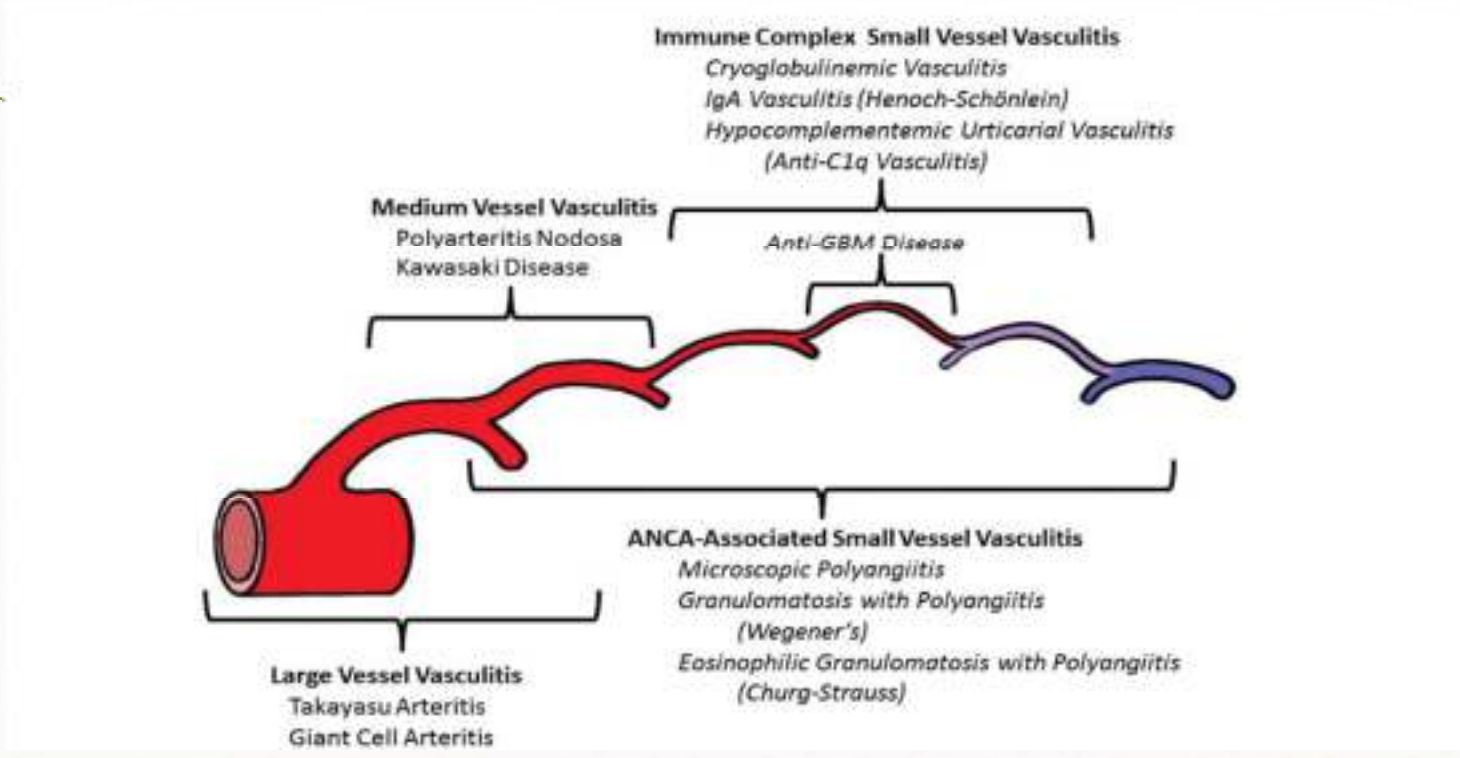
Assistant professor of pediatrics, The Hashemite University

Pediatric nephrologist, Prince Hamza Hospital.

Vasculitis

- Vasculitis is defined as the presence of inflammation in the blood vessel wall. The site of vessel involvement, size of the affected vessels, extent of vascular injury, and underlying pathology determine the disease phenotype and severity.
- Childhood vasculitis is a challenging and complex group of conditions that are multisystem in nature and often require integrated care from multiple subspecialties

classification



2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

Large vessel vasculitis (LVV)

- Takayasu arteritis (TAK)
- Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)

- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small vessel vasculitis (SVV)

- **Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)**
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (Wegener's) (GPA)
  - Eosinophilic granulomatosis with polyangiitis (ChurgStrauss)(EGPA)
- **Immune complex SVV**
  - Anti–glomerular basement membrane (anti-GBM) disease
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Cryoglobulinemic vasculitis (CV)
  - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Variable vessel vasculitis (VVV)

- Behcet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)

- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease

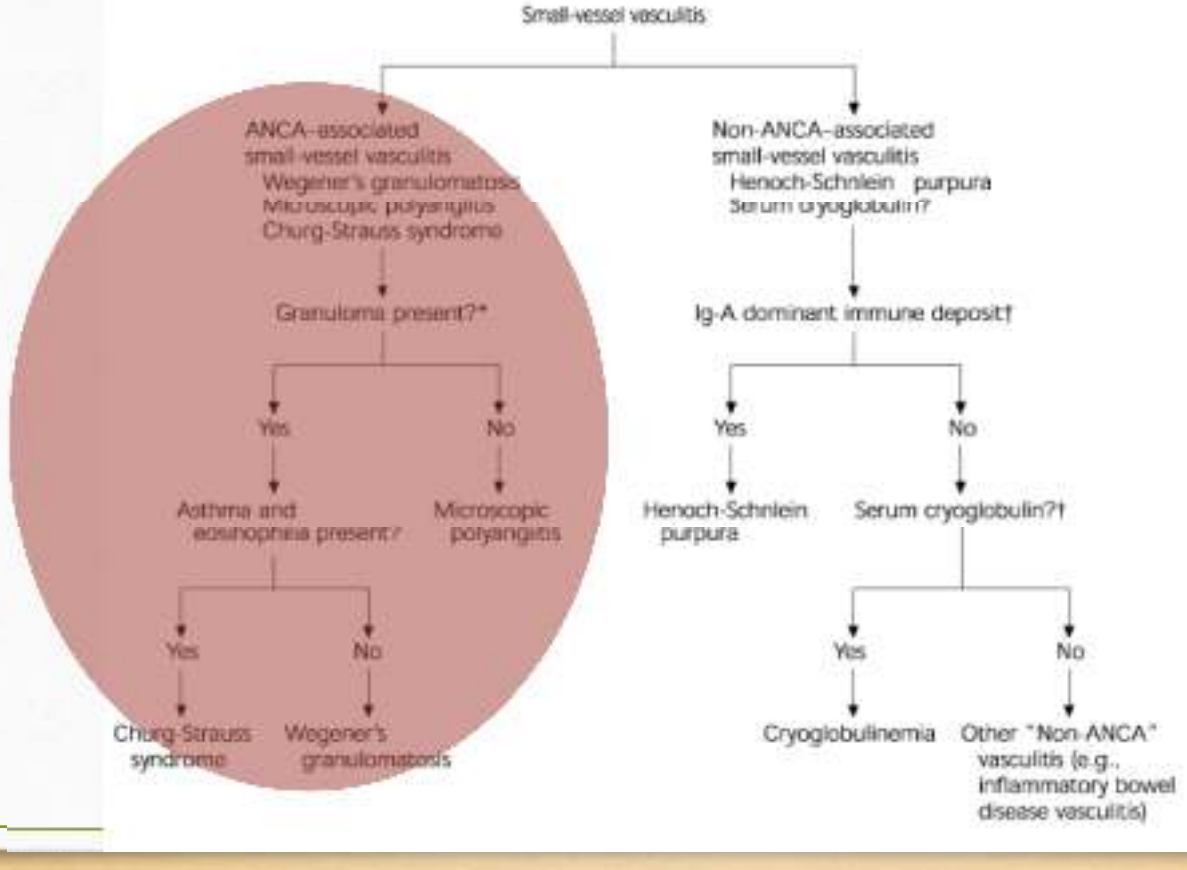
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology

- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- *Drug-associated immune complex vasculitis*
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

Arthritis Rheum 2013;65:1-11

Differential Diagnosis of Small-Vessel Vasculitis



Childhood-onset anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAVs)

- A group of systemic autoimmune diseases characterized by inflammatory cell infiltration, small-medium blood vessel necrosis, and autoantibodies to the neutrophil proteins leukocyte proteinase 3 (PR3-ANCA) cANCA or myeloperoxidase (MPO-ANCA) pANCA.

- Primary AAVs in children are rare.
- Higher female preponderance.
- Peak age at onset in the second decade.
- Median age at diagnosis 12–14 years.

ANCA Associated Vasculitis (AAV)

- There are three main conditions characterized by necrotizing inflammation of small to medium vessels in association with autoantibodies against the cytoplasmic region of the neutrophil (ANCA).

-including :

-Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis).(the commonest)

-Microscopic polyangiitis (MPA).

- Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome).

ANCA Associated Vasculitis (AAV)

- Can result in rapidly progressing glomerulonephritis (RPGN) with a chronic, frequently relapsing illness that can be organ or life-threatening, with substantial morbidity and death despite immunosuppression.
- Necrotizing glomerulonephritis (capillaritis) is characterised by an absence of immune deposits (Pauci immune).

ANCA-associated vasculitis

- Systemic vasculitis of small vessels accompanied by the presence of Anti- neutrophil cytoplasmic Antibodies (ANCAs) in the serum.

ANCAs were discovered in 1982

ANCAs are antibodies directed against cytoplasmic antigens in the primary granules of neutrophils and lysosomes of monocytes.

The antigens responsible for these patterns

- Proteinase 3 (PR3) for c-ANCA
- Myeloperoxidase (MPO) for p-ANCA

ANCAs - described based on their IF staining patterns

- Cytoplasmic (c-ANCA)
- Perinuclear (p-ANCA)

Table 1. Frequency of ANCA Positivity in Different Conditions

	PR3-ANCA (mostly cANCA)	MPO-ANCA (mostly pANCA)	Other
ANCA-Associated Vasculitis			
GPA	75%	20%	5% ANCA negative
MPA	30%	60%	10% ANCA negative
EGPA	5%	45%	50% ANCA negative
Renal-limited vasculitis	10%	80%	10% ANCA negative
Drug-induced vasculitis	10%	90%	Often high titer, dual positivity for MPO and PR3
Nonvasculitis Conditions			
Systemic lupus	2%	10%	10% atypical ANCA
Endocarditis	15%	5%	
Inflammatory bowel disease	Negative	Negative	Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%)
Primary sclerosing cholangitis	Negative	Negative	Atypical ANCA, various antigens: 60%-80%
Cystic fibrosis	Negative	Negative	Atypical ANCA pattern, directed against BPI (90%)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BPI, bactericidal/permeability-induced protein; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3.

AAV

- Microscopic Polyangiitis(MPA) is more frequent in children.
- Granulomatosis Polyangiitis (GPA). (Wegener Granulomatosis).
- Eosinophilic Granulomatosis with Polyangiitis (EGPA).(Churg-Strauss Syndrome)
- Renal limited vasculitis

Microscopic polyangiitis (MPA)

- MPA is considered to be the prototypic AAV since the mechanisms involved in its pathogenesis are shared with all kinds of AAV.
- Necrotizing vasculitis characterised by little or no immune deposits and affects small blood vessels.
- A diagnostic criteria for MPA in children is not available.

Microscopic polyangiitis (MPA)

Renal disease :

- is the most common presentation, with segmental pauci-immune necrotizing and crescentic glomerulonephritis (NCGN) characterized by hypertension, edema, proteinuria, and haematuria.
- 75-100%.
- renal involvement tends to be more severe than GPA.

Respiratory system:

Often spares the upper respiratory tract and affects the lower respiratory tract, resulting in hemoptysis, persistent anemia, pulmonary hemorrhage, and lung hemosiderosis.

pulmonary manifestations are milder and less frequent than GPA.

eyes : episcleritis and conjunctivitis.

CNS involvement: peripheral neuropathy

Cardiovascular system.

SKIN: Purpuric rash is common

Female predominance as high as 6:1

Patients are significantly younger than GPA patients.

Onset is insidious and associated with constitutional symptoms in almost all patients

MPO-ANCA positivity is typically detected in 60% of cases.

Granulomatosis with polyangiitis GPA

<Named after Friederich Wegener who described it in 1936>

- **Renal disease:** kidneys with pauci-immune crescentic glomerulonephritis.

chronic course as localized granulomatosis or acute manifestations of small vessel vasculitis (pulmonary hemorrhages and/or rapidly progressive renal involvement).

- **Respiratory system:** involves upper and lower respiratory tract/ pulmonary hemorrhage.
- **eyes**: episcleritis, orbital pseudotumor, uveitis, conjunctivitis.
- **CNS involvement:** headache, peripheral neuropathy.
- **cardiovascular system:** venous thrombosis, valvular lesions.
- PR3- ANCA positivity in 75%

At least three of the following six are required for a diagnosis GPA:

•Typical histological features, (inflammation granulomatous).

• Involvement of upper airways

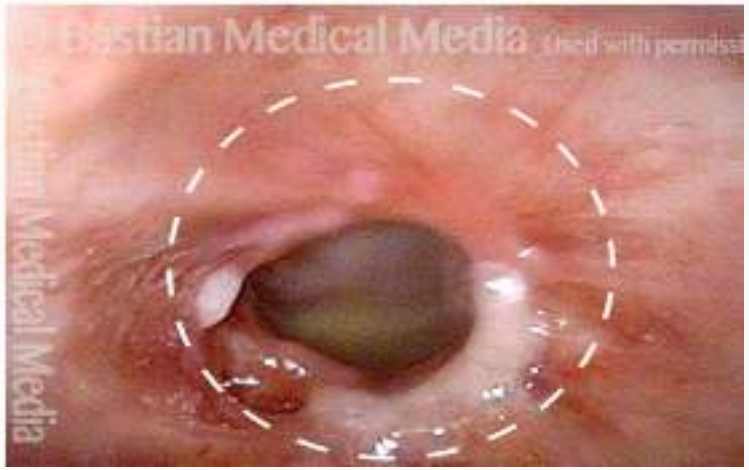
• Pulmonary involvement (chest CT scan or x-ray with nodules, cavities, or fixed infiltrates).

• Laryngo-tracheo-bronchial stenosis.

• Positive ANCA.

• Renal involvement.

Compared to adults, children had a greater incidence of early GPA-associated ischemic abdominal pain as well as an increased risk of developing saddle nose deformity and subglottic stenosis.



Pathophysiology

- Neutrophil priming and ANCA-mediated excessive activation of neutrophils occur in both GPA and MPA.

- Necrotizing granulomas in the respiratory tract and PR3-ANCA production are characteristics of GPA.

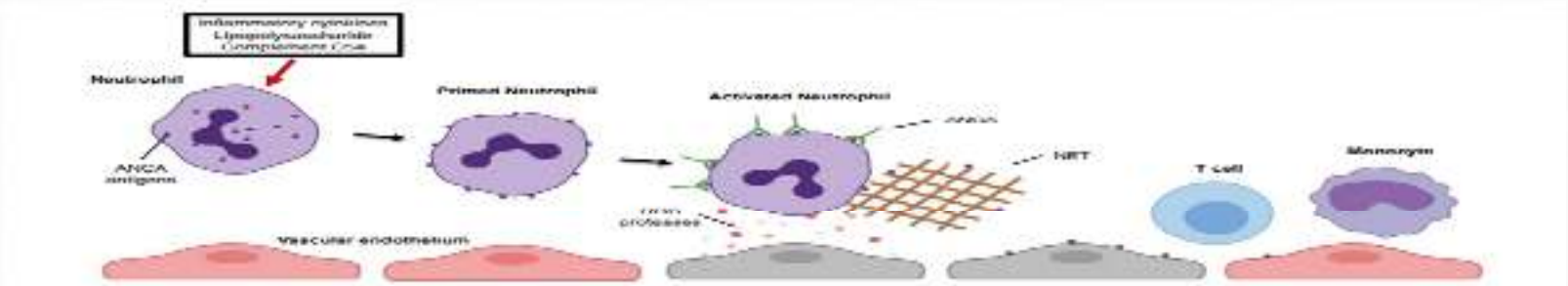
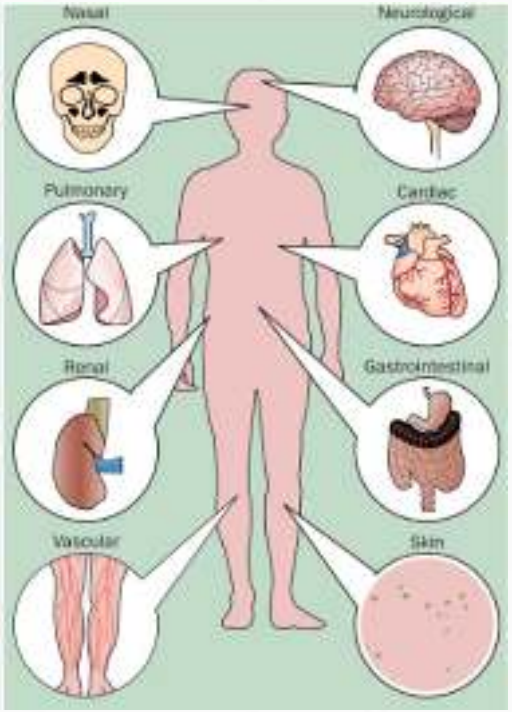


Figure 1. Pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA autoantigens (proteinase 3 [PR3] and myeloperoxidase [MPO]) are normally sequestered in the primary granules of neutrophils. Infection or other environmental stimuli result in neutrophil priming, with movement of PR3 and MPO to the cell surface. Binding of ANCA to these autoantigens results in activation of neutrophils, which adhere to vascular endothelium. Neutrophil degranulation leads to the release of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), damaging the endothelium. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes augmenting tissue injury. Drawings created with BioRender.

Eosinophilic granulomatosis with polyangiitis

Churg-Strauss syndrome

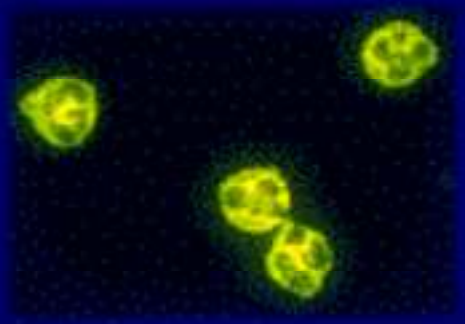
- Patients present with asthma, sinusitis, lung infiltrates, eosinophilia, and nasal polyps.
- Literature reports associated cardiomyopathy, skin lesions such as purpura and urticarial skin rash, gastrointestinal involvement and neuropathy. Kidney biopsy is characterized by prominent eosinophil rich inflammation in granulomas surrounding necrotizing vasculitis of interlobular-sized and larger vessels.
- MPO-ANCA are detected.


Nasal
Neurological
Pulmonary
Cardiac
Renal
Gastrointestinal
Vascular
Skin

Renal limited vasculitis

- Characterized by renal histopathology pattern of pauci immune, necrotizing crescentic or ANCA-associated glomerulonephritis (AAGN) without vasculitis in other organs, associated with MPO-ANCA.
- In children AAGN is the second cause of rapidly progressive glomerulonephritis, after immune-mediated diseases.

No substantial staining for immunoglobulins



Idiopathic glomerulonephritis

ANCA glomerulonephritis

No systemic vasculitis

Vasculitis with no asthma or granulomas

Granulomas but no asthma

Asthma, granulomas, & eosinophilia

ANCA-GN or RLV

Microscopic polyangiitis

Wegener's granulomatosis

Churg-Strauss syndrome

Clinical Presentation

- General symptoms such as weight loss, poor feeding and fever preceding systemic manifestations.
- Gastrointestinal manifestations (chronic nausea, diarrhea, abdominal pain),
- Mucocutaneous manifestations (oral and genital ulcers, palpable purpura, petechial rash, subcutaneous nodules)
- Musculoskeletal manifestations (arthralgia, myalgia, arthritis)

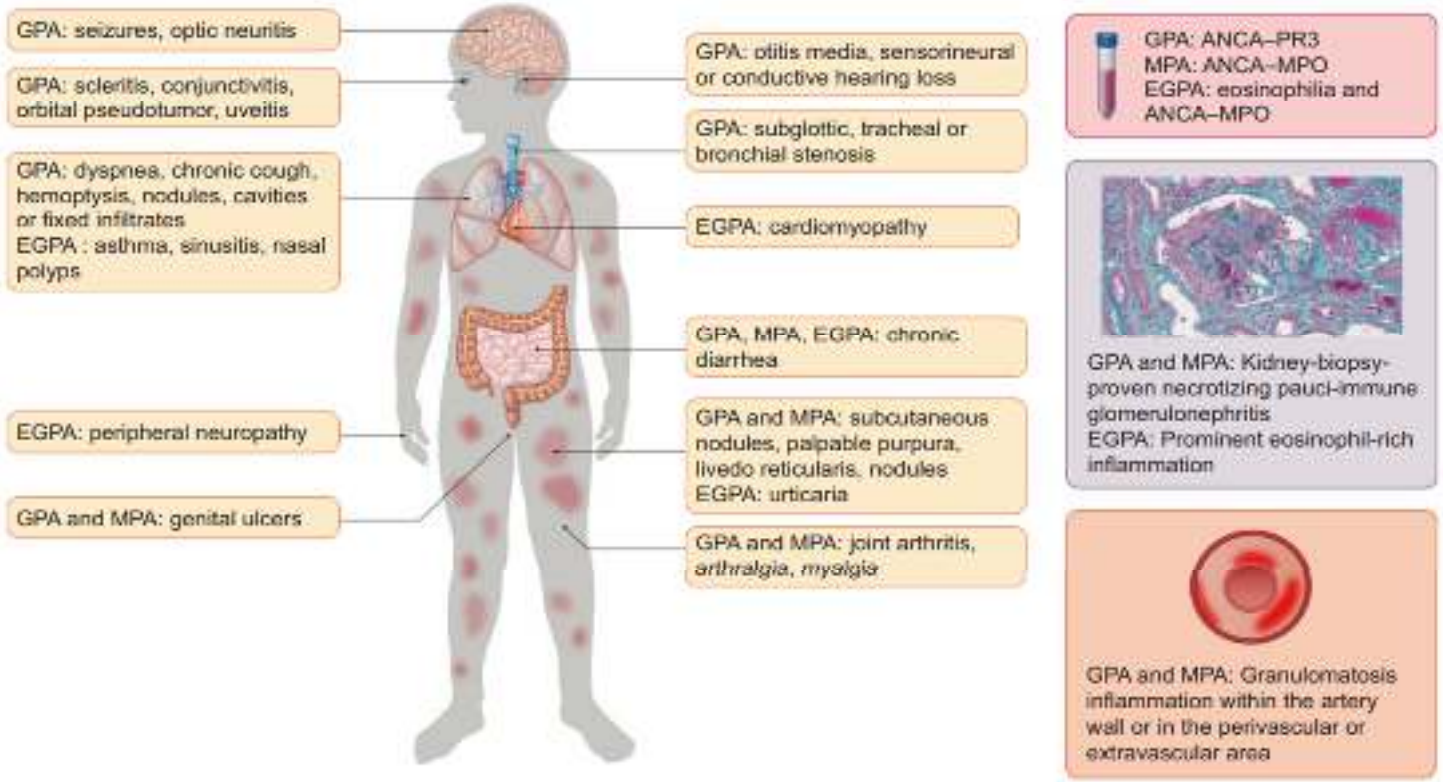
Clinical Presentation.

- Microscopic hematuria with dysmorphic red blood cells and red cell casts.
- Proteinuria that is usually moderate (1–3 g/d).
- Rapidly declining glomerular filtration rate (GFR) over days or weeks.
- Acute kidney injury (AKI) can present together with alveolar hemorrhage and is often referred to as a “pulmonary–renal syndrome.”

- Patients with systemic vasculitis may present with extrarenal manifestations affecting one or several organ systems, with or without kidney involvement. Commonly involved systems are the upper and lower respiratory tract, skin, eyes, and nervous system.
- Pulmonary hemorrhage affects 10% of patients with AAV and is associated with an increased risk of death.

ANCA-associated vasculitis in children

Diagnostic features: anorexia, fever, lethargy, malaise and loss of weight associated with:



Frequency of organ involvement in AAV.

Organ system	Microscopic polyangiitis (MPA) (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (EGPA) (%)
Cutaneous	40	40	60
Kidney	90	80	45
Pulmonary	50	90	70
Ear, nose, and throat	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

Figure 4 | Frequency of organ involvement in AAV. Reproduced from *The New England Journal of Medicine*, Jennette JC, Falk RJ. Small vessel vasculitis, Volume 337, Pages 1512–1523.[7] *Copyright* © 1997 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody.

Causes of AAVS

Primary or Secondary.

- **Genetic:**

the strongest associations with AAV are major histocompatibility complex class II (MHC II) genes

GPA with PR3 -ANCAs is most strongly associated with the HLA -DP region

MPA with MPO -ANCAs is highly associated with the HLA - DQ region

HLA genomic signature was associated with ANCA specificity (PR3 or MPO) rather than with the clinical manifestation (GPA or MPA)

- **Dysregulation of adaptive and innate immunity**:

involving B- and T-CD8+ memory cells, leading to a pathogenic production of ANCA and neutrophils activation.

A role of complement alternative pathways has been proposed, especially of *anaphylatoxin C5a and C5a receptor.*

- **Environmental triggers**: silica, farming, or organic solvents, associated with an increased risk of EGPA.
- **Infections**: Staphylococcus aureus, HIV or COVID-19 can be trigger
- **Drugs**: penicillamine, propylthiouracil, dapsone and cocaine adulterated with levamisole. The presence of both anti-MPO and anti-PR3 antibodies in the same patient suggests drug-induced vasculitis.

DIAGNOSIS OF AAVS

Biopsy of an affected organ remains the gold standard. (renal biopsy)

First-line investigations include:

• Laboratory analysis: inflammatory markers, complete blood count, kidney, liver, thyroid, and pancreatic function tests.

• Immunological screening: diagnosis is strongly suggested by ANCA positivity.

GPA: PR3-ANCA account for the majority of ANCA with cytoplasmic immunofluorescence patterns (C-ANCA)

MPA, EGPA and renal-limited vasculitis :MPO-ANCA that commonly match with perinuclear immunofluorescence pattern (P-ANCA).

• Infectious disease screening: particularly bacterial endocarditis.

• Imaging: chest ray, computed tomography, or magnetic resonance to assess organ involvement.

Renal involvement in AAV .

- Microscopic hematuria with dysmorphic red blood cells and red cell casts.
- Proteinuria that is usually moderate (1–3 g/d).
- Rapidly declining glomerular filtration rate (GFR) over days or weeks.
- Acute kidney injury (AKI) can present together with alveolar hemorrhage and is often referred to as a “pulmonary–renal syndrome.”

Diagnostic strategy in rapidly progressive glomerulonephritis

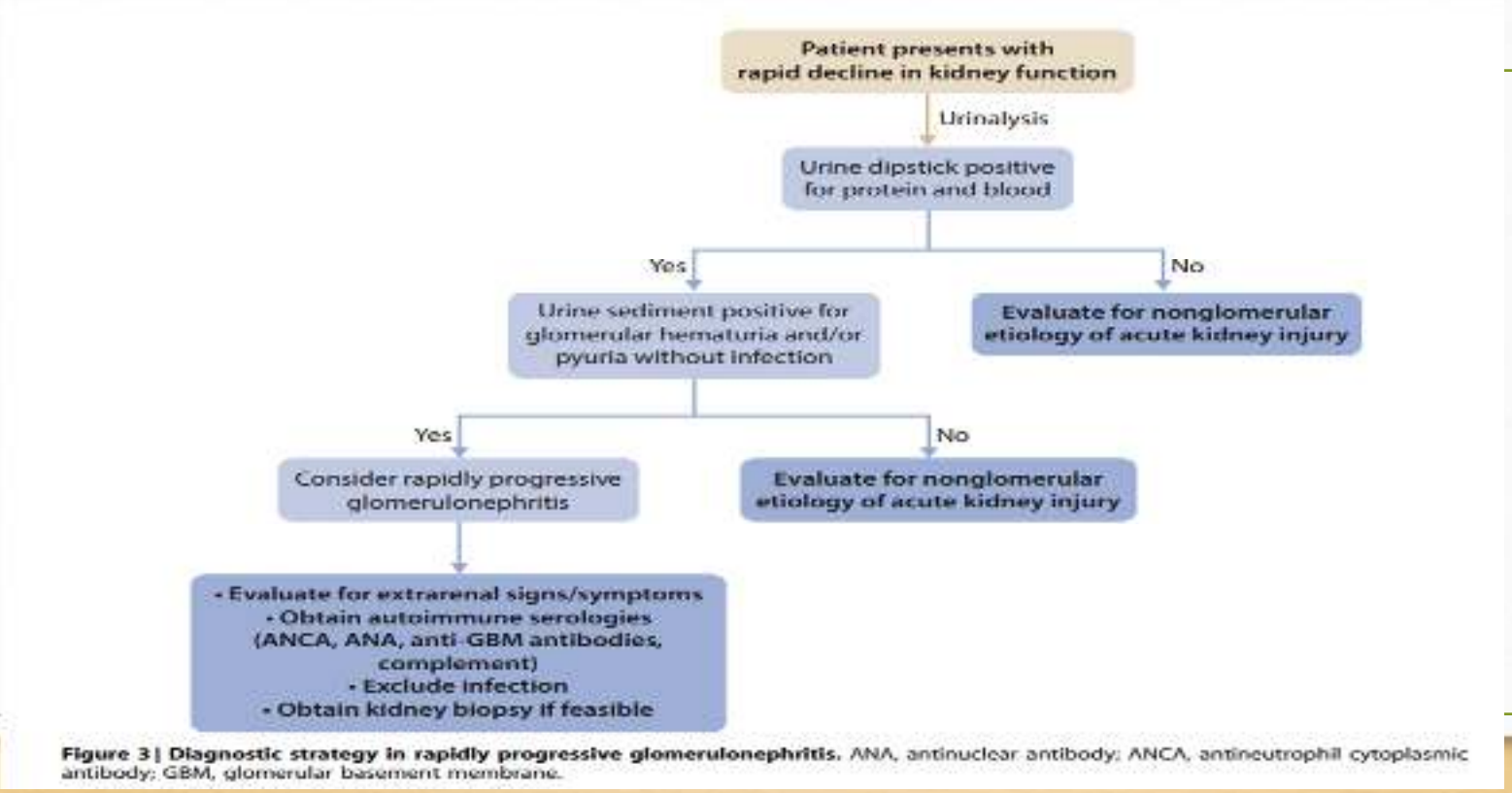


Figure 3 | Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

Biopsy strategy in suspected kidney vasculitis

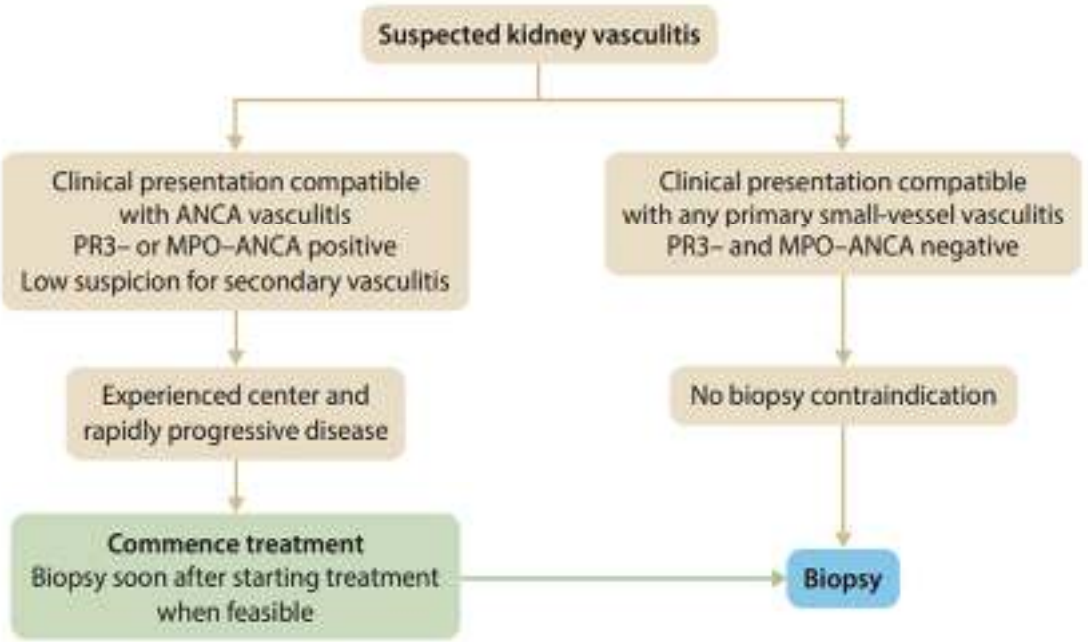


Figure 1 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

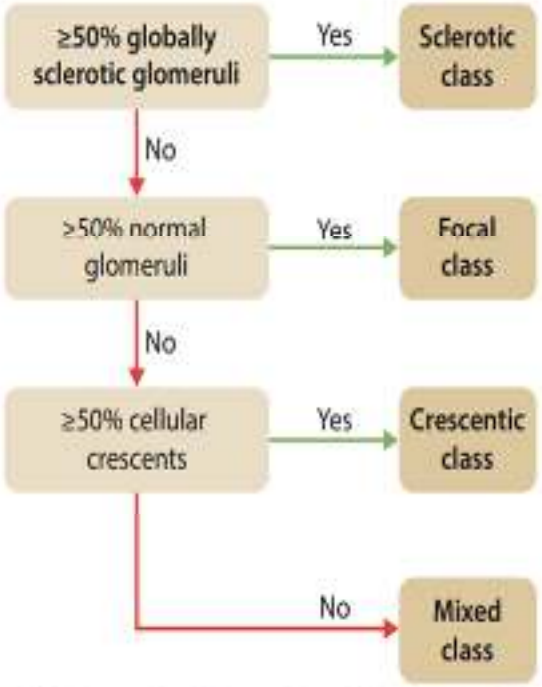
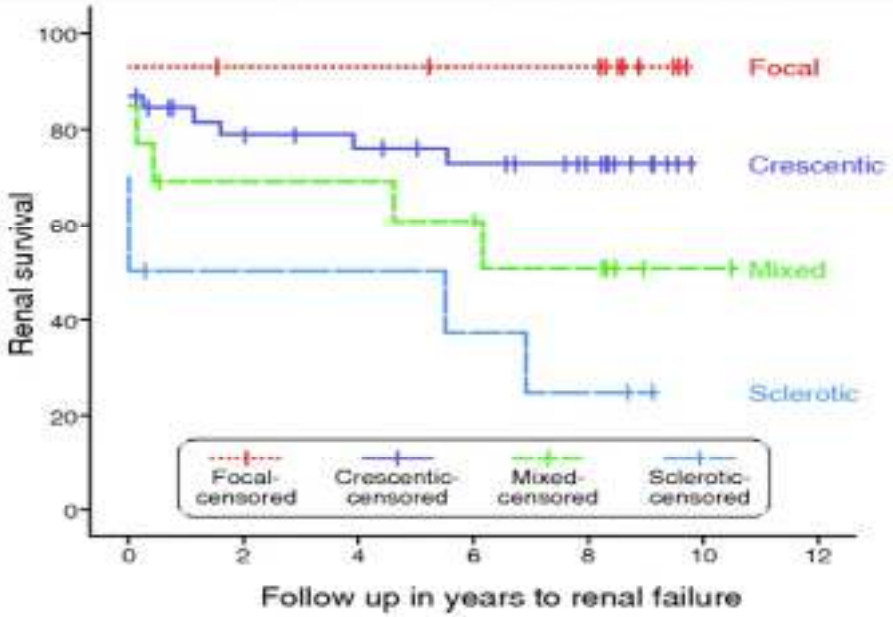


Figure 5| Histopathologic classification of ANCA-associated glomerulonephritis. Biopsies should be scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli, and glomeruli with cellular crescents. Biopsies that do not fit into a category based upon a predominant glomerular phenotype will be included in the mixed category.[6] ANCA, antineutrophil cytoplasmic antibody.

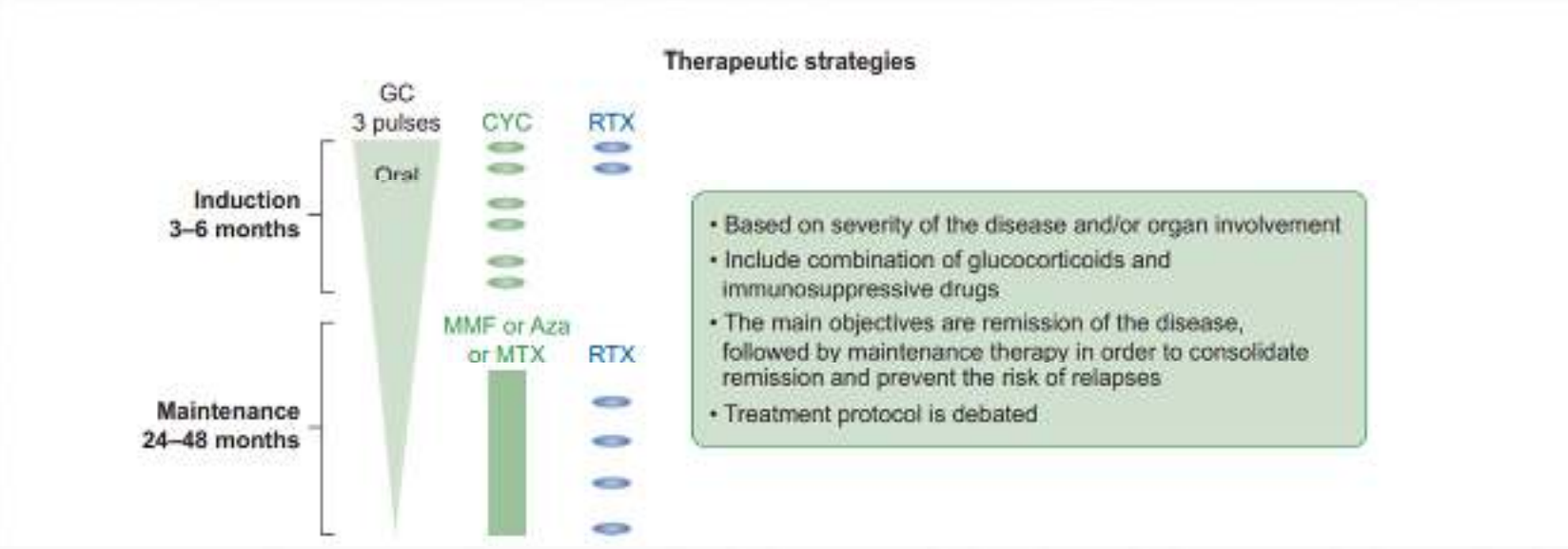


Renal survival (no development of end-stage renal failure) is depicted according to the four histologic categories. Renal survival at 1 year was 93% for patients whose renal biopsies were classified as focal at the time of diagnosis, 84% for patients whose biopsies were classified as crescentic, 69% for patients whose biopsies were classified as mixed, and 50% for patients whose biopsies were classified as sclerotic. Renal survival percentages at 5 years were 93% (focal class), 76% (crescentic class), 61% (mixed category), and 50% (sclerotic category). In the sclerotic category, renal survival at 7 years was only 25%.

Definitions:

- **Disease activity** of ANCA-associated vasculitis represents signs or symptoms attributable to active disease in any organ system.
- **Remission** is defined as the absence of manifestations of vasculitis and GN . For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease.
- **Relapse** is defined as the occurrence of increased disease activity after a period of partial or complete remission. A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided into major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse include diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis-threatening vision.
- **Treatment-resistant** disease is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy.

MANAGEMENT


Therapeutic strategies
GC
3 pulses
CYC
RTX
Oral
Induction
3–6 months
MMF or Aza
or MTX
RTX
Maintenance
24–48 months
• Based on severity of the disease and/or organ involvement
• Include combination of glucocorticoids and immunosuppressive drugs
• The main objectives are remission of the disease, followed by maintenance therapy in order to consolidate remission and prevent the risk of relapses
• Treatment protocol is debated

The aim of therapy

- To induce remission quickly to minimize active inflammation
- To minimise frequency and severity of relapses with minimal side-effects
- To reduce chronic damage from active and subclinical disease

Treatment

- Induction phase:

  Glucocorticoids in combination with rituximab or cyclophosphamide be used as the initial treatment of new-onset AAV

- Maintenance phase:

  Rituximab, or azathioprine and low-dose glucocorticoids after induction of remission

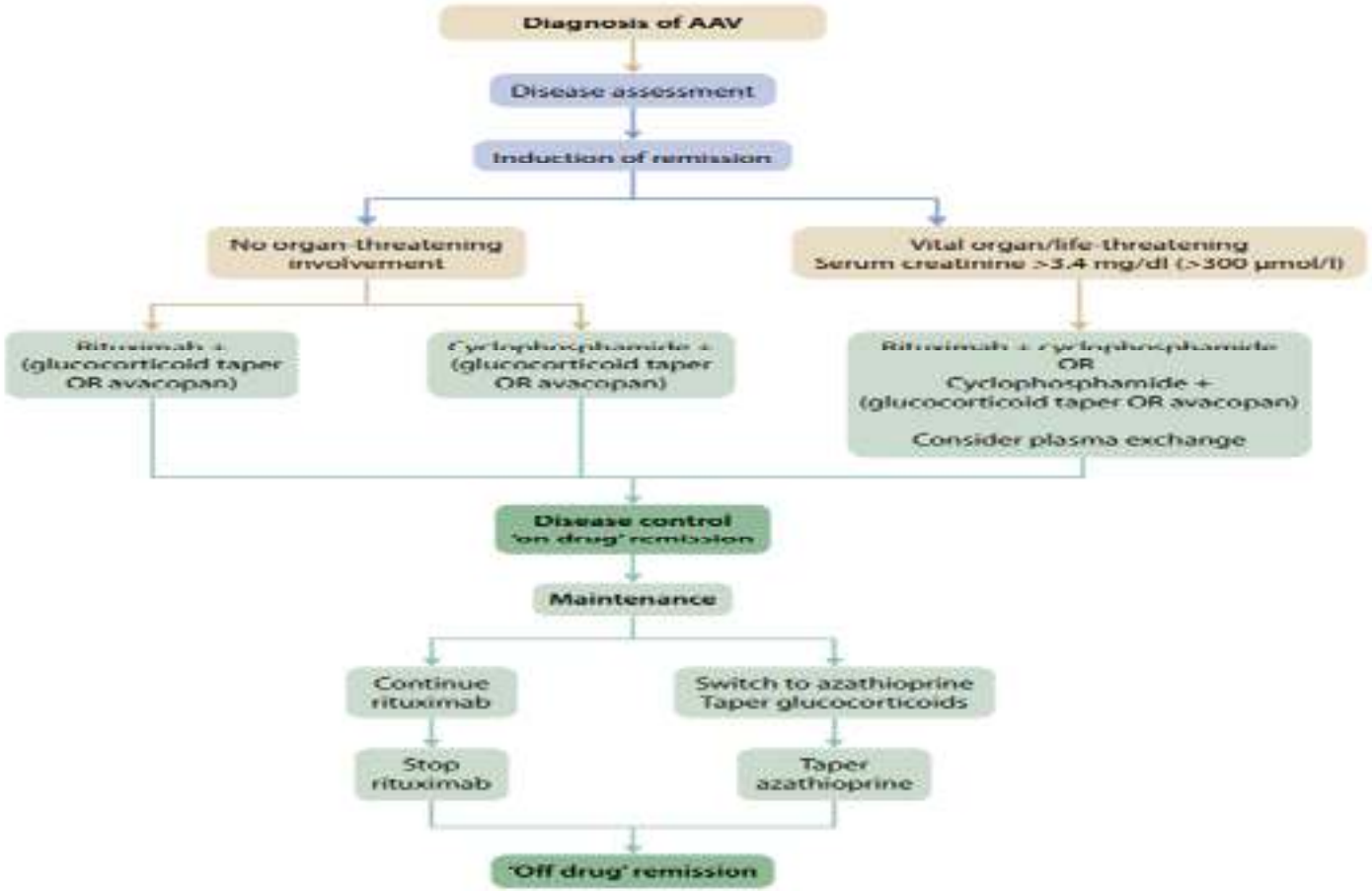


Figure 6 | Practical treatment regimen for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody.

INDUCTION

- Cyclophosphamide and glucocorticoids have been the cornerstone of remission-induction therapy for severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis for 40 years.
- a multicenter, randomized, double-blind, double-dummy, noninferiority trial of rituximab (375 mg per square meter of body-surface area per week for 4 weeks) as compared with cyclophosphamide (2 mg per kilogram of body weight per day) for remission induction was conducted 2010.
- Concluded that Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease.

Rituximab vs cyclophosphamide

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered

Figure 7 | Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF	Avacopan
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m²/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m²/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with i.v. cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response	30 mg twice daily as alternative to glucocorticoids, in combination with rituximab or cyclophosphamide induction
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m²	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m²				

Figure 10 | Immunosuppressive drug dosing for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil.

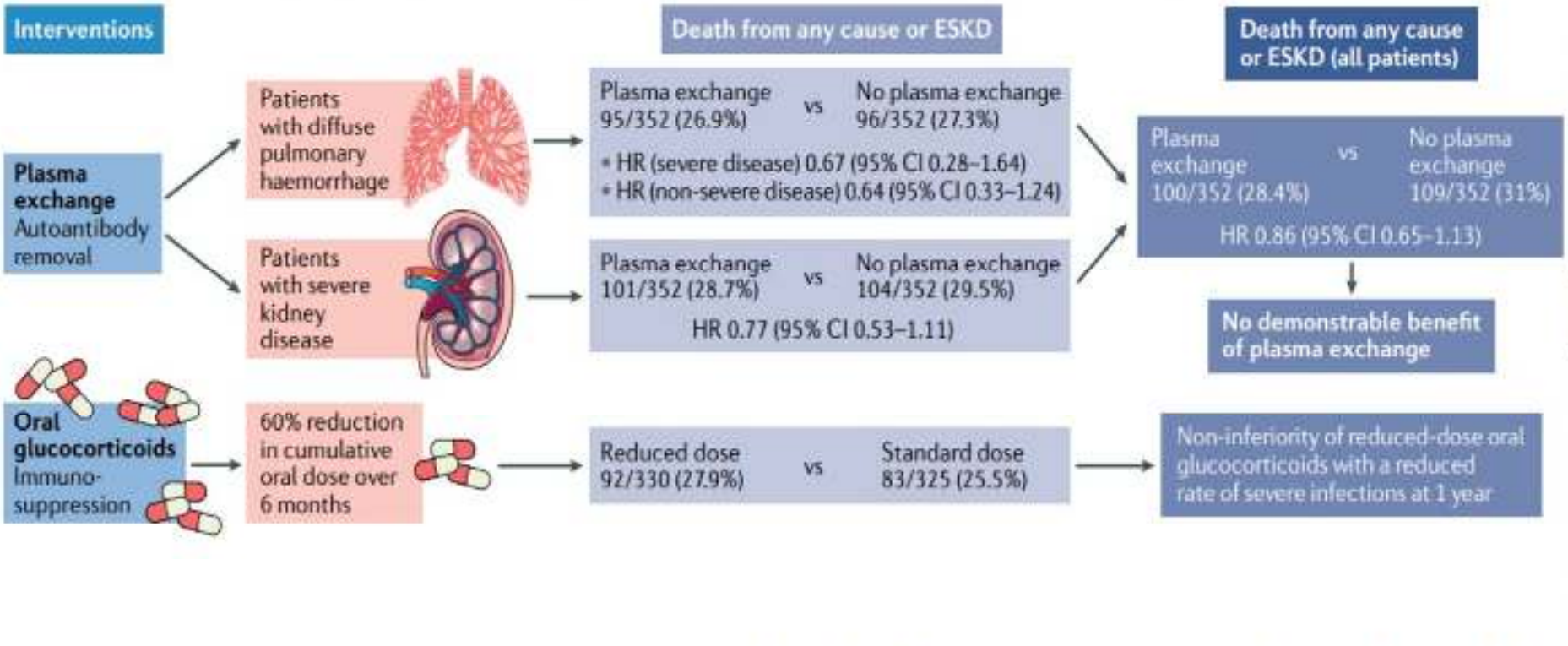
Avacopan

- Avacopan is a complement 5a receptor (C5aR) antagonist that blocks C5a-induced upregulation of C11b (integrin alpha M) on neutrophils and inhibits C5a-mediated neutrophil activation and migration.
- Avacopan is a cytochrome P450 3A4 inhibitor.
- Avacopan, sold under the trade name Tavneos, can be used as an alternative to glucocorticoids.
- Patients at high risk of glucocorticoid toxicity are likely to benefit from avacopan.
- FDA approved.

Plasma exchange

- Consider plasma exchange in the following scenario:
- patients with SCr >3.4 mg/dl (>300 mmol/l),
- patients requiring dialysis, or with rapidly increasing SCr.
- patients with diffuse alveolar hemorrhage who have hypoxemia.
- patients with an overlap syndrome of ANCA-associated vasculitis and anti-glomerular basement membrane (GBM)

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable



Walsh, M. et al. N. Engl. J. Med. 382, 622–631 (2020)

- Results of PEXIVAS trial indicate that PEX does not reduce the risk of ESKD and death in AAV
- However, this study has limitations it included

- patients with eGFR<50 ml/min per 1.73 m2 ,

- evidence of pulmonary hemorrhage only in one-third of cases (and with <85% ox saturation only in 61 out of 191)

- hemodialysis requirement in one-fifth.

The inclusion of a substantial proportion of patients **with mild disease** might have obscured the detection of benefit for the most critical outcomes

Maintenance therapy

- Is given to all patients with AAV after induction of remission with either cyclophosphamide or rituximab.

This maintenance therapy aims to prevent relapse of disease after induction of remission.

Rituximab maintenance after cyclophosphamide induction is superior to azathioprine for preventing relapses in 1 RCT.

longer maintenance reduces the relapse rate but could be associated with more adverse events

- The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.
- When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur.
- Consider mycophenolate mofetil (MMF) or methotrexate as alternatives to azathioprine for maintenance therapy in patients intolerant of azathioprine.

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Limited availability of rituximab

Figure 13 | Considerations for using rituximab or azathioprine for AAV maintenance therapy. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; IgG, immunoglobulin G; PR3, proteinase 3.

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until 1 yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yr
	Extend azathioprine at complete remission until 4 yr after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yr after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yr and then slowly reduced by 1 mg every 2 mo	

Figure 14 | Immunosuppressive dosing and duration of AAV maintenance therapy. MAINRITSAN, MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis; MMF, mycophenolate mofetil; RITAZAREM, Rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasm antibody-associated vasculitis (AAV). *RITAZAREM was in relapsing AAV.

Risk Factors for Relapse

- Cardiovascular or lung involvement.
- Persistent ANCA-positivity after induction of remission/ • Rise in ANCA
- Diagnosis of granulomatosis with polyangiitis .
- PR3–ANCA subgroup.
- Higher serum creatinine.
- More extensive disease .
- Ear, nose, and throat disease.
- History of relapse.

Special situations

Refractory disease

- Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa.
- Plasma exchange can be considered

- In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange can be considered in addition to glucocorticoids with either cyclophosphamide or rituximab
- Delay transplantation until patients are in complete clinical remission for >6 months.
- The persistence of ANCA should not delay transplantation.

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- Thank you
- Questiones ???

PEDIATRIC NEPHROLOGY UNIT
(PNU)

Proteinuria After Renal Transplantation in Children

Dr. Fatina Fadel

Professor of Pediatric Nephrology

Cairo university

Renal Tx in children

Best renal replacement therapy for children with ESRD with the best survival

Growth

Quality of life

Social adjustment

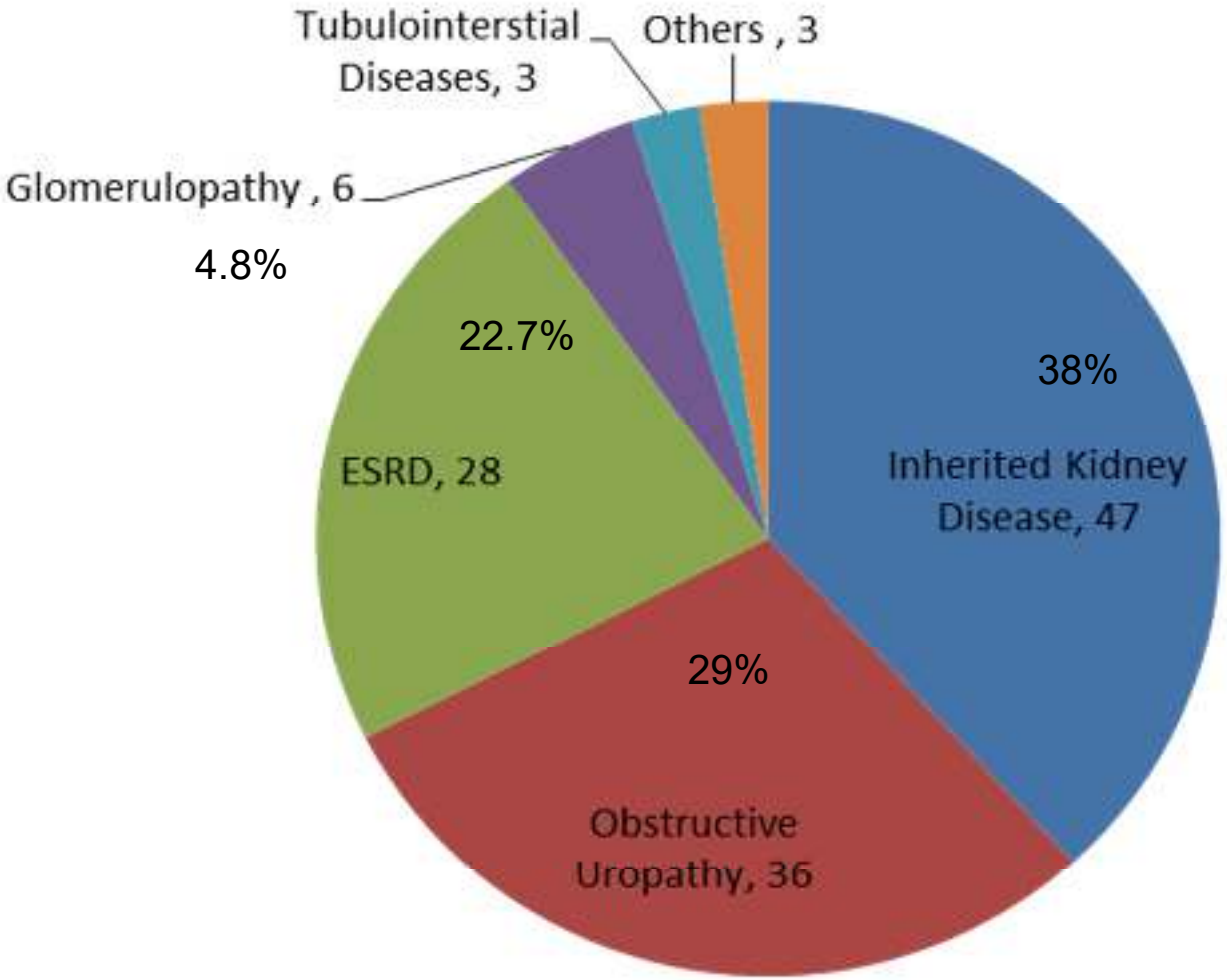
Children are "SPECIFIC patients", and not "small ADULTS

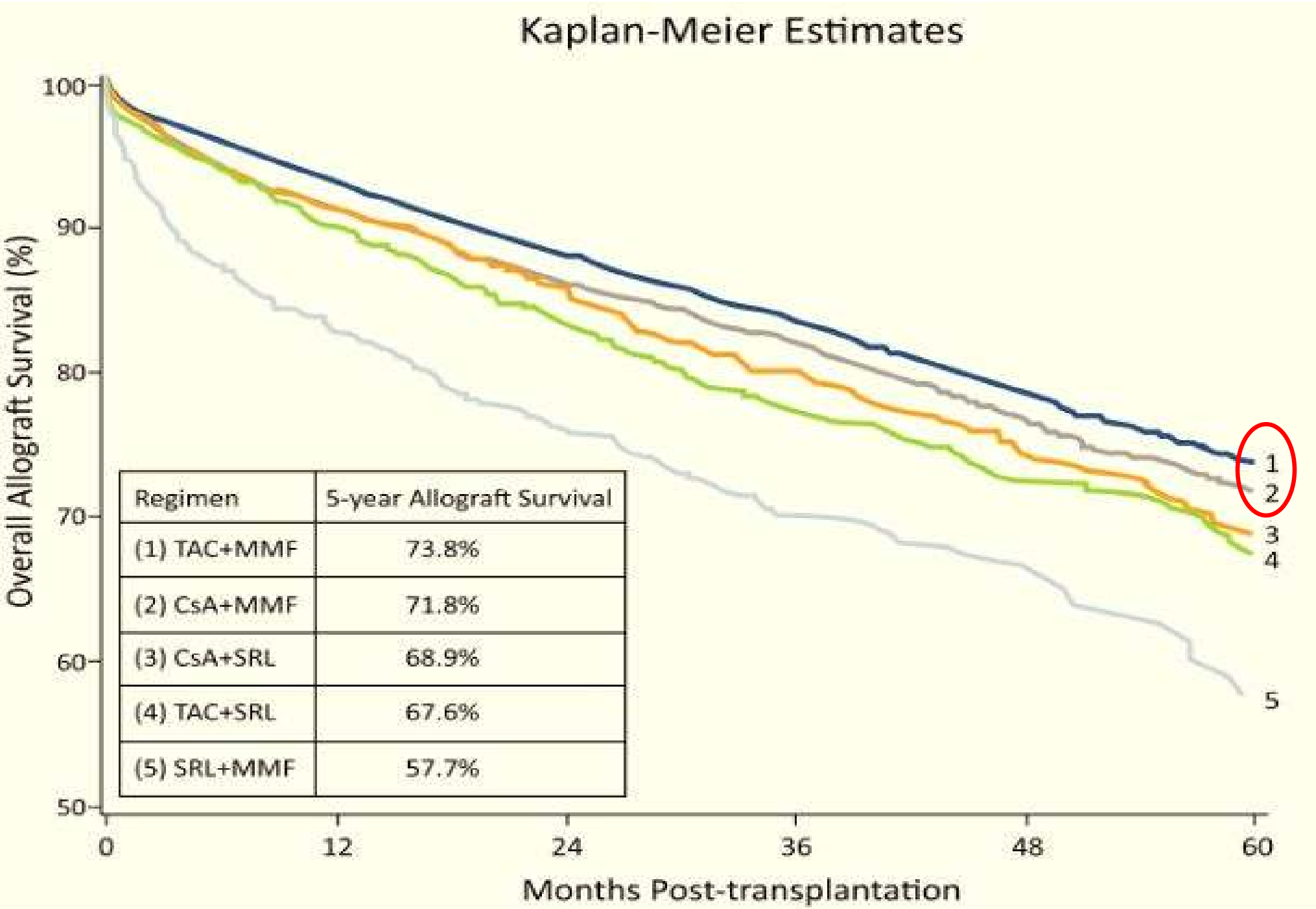
RTx in children is more challenging than adults

- Low circulatory volume
- Size mismatch
- Unique immune system
- Etiology

Original Disease of Transplanted Children At Cairo University Children's Hospital

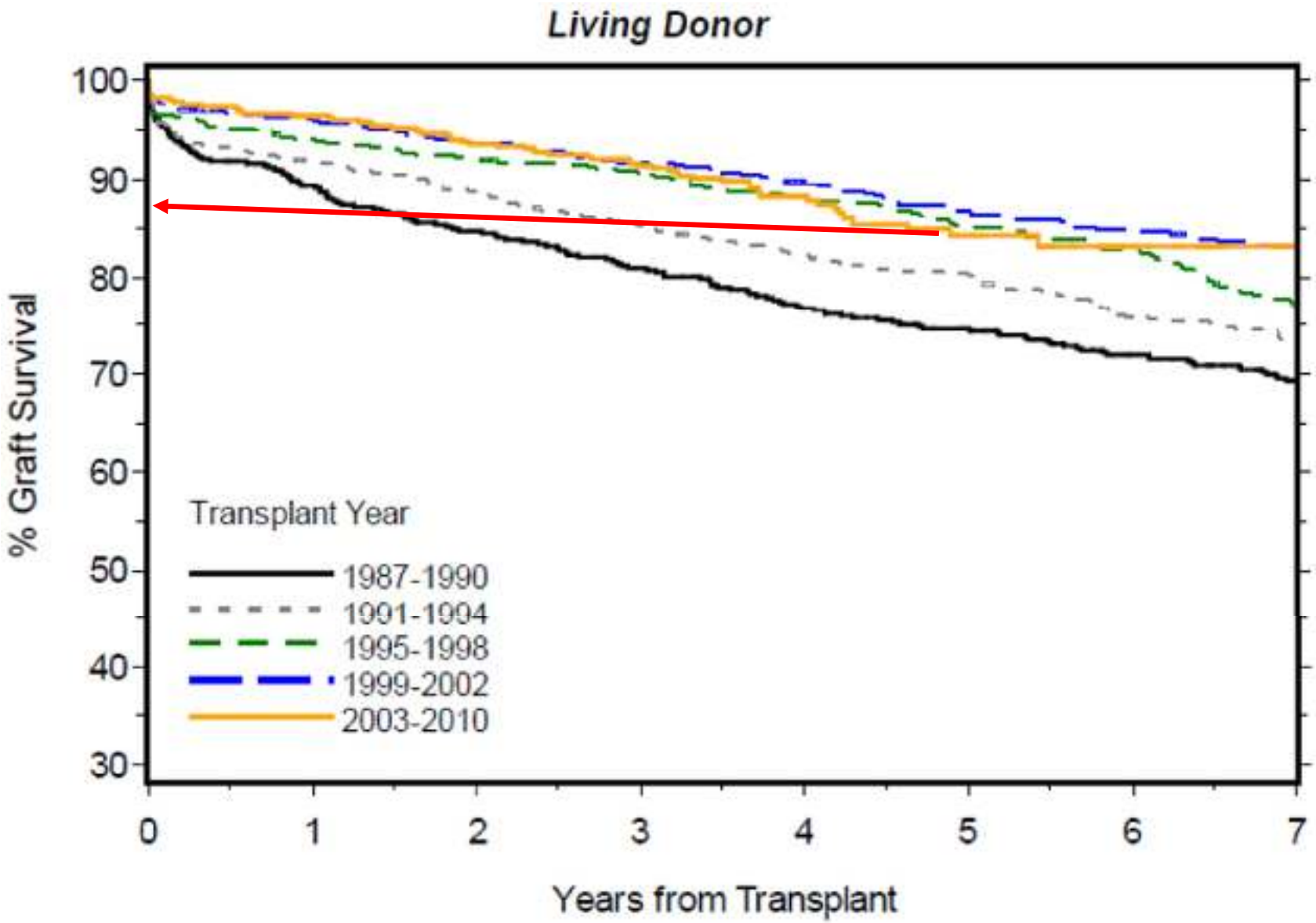
PEDIATRIC NEPHROLOGY UNIT (PNU)





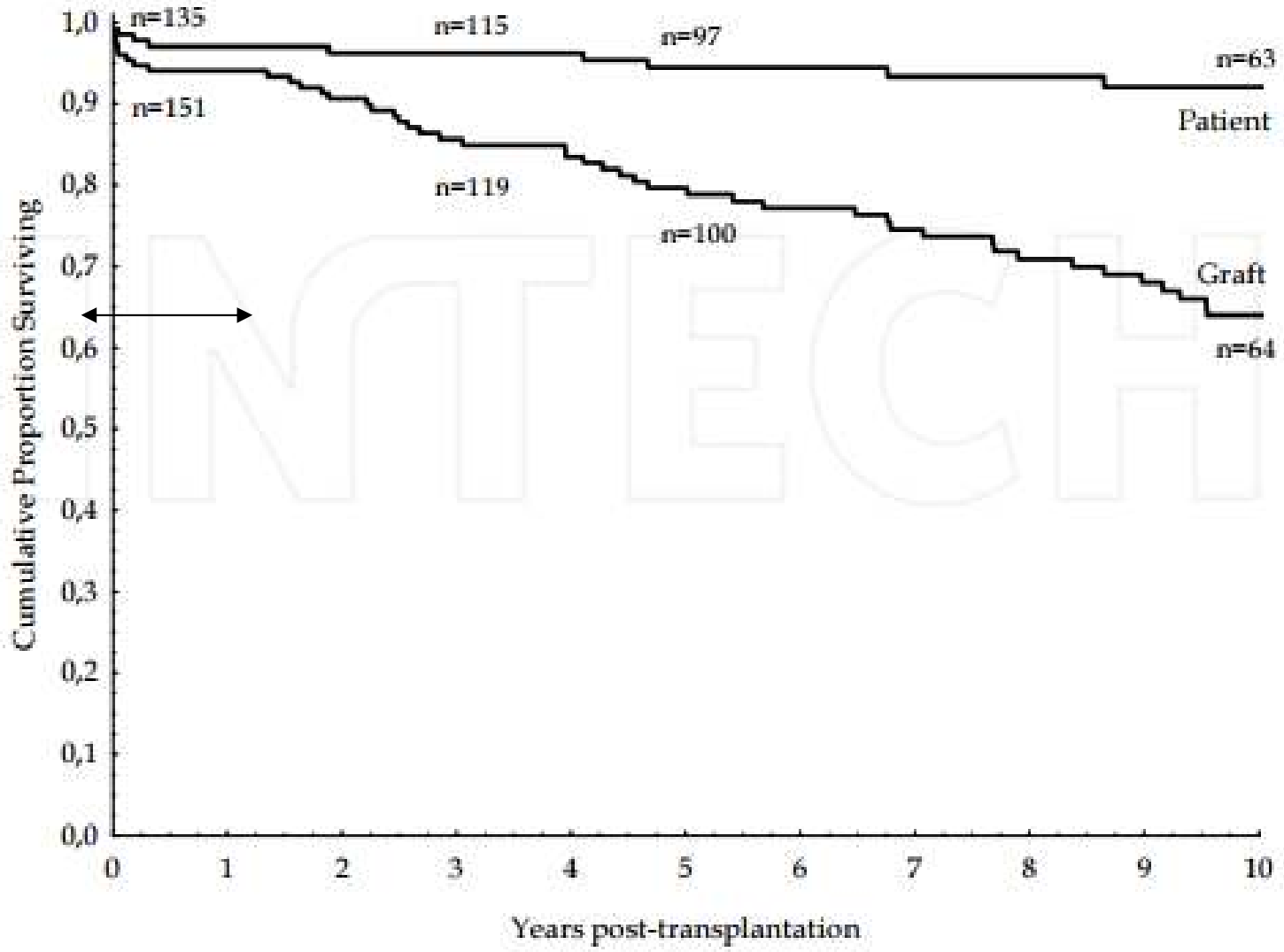
TAC = tacrolimus; MMF = mycophenolate mofetil; SRL = sirolimus; CsA = cyclosporine microemulsion

Long-term outcomes of children after solid organ transplantation



Kim JJ and Marks SD, Clinics vol.69 supl.1 São Paulo 2014

Graft Outcome in Pediatric Renal Transplantation: a Single Center Study



Herman J and Damme-Lombaerts RV, 2011 www.intechopen.com

Outcome of Pediatric Kidney Transplantation in Iran

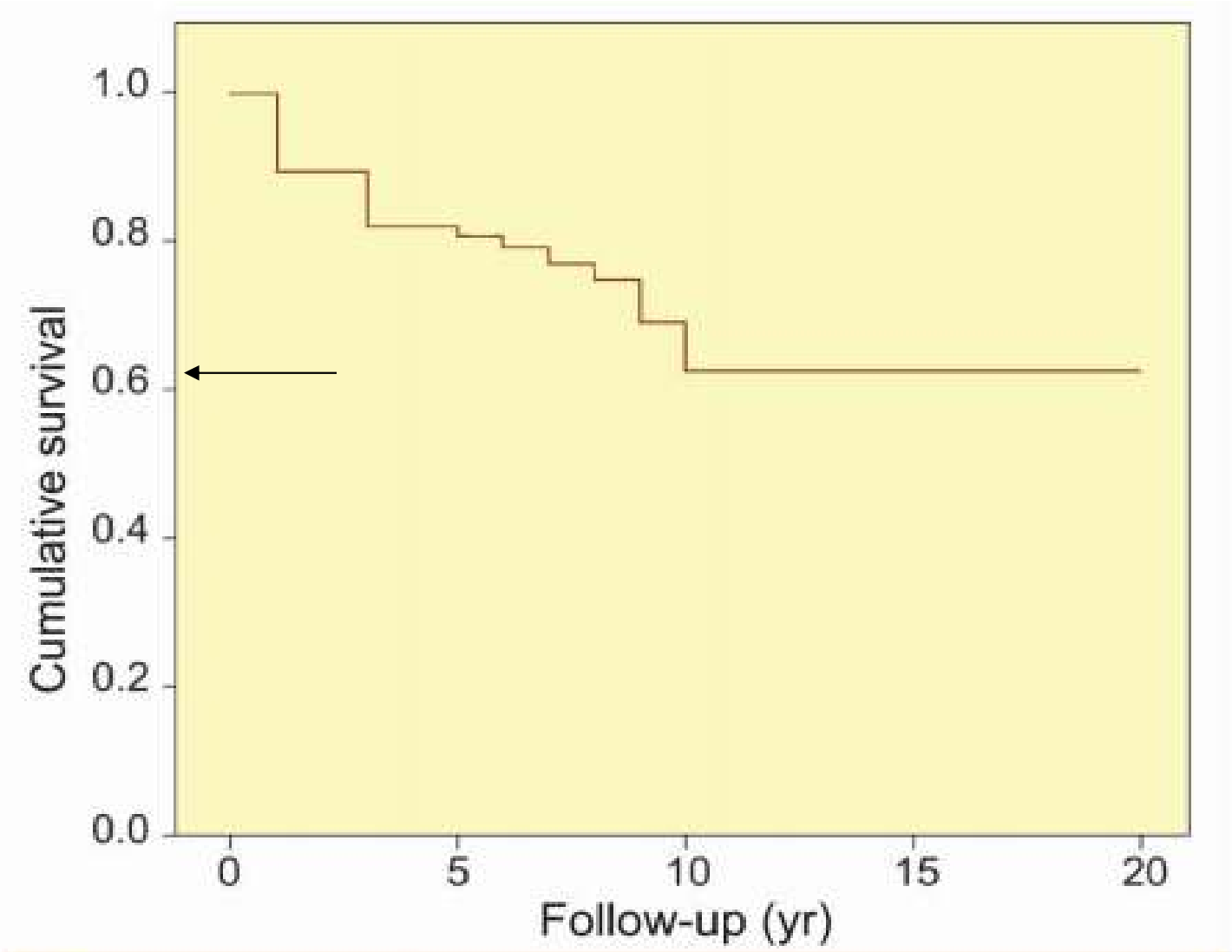
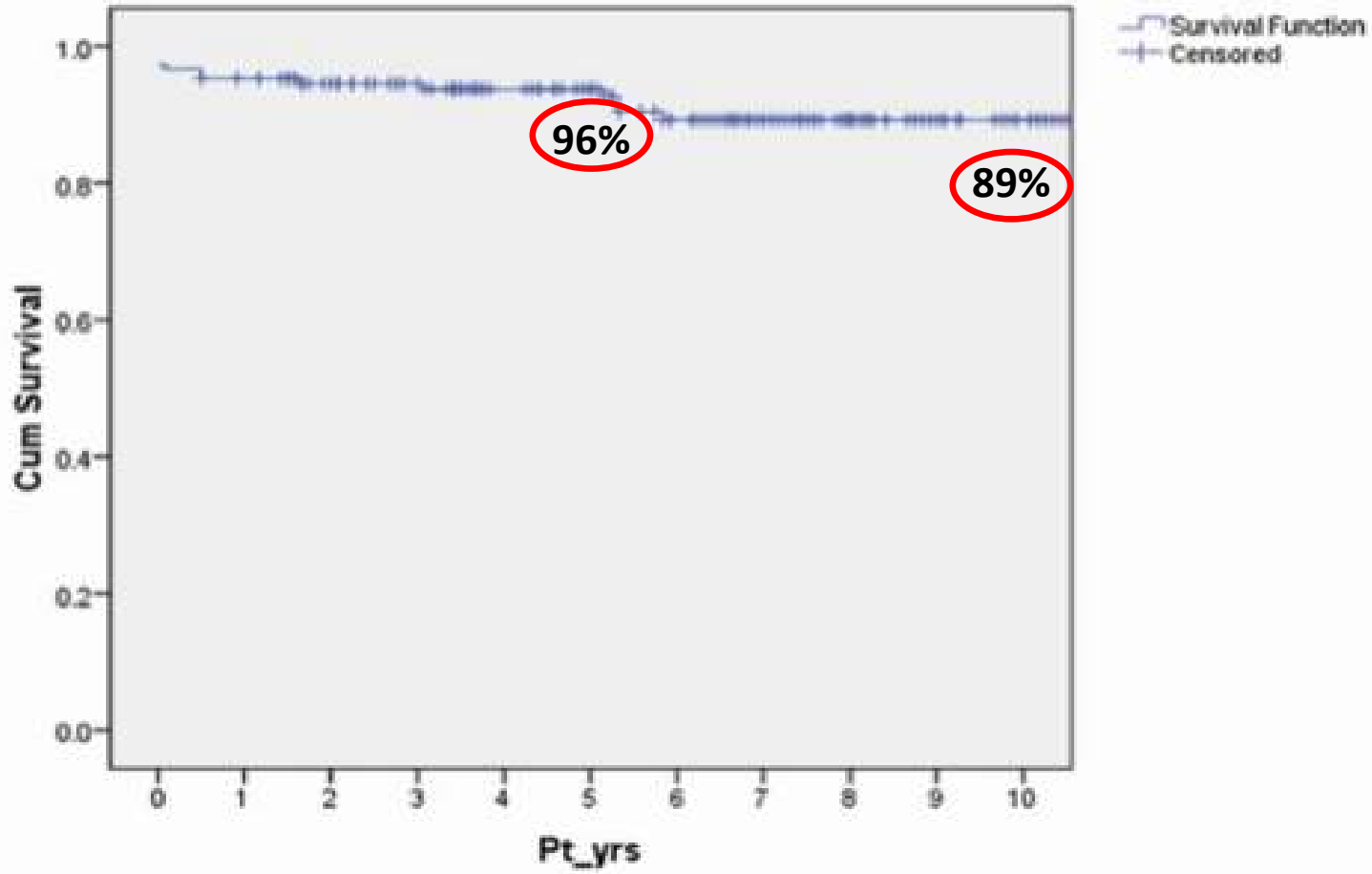
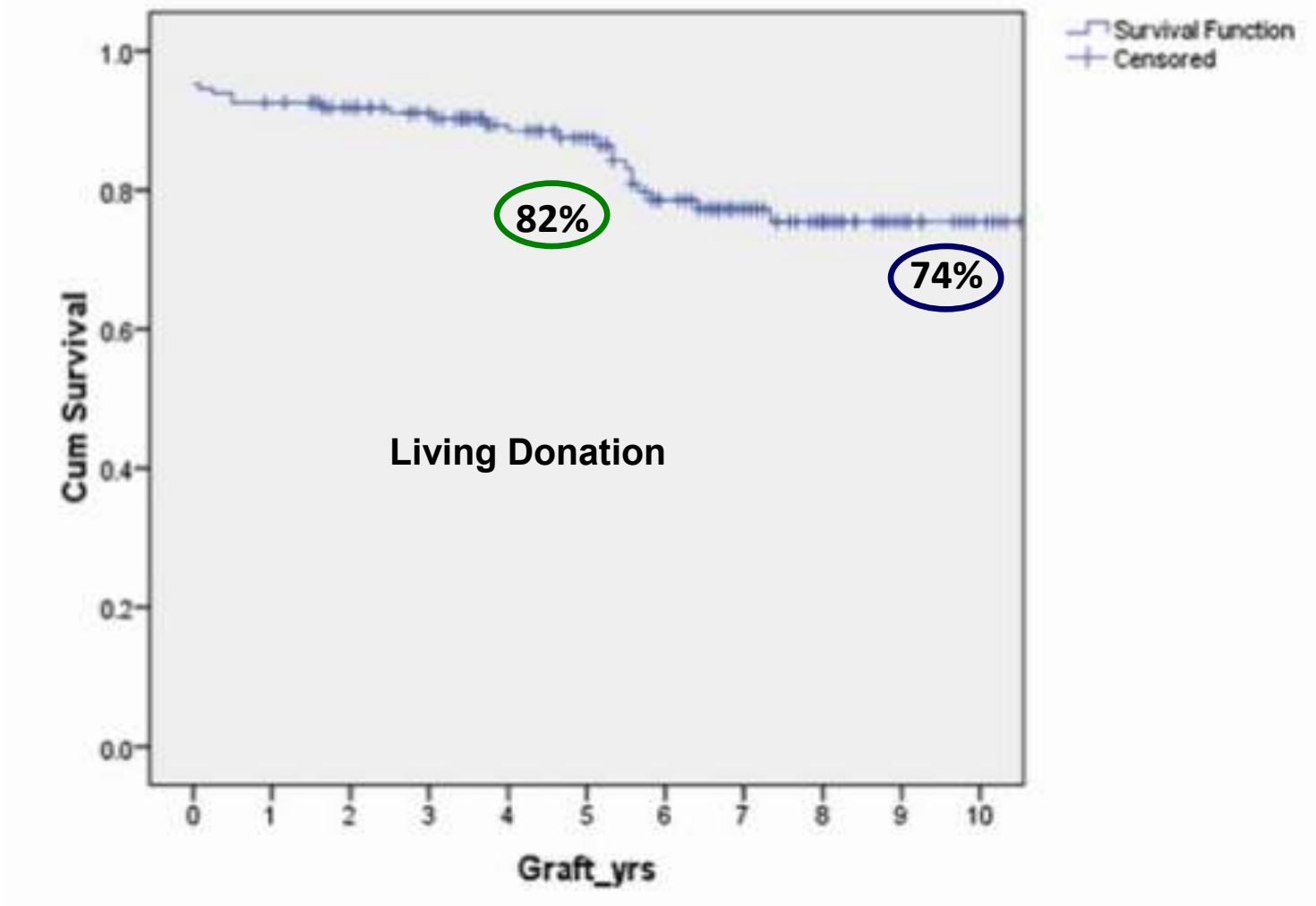


Figure 1: The overall graft survival among pediatric recipients of kidney transplantation

Naderi G et al, Int J Org Transplant Med 2017; Vol. 8 (2) : 85 - 96



Fadel F, et al, Pediatr Transpl, 2020, 24 (6) / e13724



Fadel F, et al, Pediatr Transpl, 2020, 24 (6) / e13724

Long-term outcomes of children after solid organ transplantation

Organ	Patient survival (%)			Allograft survival (%)		
	1 year	5 year	10 year	1 year	5 year	10 year
Kidney, LD (top), DD (bottom) (1)	98.4	96.1	92.4	96.5	84.3-87	54
	97.4	93.3	86.6	95.1	66-78.0	51
Liver (15)	84-89.8	82-84.8	77	84-93	81-88	75
Heart (13)	80	68	58	86-90	68-75	
Lung (12)	83	54	44 (7 yr)	78-88	35-41	
Intestinal (34)	80-95	77	46	88	74	58

Patient and allograft survival of children after kidney, liver, heart, lung and intestinal transplantation. Living Donor, Deceased Donor.

Kim JJ and Marks SD, Clinics vol.69 supl.1 São Paulo 2014

Graft Outcome in Pediatric Renal Transplantation: a Single Center Study

	df	HR	95% CI	p Value
Time on dialysis (years)	1	1.17	1.02-1.34	0.030
>5 Transfusions pre-Tx	1	1.82	1.12-2.97	0.016
HLA-A mismatch (2 vs. 0-1)	1	1.96	0.96-3.98	0.064
Cold ischemia time (h) (DD)				
continue variable	1	1.03	1.002-1.065	0.034
>30 h vs. ≤ 30 h	1	2.63	1.31-5.26	0.006
Warm ischemia time (min)				
as continue variable	1	1.016	0.996-1.037	0.11
>40 min vs. ≤ 40 min	1	1.66	1.02-2.71	0.042
Year of transplantation	1	0.95	0.91-0.99	0.008
Absence of calcineurin inhibitors	1	4.31	2.44-7.63	<0.0001
Dialysis in the first week post-Tx (DGF)	2			0.001
Risk graft failure within first 3 months	1	16.89	3.41-83.80	0.001
Risk graft failure after first 3 months	1	1.05	0.54-2.04	0.88
Acute rejection	1	2.61	1.55-4.40	0.0003
Proteinuria (>1 g/24 h) at 1 year	1	4.13	2.01-8.48	0.0001
Hemoglobin at 1 year (g/dl)	1	0.67	0.54-0.82	0.0002
Creatinine clearance at 1 year (ml/min/1.73 m²)	1	0.97	0.95-0.98	<0.0001

df: degrees of freedom; HR: hazard ratio; CI: confidence interval

Table 3. Predictors of graft outcome in univariable analysis (p<0.10)

Herman J and Damme-Lombaerts RV, 2011 www.intechopen.com

Post-transplant proteinuria

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Post-transplant proteinuria (Classification)

Onset of proteinuria

Early

Late

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Main causes of proteinuria in kidney transplantation.

Main causes of tubular proteinuria	Main causes of glomerular proteinuria
Ischemia-reperfusion injury	Recurrent glomerular diseases
Acute kidney injury	*De novo* glomerular or systemic diseases
Acute rejection	Transplant glomerulopathy
mTOR inhibitors	Chronic rejection
CNI	mTOR inhibitors
Aminoglycosides	CNI
Antiviral drugs	Obesity
	Arterial hypertension
	Hepatitis C or B

Ponticelli C and Graziani G, Transplant International 25 (2012) 909–917

Proteinuria in pediatric renal transplant recipients during the first 60 post-transplant days

Abstract: Although normative values of post-transplant proteinuria have been reported in adults, data for pediatric renal transplant recipients have not been previously published. We hypothesized that pediatric renal transplant recipients achieve normal urinary protein to creatinine (UProt/UCr) ratios (< 0.2) by 60 days post-transplant in the absence of early recurrent disease. Retrospective chart review of 108 consecutive pediatric renal transplant recipients at Stanford University was performed. Thirty-two (30%) patients who were eligible had ≥1 UProt/UCr ratio obtained during the first 60 post-transplant days. Mean age at transplant was 13.9 ± 4.2 yr. UProt/UCr ratios were grouped by week post-transplant for quantile analysis. Mean weekly UProt/UCr values were not lower than 0.2 until the ninth post-transplant week. No difference in post-transplant proteinuria existed between nephrectomized and non-nephrectomized transplant recipients. Experience with a single patient with proven focal segmental glomerulosclerosis (FSGS) recurrence suggests that normative UProt/UCr data may be useful in early identification of patients experiencing disease recurrence. Univariate correlations demonstrated that UProt/UCr negatively correlated with serum albumin levels (−0.415, $p < 0.0001$) and days post-transplant (−0.531, $p < 0.0001$).

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Transplant Proc. 2014 Jan-Feb;46(1):141-4. doi: 10.1016/j.transproceed.2013.06.022.

Early proteinuria after renal transplantation and allograft outcomes.

Gulleroglu K[1], Baskin E[2], Bayrakci U[2], Akdur A[3], Moray G[3], Haberal M[3].

Author information

Abstract

BACKGROUND: Proteinuria is among the major and nonspecific sign of the renal disease. It is well known that late-onset proteinuria after renal transplantation has been associated with poor allograft outcomes and with mortality. Knowledge about the impact of early proteinuria on the various outcomes is limited. We have evaluated the utility of measuring early proteinuria in the management of pediatric renal transplant recipients.

METHODS: We analyzed the effect of proteinuria at 3 months of posttransplantation on allograft rejection, graft loss, and estimated glomerular filtration rate (GFR) at 3 years. Proteinuria was assessed using 24-hour urine protein excretion. Renal biopsy was performed when elevated creatinine levels were elevated during routine follow-up and an acute rejection episode was proven with biopsy.

RESULTS: Sixty-seven pediatric renal transplant recipients were included to the study. Mean follow-up time after transplantation was 48.8 ± 12.1 months. Thirty-nine recipients (58%) have proteinuria >500 mg/d. The relationship could not be shown between proteinuria at posttransplant month 3 and other outcomes parameters, such as graft loss and lower estimated GFR. A significant positive correlation between acute rejection and the proteinuria at posttransplant month 3 was shown.

CONCLUSION: We demonstrated that

Proteinuria in pediatric renal transplant recipients during the first 60 post-transplant days

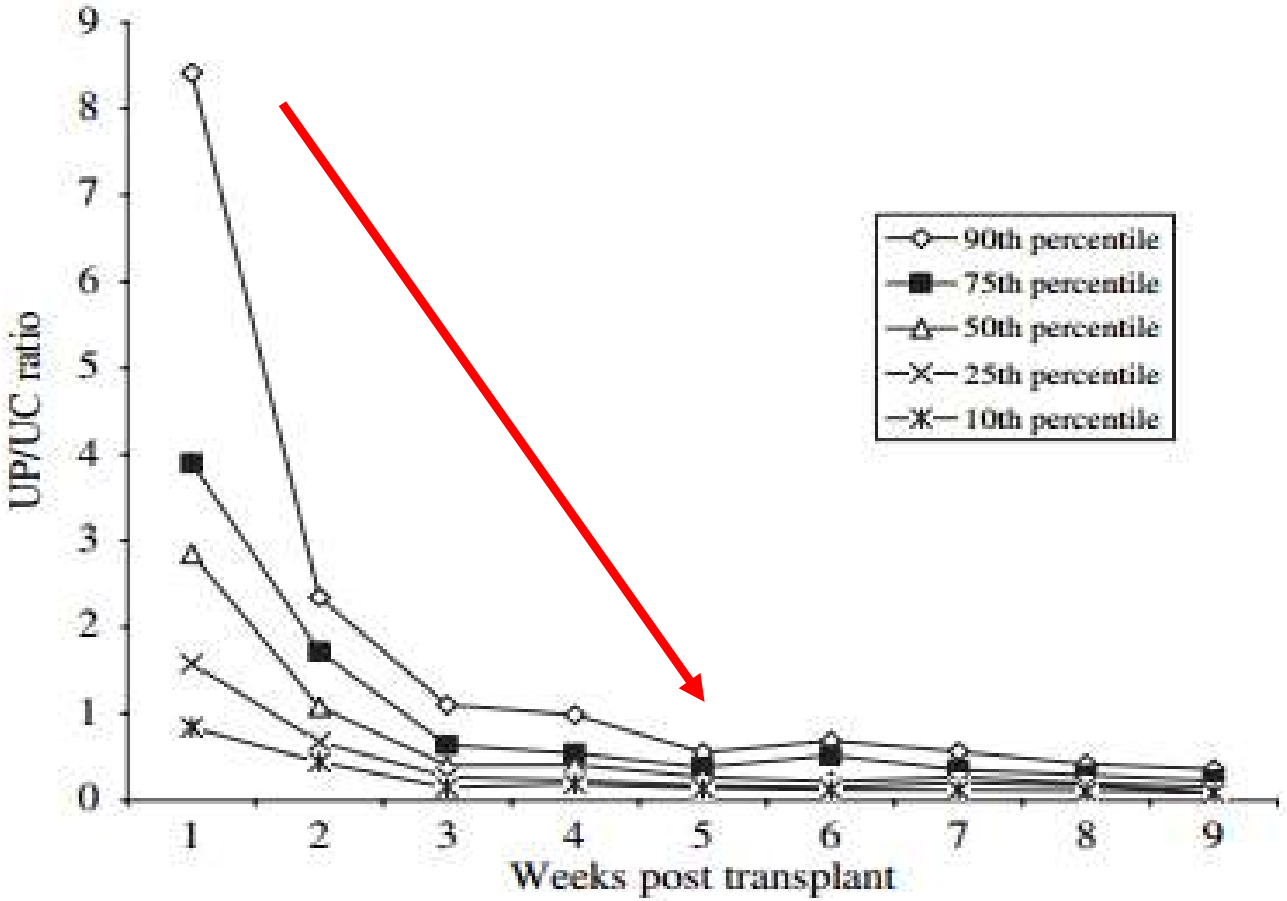


Fig. 1. Quantiles for urinary protein/urinary creatinine (mg/mg) ratios are plotted for the first 9 wk post-transplant.

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Proteinuria in pediatric renal transplant recipients during the first 60 post-transplant days

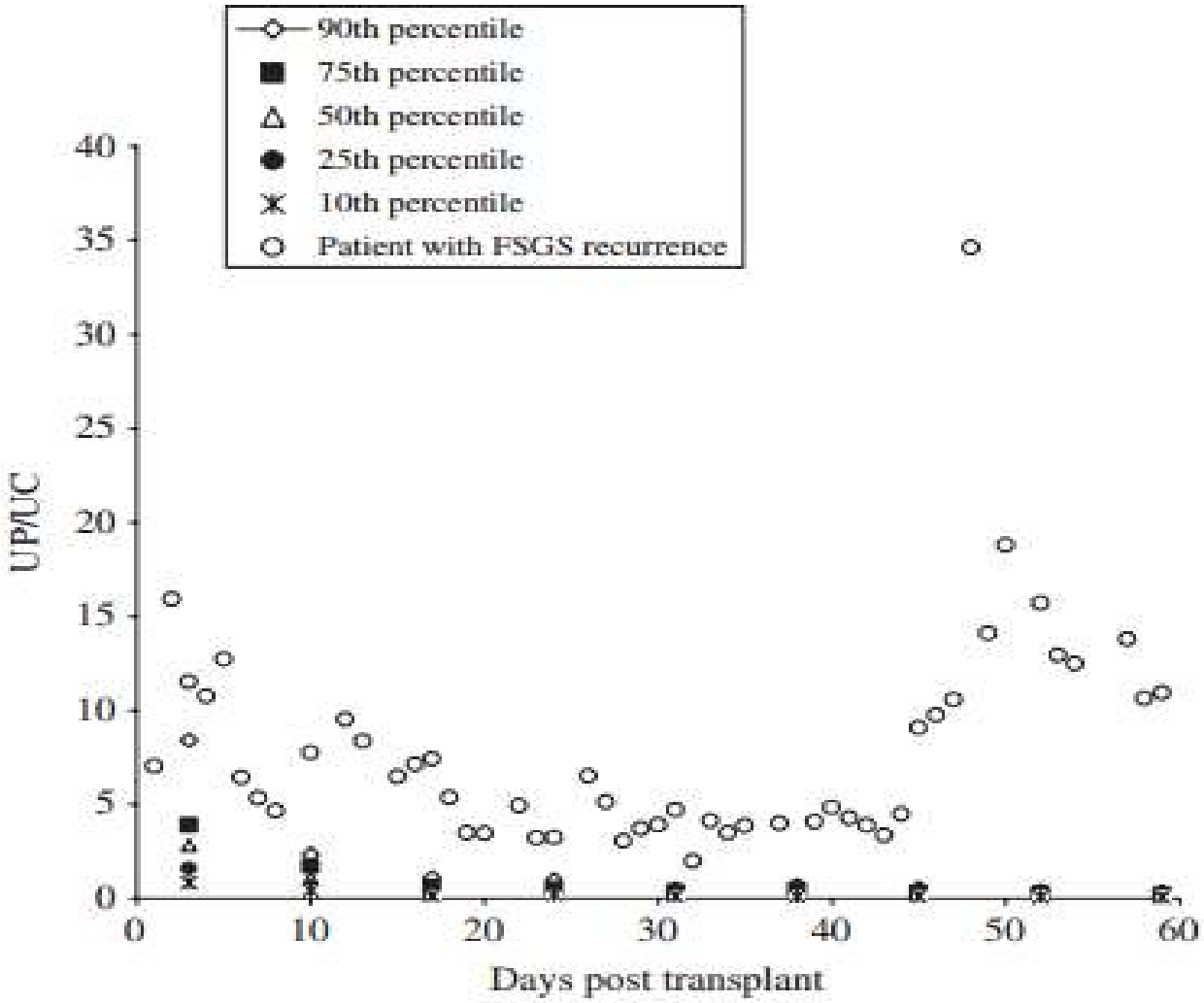


Fig. 2. Urinary protein/urinary creatinine (mg/mg) ratios of patient who experienced recurrence of FSGS shortly after transplant (open circles) plotted in relation to the quantiles.

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Transplant Proc. 2012 Jun;44(5):1227-30. doi: 10.1016/j.transproceed.2012.01.122.

Early renal transplantation after donor renal angiography affects initial graft function.

Tutal E[1], Canver B, Can S, Colak T, Sezer S, Haberal M.

Author information

Abstract

BACKGROUND: Renal angiography of a living donor is a common radiologic examination before transplantation. However, the contrast agent used during this procedure can cause contrast nephropathy. There are insufficient data regarding whether this radiocontrast exposure detoriates renal function and survival after transplantation. In this study, we analyzed the effects of radiocontrast exposure to donors before transplant surgery on the incidence of delayed graft function (DGF) and on the outcomes of recipients at 1 year posttransplantation.

METHODS: We divided 80 living donor transplantations according to the duration between the renal angiography and the transplantation procedure: Group 1 as early transplantation at ≤ 20 days (n = 42) versus group 2 of late transplantation at ≥ 20 days (n = 38). We retrospectively collected acute rejection episodes and graft survival at 1 year, monthly serum creatinine values of, DGF, proteinuria at 1 month, GFR at posttransplant day 3 month 1, and 1 year.

RESULTS: There were 10 group 1 recipients (23.8%) and 2 group 2 (5.3%) subjects who experienced ≥ 1 acute rejection episode in the 1st posttransplant year (P = .02); 1 patient in each group experienced graft loss at 1 year (P = .941). DGF was observed in 9 (22%) versus 1 patient (2.6%) in group 2 (P = .009). Posttransplant day 3 creatinine values were significantly higher (P = .005) with significantly lower GFR values (P = .043) in group 1. However, creatinine and GFR levels were similar at 1 month and 1 year. Month 1 proteinuria levels were significantly higher in group 1 (P = .014). There was a significant negative correlation between renal angiography time and month 1 proteinuria (P = .014).

Pediatr Nephrol. 2015 Oct;30(10):1853-60. doi: 10.1007/s00467-015-3114-6. Epub 2015 Apr 30.

Proteinuria 1 year after renal transplantation is associated with impaired graft survival in children.

Rosík T[1], Chadimová M, Dušek J, Háček J, Šimánková N, Vondrák K, Zieg J, Seeman T.

Author information

Abstract

BACKGROUND: Proteinuria is a common manifestation of chronic kidney disease (CKD), and there is a high incidence of CDK and its complications following renal transplantation. However, little data are available on the association between proteinuria and graft/patient survival in the paediatric transplant population. The primary aim of this study was to investigate the associations between posttransplant proteinuria and graft/patient survival in children after renal transplantation.

METHODS: In this retrospective study, we screened all 91 children receiving renal allografts at a single institution between 1997 and 2007. The inclusion criteria were a functioning graft at 1 year posttransplant, data availability and no recurrence of focal-segmental glomerulosclerosis. The final cohort included 75 patients. Proteinuria was considered to be pathologic if the urinary protein/creatinine ratio was >30 mg/mmol. Donor and recipient characteristics, data on proteinuria, estimated glomerular filtration rate (eGFR) and rejection episodes were analysed. The most recent of the biopsies performed during the follow-up after 1 year posttransplant were analysed separately in the proteinuric group and the non-proteinuric group.

RESULTS: Proteinuria at 1-year posttransplant was pathologic in 35 % of patients. The 5-year graft survival rate was significantly lower in the proteinuric group than in the non-proteinuric group (77 vs. 100 %; $p < 0.001$). Proteinuria at 1 year posttransplant was associated with reduced long-term graft survival independent of other risk factors, including decreased eGFR or episodes of acute corticosensitive and corticoresistant rejection. The most frequent histologic finding in the proteinuric group was chronic rejection. There was no significant difference in the 5-year patient survival rate between the proteinuric group and the non-proteinuric group.

CONCLUSION: This study emphasizes the importance of proteinuria as a prognostic factor of renal allograft survival in children.

Proteinuria after kidney transplantation

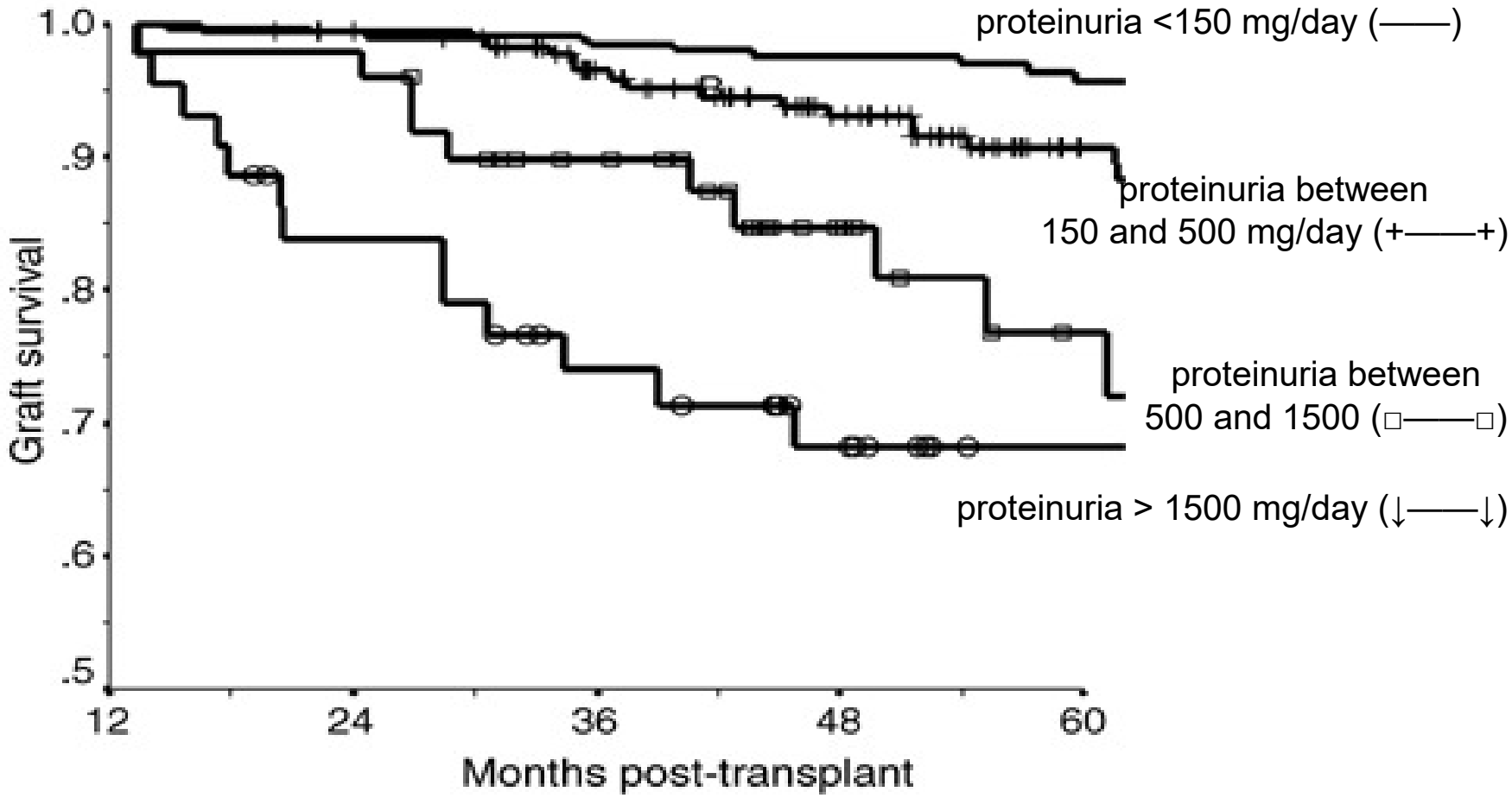
	Hazard ratio for death	Hazard ratio for graft failure
Roodnat (15)	1.98	2.03
Fernandez-Fresnedo (16)	2.05 for proteinuria 0.5–1 g/day 2.3 for proteinuria >1 g/day	2.33 for proteinuria 0.5–1 g/day 3.46 for proteinuria >1 g/day
Amer (18)	–	1.40 for proteinuria >0.2 g/day
Halimi (48)	5.37 for presence of NAP 4.12 for presence of macroalbuminuria	4.0 for every g/day of NAP 1.86 for every g/day of macroalbuminuria
Cherukun (49)	2.6 if proteinuria >1 g/day	7.1 if proteinuria 0.16–0.5 g/day 10.5 if proteinuria 0.51–1 g/day 16.0 if proteinuria >1 g/day

NAP, non albuminuric proteinuria.

Risk of death and graft failure in patients with proteinuria

Ponticelli C and Graziani G, Transplant International 25 (2012) 909–917

Proteinuria After Kidney Transplantation, Relationship to Allograft Survival



Amer H et al, January 2008 *with* 57 ReadsDOI: 10.1111/j.1600-6143.2007.02006.x ·

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Aminoglycosides	CNI
Antiviral drugs	Obesity
	Arterial hypertension
	Hepatitis C or B

Ponticelli C and Graziani G, Transplant International 25 (2012) 909–917

Disease recurrence in paediatric renal transplantation

Primary disease	Recurrence rate	Graft loss to recurrence
FSGS	14–50%	40–60%
Atypical HUS	20–80%	10–83%
Typical HUS	0–1%	0–1%
MPGN type 1	30–77%	17–50%
MPGN type 2	66–100%	25–61%
SLE nephritis	0–30%	0–5%
IgA nephritis (Berger disease)	35–60%	7–10%
Henoch–Schönlein nephritis	31–100%	8–22%
Primary hyperoxaluria type 1	90–100%	80–100%

Cochat P, et al, Pediatr Nephrol (2009) 24:2097–2108
DOI 10.1007/s00467-009-1137-6

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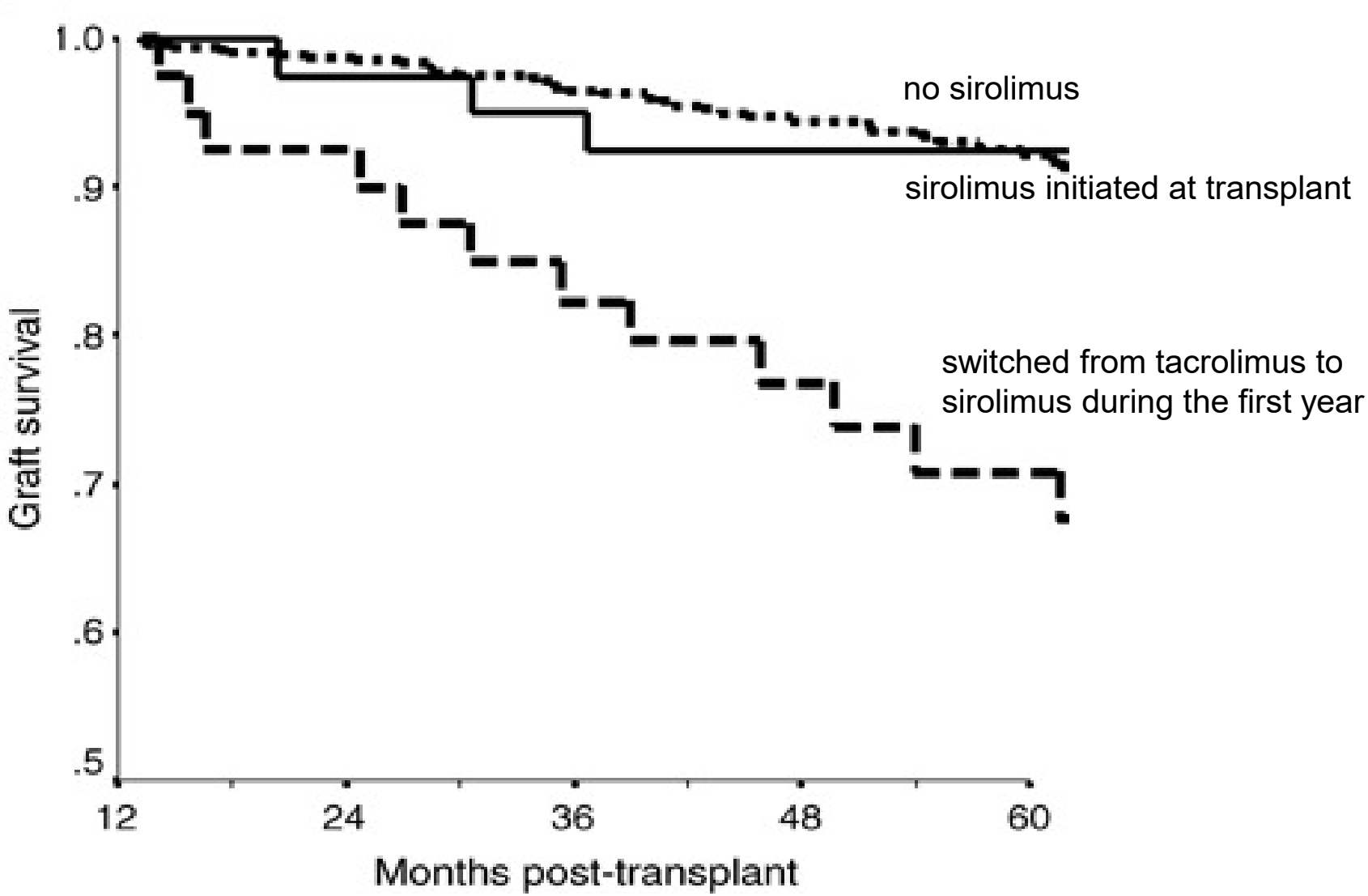
Cochat P, et al, Pediatr Nephrol (2009) 24:2097–2108
DOI 10.1007/s00467-009-1137-6

mTOR inhibitors-induced proteinuria

- **May interfere with the protein endocytosis in the tubular epithelial cell**

- **↑intraglomerular pressure with a concomitant reduction of kidney reserve, suggesting that proteinuria may be caused at least partially by glomerular hyperfiltration**

Sirolimus related Proteinuria After Kidney Transplantation, Relationship to Allograft Survival



Amer H et al, January 2008 *with* 57 ReadsDOI: 10.1111/j.1600-6143.2007.02006.x ·

Pre-transplantation preparation to decrease risk of recurrence

- Pretransplant evaluation to detect any risk factor
- Determining the underling etiology
- Proper donor selection
- Pretransplant and early management of the recipient to decrease risk of recurrence
- Nephrectomy when indicated

Recurrent Disease in Pediatric Renal Transplantation

Risk factors for recurrence/graft loss in patients with steroid-resistant NS

Proven increased risk	Independent/ controversial risk factors	Proven decreased risk
	Gender	
	Mesangial hypercellularity	
	Age at onset over 6 years	
Recurrence in a first graft ++	Presence of FSGS circulating factor	Start of RRT <6 years of age
Start of RRT >12 years of age	Donor source	African-American recipients
White and Asian recipients	HLA typing/matching	Genetic and syndromic NS
Rapid course to ESRD (<3 years)	Time interval on dialysis prior to Tx	
	Type of immunosuppressive therapy	
	Use of induction therapy	
	Bilateral nephrectomy of native kidneys	

Cochat P et al, 2013
Current Pediatrics Reports
DOI 10.1007/s40124-012-0004-2

Post-transplant recurrence of steroid resistant nephrotic syndrome in children: the Italian experience

Abstract Background Steroid resistant nephrotic syndrome (SRNS) is a frequent cause of end stage renal disease in children and post-transplant disease recurrence is a major cause of graft loss. Methods We identifed all children with SRNS who underwent renal transplantation in Italy, between 2005 and 2017. Data were retrospectively collected for the presence of a causative gene mutation, sex, histology, duration of pre-transplant dialysis, age at onset and transplant, HLA matching, recurrence, therapy for recurrence, and graft survival. Results 101 patients underwent a frst and 22 a second renal transplant. After a median follow-up of 58.5 months, the disease recurred on the frst renal transplant in 53.3% of patients with a non-genetic and none with a genetic SRNS. Age at transplant >9 years and the presence of at least one HLA-AB match were independent risk factors for recurrence. Duration of dialysis was longer in children with relapse, but did not reach statistical signifcance. Overall, 24% of patients lost the frst graft, with recurrence representing the commonest cause. Among 22 patients who underwent a second transplant, 5 suffered of SRNS recurrence. SRNS relapsed in 5/9 (55%) patients with disease recurrence in their frst transplant and 2 of them lost the second graft. **Conclusions** **Absence of a causative mutation represents the major risk factor for post-transplant recurrence in children with SRNS**, while transplant can be curative in genetic SRNS. A prolonged time spent on dialysis before transplantation has no protective efect on the risk of relapse and should not be encouraged. Retransplantation represents a second chance after graft loss for recurrence.

Morello W, et al. Journal of Nephrology **2019**, October
doi.org/10.1007/s40620-019-00660-9

- **Nevertheless , a subgroup of patients with the Finnish type of CNS, shows, clear risk for post-RTx proteinuria**

- **Most of these patients have *a homozygous truncating mutation (Fin-major mutation) in the nephrin gene (NPHS1)*, leading to total absence of the major podocyte protein, nephrin**

- **After RTx, these patients develop *anti-nephrin antibodies* resulting in nephrotic range proteinuria**

- **Plasma exchange combined with cyclophosphamide and anti-CD20 antibodies has proved to be successful therapy for these episodes with good long term prognosis**

Holmberg and Jalanko , Pediatr Nephrol 2014

Incidence of recurrence, stratifed by genetic testing results

Characteristics	Total, n = 101	Recurrence, n = 32	No recurrence, n = 69
Genetic results *n*, %			
Negative	37	22 (59.5)	15 (40.5)
Unknown	23	10 (43.5)	13 (57.5)
Positive	41	0 (0.0)	41 (100.0)

Morello W, et al. Journal of Nephrology **2019**, October
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Clinical Impact of Genetic Testing in Kidney Diseases

Indication	Genetic Finding	Genetic Diagnosis	Clinical Impact	References
Steroid-resistant nephrotic syndrome	Homozygous Fin-major mutation in *NPHS1*	Nephrotic syndrome type 1 (OMIM #256300)	Increased risk of posttransplant disease recurrence	57, 58
	COQ2 mutation	CoQ_{10} deficiency 1 (OMIM #607426)	CoQ_{10} supplementation can attenuate proteinuria and extrarenal complications such as encephalopathy	59, 60
	COL4A3 or *COL4A4* missense mutation	Alport syndrome (OMIM #104200; #203780) or TBMD (OMIM #141200)	• Distinguishes between autosomal (*COL4A3* or *COL4A4*) and X-linked (*COL4A5*) inheritance, informing family counseling • Missense mutations are associated with less severe disease and slower progression to kidney failure and loss-of-function mutations • Avoids immunosuppression (a commonly used therapy for nephrotic syndrome)	61-64
Cystic renal dysplasia	17q12 deletion	Renal cysts and diabetes syndrome (OMIM #137920)	Multisystem work-up for associated extrarenal complications, including testing for diabetes, exocrine pancreatic insufficiency, hepatic function, neurologic anomalies, and/or neurocognitive impairment	65-67
Nephrolithiasis	*APRT* mutation	APRT deficiency (OMIM #614723)	Xanthine dehydrogenase inhibition to prevent crystalline nephropathy and allograft loss	68, 69
Episodic hypertension	*SDHD* mutation	Hereditary paraganglioma-pheochromocytoma syndrome (OMIM #168000)	• Imaging studies to screen for additional tumors • Catecholamine antagonists and/or surgical tumor resection • Knowledge of parent-of-origin effect due to maternal imprinting informs genetic counseling • Lower risk of malignancy than other genetic causes of familial paraganglioma-pheochromocytoma syndromes informs prognosis	70, 71
Failure to thrive, hepatomegaly, and hyperuricemia	*G6PC* mutation	Glycogen storage disease Ia (OMIM #232200)	• Dietary therapy (frequent meals, nasogastric tube, and/or raw starch to prevent hypoglycemia; oral bicarbonate and avoidance of fructose and glucose to prevent acidosis) • Surveillance for hepatic adenoma; liver transplant may be needed	72, 73

Devarajan P, et al. Kidney Med. 2022, 4 (4): 100435 doi: 10.1016/ j.xkme.2022.100435

Recurrent Disease in Pediatric Renal Transplantation

Risk factors for recurrence/graft loss in patients with steroid-resistant NS

Proven increased risk	Independent/ controversial risk factors	Proven decreased risk
	Gender	
	Mesangial hypercellularity	
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Cochat P et al, 2013
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Second Transpants

Recurrent Glomerulonephritis after Renal Transplantation: The Clinical Problem

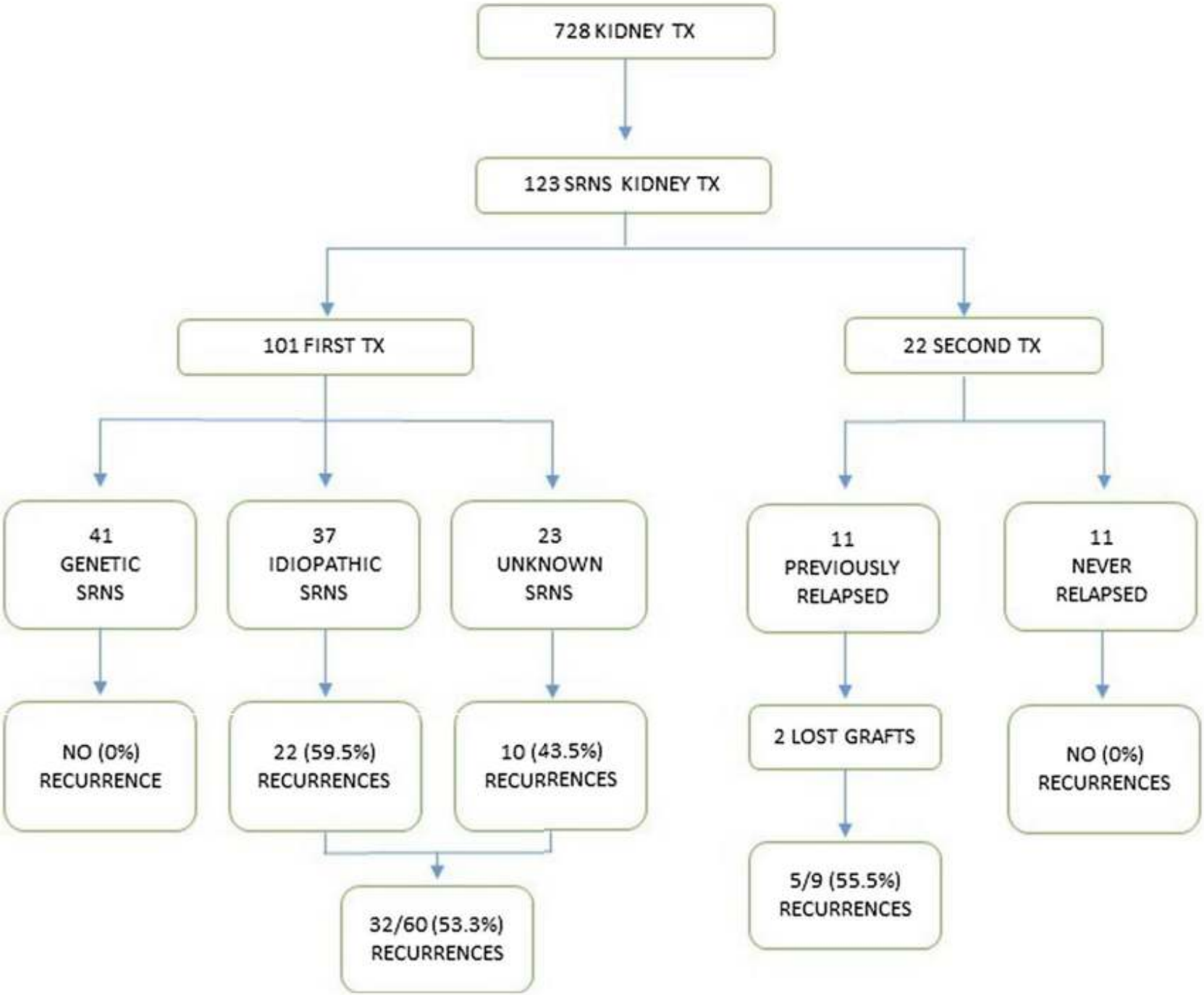
Abstract: Glomerulonephritis (GN) continues to be one of the main causes of end-stage kidney disease (ESKD) with an incidence rating from 10.5% to 38.2%. Therefore, recurrent GN, previously considered to be a minor contributor to graft loss, is the third most common cause of graft failure 10 years after renal transplantation. However, the incidence, pathogenesis, and natural course of recurrences are still not completely understood. This review focuses on the most frequent diseases that recur after renal transplantation, analyzing rate of recurrence, epidemiology and risk factors, pathogenesis and bimolecular mechanisms, clinical presentation, diagnosis, and therapy, taking into consideration the limited data available in the literature. First of all, the risk for recurrence depends on the type of glomerulonephritis. For example, recipient patients with anti-glomerular basement membrane (GBM) disease present recurrence rarely, but often exhibit rapid graft loss. On the other hand, recipient patients with C3 glomerulonephritis present recurrence in more than 50% of cases, although the disease is generally slowly progressive. It should not be forgotten that every condition that can lead to chronic graft dysfunction should be considered in the differential diagnosis of recurrence. Therefore, a complete workup of renal biopsy, including light, immunofluorescence and electron microscopy study, is essential to provide the diagnosis, excluding alternative diagnosis that may require different treatment. We will examine in detail the biomolecular mechanisms of both native and transplanted kidney diseases, monitoring the risk of recurrence and optimizing the available treatment options.

Infante B, et al. Int. J. Mol. Sci. **2020**, 21, 5954
doi:10.3390/ijms21175954

To eliminate circulating factors..

- Preemptive **plasmapheresis/** immunoadsorption 3 to 5 sessions prior to the Tx followed by immediate post-transplant 3- 5 sessions
- Additional single dose of **rituximab** (375 mg/m2) along with immunosuppression of **corticosteroid, calcineurin inhibitor,** and **mycophenolate mofetil** for two weeks prior to kidney transplantation was shown to prevent recurrence

Hee G K et al 2016



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Donor selection

Donor selection

- Recurrent Allograft Disease Registry (RADR) found a similar rate of recurrence among adult recipients of living or deceased donor kidneys

- A deceased donor kidney was more likely than a living-related kidney to be lost in patients with recurrent disease

- In adult recipients graft survival advantage for living donor kidneys over deceased donor kidneys

Donor selection

Donor selection

The North American Pediatric Renal Transplant Cooperative Study database (NAPRTCS) concluded that in both children and adolescents :

- Graft survival was markedly worse in pediatric patients with FSGS compared with those with other kidney diseases, a difference that was not accounted for by recurrence alone

- In FSGS graft survival at five years was not statistically different between living donors and deceased donors (69 versus 60 percent)

Transplantation. 2015 Oct;99(10):2049-60. doi: 10.1097/TP.0000000000000894.

Evaluation and Management of Proteinuria After Kidney Transplantation.

Tsampalieros A[1], Knoll GA.

Author information

Abstract

Proteinuria occurs commonly after kidney transplantation. Because there are no specific guidelines for defining and detecting proteinuria in transplant recipients, its prevalence can vary depending on the methods used. Most often, the same cutoffs for defining proteinuria in the nontransplant population are applied. There are several risk factors for proteinuria, including some transplant-specific diagnoses and immunosuppressive medications. Posttransplantation proteinuria is associated with reduced graft survival as well as an increased risk of cardiovascular events and death. Treatments to decrease proteinuria have been based on blocking the renin-angiotensin-aldosterone system with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. This review describes the measurement, prevalence, etiology, prognostic significance, and management of proteinuria in both adult and pediatric transplant recipients.

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Induction therapy

- Recurrent glomerulonephritis, including FSGS, tended to be lower in patients who received thymoglobulin (polyclonal rabbit-antithymocyte globulin) compared with interleukin 2 receptor antagonists

Pascual J et al, Transpl 2007, 83

Recurrent Disease in Pediatric Renal Transplantation

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Cochat P et al, 2013
Current Pediatrics Reports
DOI 10.1007/s40124-012-0004-2

Native nephrectomy in pediatric transplantation

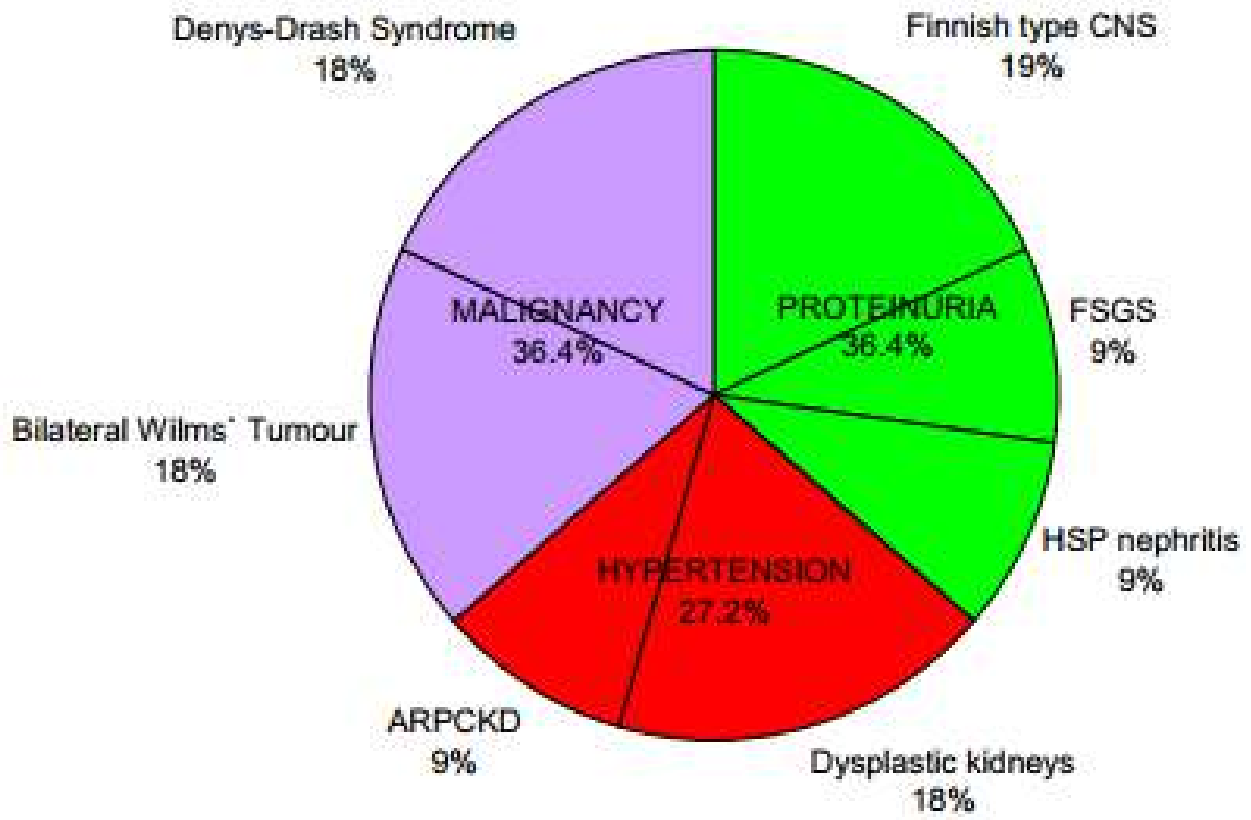
Abstract *Objective:* Indications for pre-transplantation native nephrectomy (PTNN) include chronic renal parenchymal infection, proteinuria, intractable hypertension, polycystic kidneys and malignancy. Our aim was to establish the frequency and reasons for PTNN in children undergoing renal transplant at our center.

Materials and methods: Children listed for renal transplant between 1998 and 2010 who underwent PTNN were analyzed. Etiology of established renal failure, indication for nephrectomy, stage of chronic kidney disease, laterality, complications, and timing of subsequent transplant were determined. Outcome of children, and that of preserved native kidneys following transplant, was reviewed.

Results: 21/203 children listed for transplant (10.3%) underwent PTNN (32 nephrectomies). Indications were drug-resistant proteinuria (6 children), recurrent upper tract urosepsis (6), refractory hypertension (4), malignancy/malignant predisposition (4), concomitant procedure during ureterocystoplasty (1). Median age at nephrectomy was 3.3 years; 86% had impaired renal function at time of (first) nephrectomy. Median time until transplantation following bilateral nephrectomy was 1.7 years. 19/21 children have been transplanted; 17 reached stable graft function. Only 2 children who did not undergo PTNN required nephrectomy post-transplant.

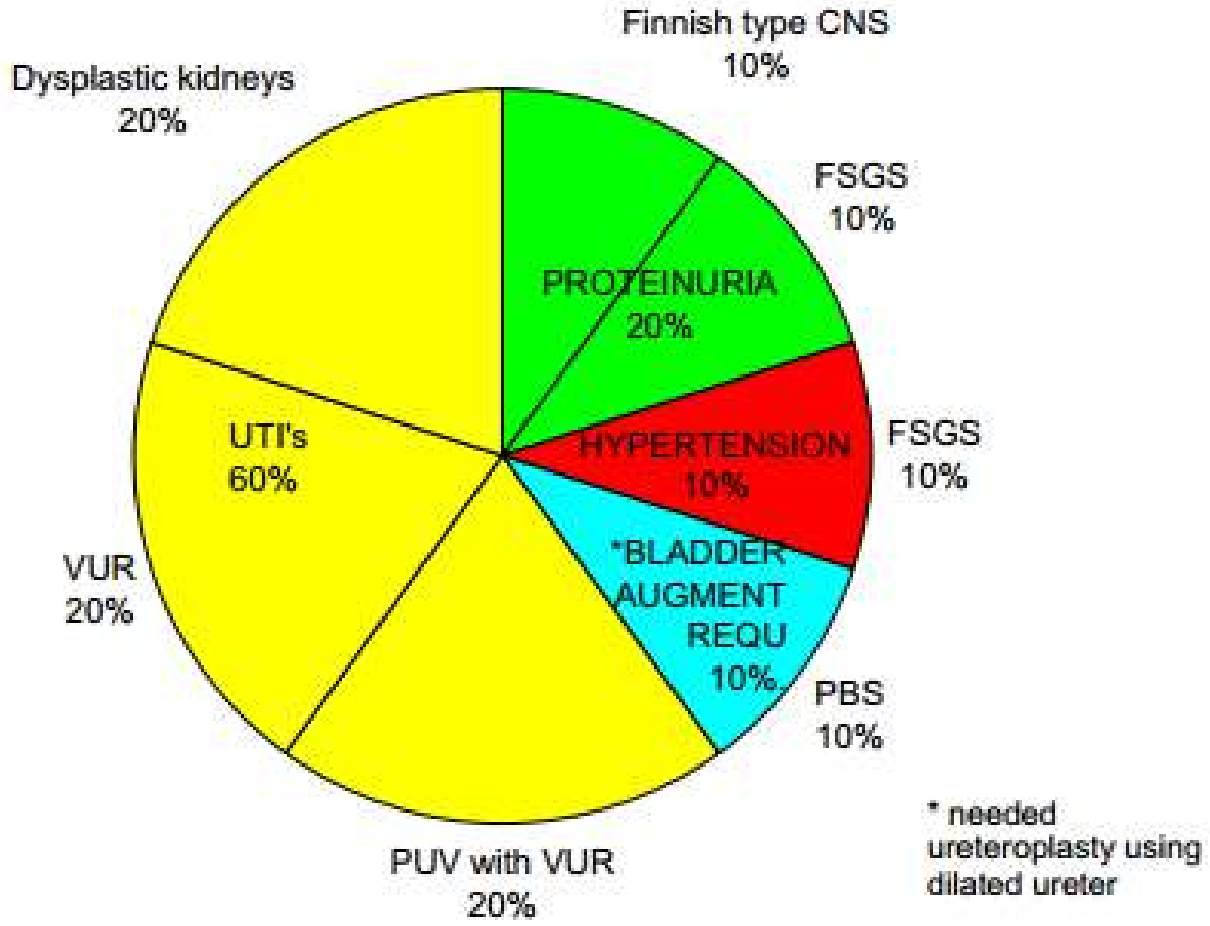
Conclusion: When malignancies were excluded, PTNN was performed in a minority (8.4%) of children, mainly for proteinuria. This adds great advantage by reducing morbidity. Resulting graft function seems favorable.

Fraser N et al, Journal of Pediatric Urology (2012) 9, 84e91



Indications for BILATERAL pre-transplant nephrectomy

Fraser N et al, Journal of Pediatric Urology (2012) 9, 84e91



Indications for UNILATERAL

Pretransplant nephrectomy

Fraser N et al, Journal of Pediatric Urology (2012) 9, 84e91

Preparing for a kidney transplant: Medical nephrectomy in children with nephrotic syndrome

Abstract Nephrotic syndrome is characterized by proteinuria, hypoalbuminemia, and general edema. These symptoms may persist in children who reach ESRD, which is unfavorable for the patient's allograft outcome. In addition, this may hamper early diagnosis of a relapse after transplantation. Surgical bilateral nephrectomy is often considered for that reason, but medical nephrectomy may be a less invasive alternative. In this retrospective single-center case series, we identified all children on dialysis with ESRD due to nephrotic syndrome in which a medical nephrectomy was attempted before kidney transplantation between 2013 and 2018. Outcome was measured by urine output and serum albumin levels. Eight patients with either congenital nephrotic syndrome or focal segmental glomerular sclerosis were included in the study. All patients received an ACE inhibitor as drug of first choice for medical nephrectomy, to which 5 patients responded with oligoanuria and a significant rise in serum albumin, and 3 patients responded insufficiently. In 1 of these 3 patients, diclofenac was added to the ACE inhibitor, with good result. In the other 2 patients, indomethacin was initiated without success, and surgical bilateral nephrectomy was performed. Overall, 6/8 patients had a successful medical nephrectomy and did not need surgical nephrectomy. No recurrence of nephrotic syndrome was found after kidney transplantation in all but one

Vos E, et al. Pediatr Transplant. **2020**; 24: e13703
doi.org/10.1111/ petr.13703

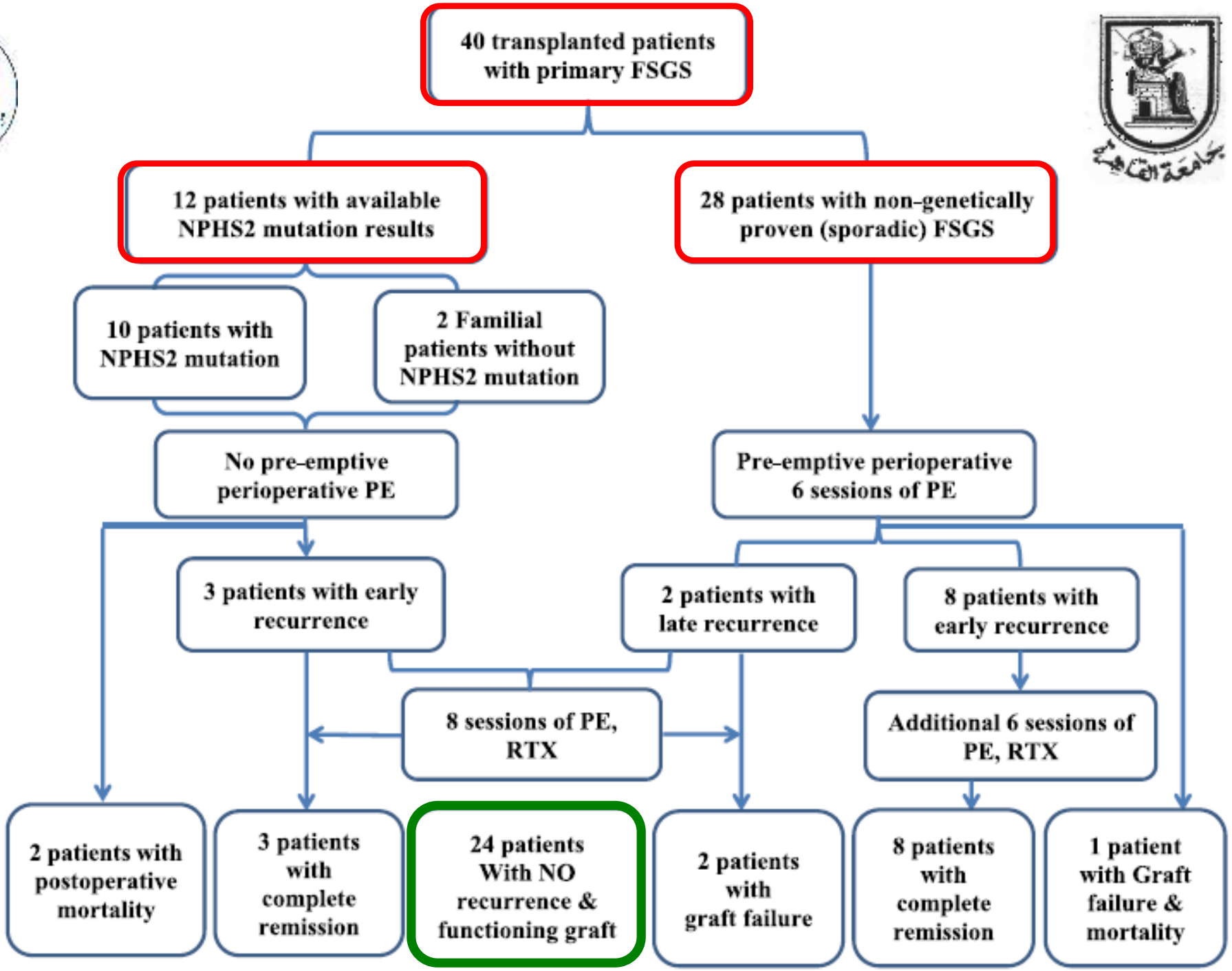
Pediatric focal segmental glomerulosclerosis: favorable transplantation outcome with plasma exchange

	Sporadic FSGS ($n = 28$)	Genetic/Familial ($n = 12$)	*P*-value
Pre-TX proteinuria (mcg/d)	3003 ± 1505	2101 ± 608	0.0388
D1 Post-TX proteinuria (mcg/d)	2514.654 ± 915	546.254 ± 100.1	0.00001
D7 Post-TX proteinuria (mcg/d)	954 ± 321	189 ± 56	0.00001
Current Proteinuria (mcg/d)	35.29 ± 60.94	10.62 ± 7.53	0.3027
Current serum creatnine (mg/dl)	0.754 ± 0.3	0.605 ± 0.3	0.1437

Comparison between genetic & sporadic FSGS patients

Fadel F, et al, Italian Journal of Pediatrics (2021) 47:236
doi.org/10.1186/s13052-021-01188-0

Pediatric focal segmental glomerulosclerosis: favorable transplantation outcome with plasma exchar



Fadel F, et al, Italian Journal of Pediatrics (2021) 47:236
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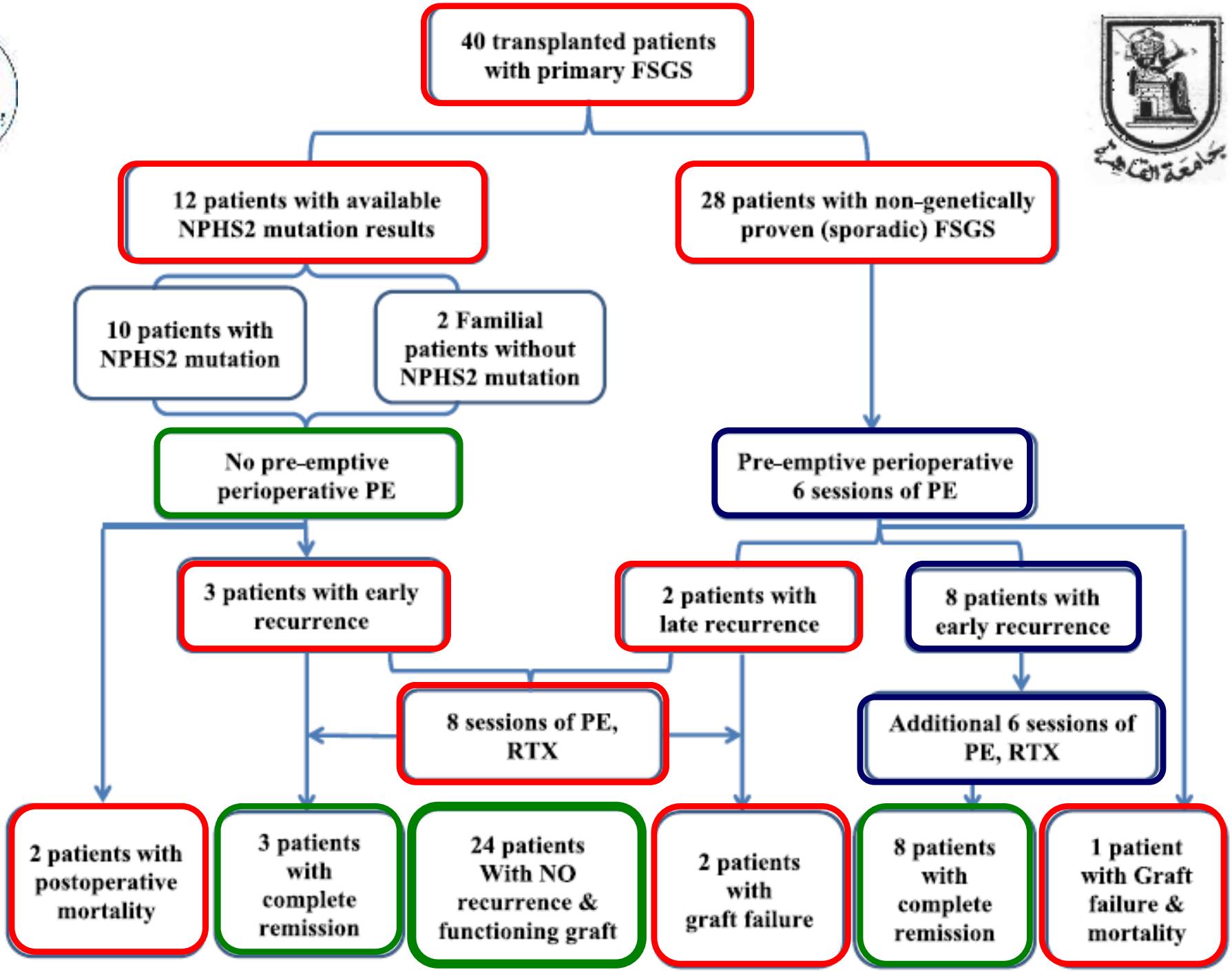


Fadel F, et al, Italian Journal of Pediatrics (2021) 47:236
doi.org/10.1186/s13052-021-01188-0

Evaluation of proteinuria

Screen with spot urine PCR or ACR
Confirm significant values with 24-hr urine collection

1st month post-transplant	Once	If ESRD was due to FSGS, then assess proteinuria daily for 1 week then every week for 4 weeks
2- 12 months post-transplant	Every 3 months	For proteinuric patients: Monthly assessment
> 1 year post-transplant	Every 12 months	For proteinuric patients: Assessment every 3 months

Consider renal allograft biopsy if:
New onset proteinuria (24 hr ≥ 300 mg/day)
Unxplained proteinuria (24 hr ≥ 1500 mg/day)

Management of Proteinuria After Kidney Transplantation

Etiologic treatment

- *FSGS recurrence*

  Plasmapharesis , IVIG, Rituximab

- *Drug Toxicity*
- *Acute rejection*

| Key studies of disease recurrence after paediatric renal transplantation

Study	Population	Conclusions
FSGS		
Van Stralen *et al.* (2013)[3]	Paediatric registry (n=407)	14.7% risk of graft loss due to disease recurrence within the first year after renal transplantation; 25.7% risk of graft loss due to disease recurrence after 5 years
Fargue *et al.* (2008)[22]	Paediatric retrospective case series (46 procedures, n=35)	Planned renal transplantation involving living donors might enable more effective pretransplantation immunosuppression and improve graft survival
Gonzalez *et al.* (2011)[19]	Paediatric retrospective case series (n=34)	Pre-emptive plasmapheresis does not decrease the rate of recurrence after renal transplantation, but might be beneficial in treating patients
Kumar *et al.* (2013)[29]	Paediatric retrospective case series (n=8)	Rituximab can be used to treat patients with disease recurrence. Results vary from no response to complete remission; however, one death and two severe adverse effects were attributed to this drug
Straatmann *et al.* (2014)[34]	Paediatric retrospective case series (n=24)	Intensive and prolonged plasmapheresis initiated early in the postoperative period is an effective treatment for recurrent FSGS and prevents graft loss without the use of additional immunosuppressive therapies

Justine Bacchetta and Pierre Cochat, Nat. Rev. Nephrol. 28 April 2015;

According to experiences of Lee et al with 38 children with FSGS,
most of those with a later onset (≥6 yrs. old) and a progression to ESRD in the 24– 72 months after onset of NS experienced recurrence,
whereas those who had an earlier onset (<6 yrs.) of NS with a faster progression (<18 months) did not have recurrence

Management of Proteinuria After Kidney Transplantation

Anti-proteinuric agents

Management of Proteinuria After Kidney Transplantation

Vitamin D status in renal transplant recipients living in a low-latitude city: association with body fat, cardiovascular risk factors, estimated GFR and proteinuria

Recent evidence suggests that vitamin D deficiency is associated with CVD, impaired kidney function and proteinuria. To date, no study has evaluated these associations in renal transplant recipients (RTR) adjusting for body adiposity assessed by a 'gold standard' method. This study aimed to evaluate the vitamin D status and its association with body adiposity, CVD risk factors, estimated glomerular filtration rate (eGFR) and proteinuria in RTR, living in Rio de Janeiro, Brazil (a low-latitude city (22°54'10"S)), taking into account body adiposity evaluated by dual-energy X-ray absorptiometry (DXA). This cross-sectional study included 195 RTR (114 men) aged 47·6 (SD 11·2) years. Nutritional evaluation included anthropometry and DXA. Risk factors for CVD were hypertension, diabetes mellitus, dyslipidaemia and the metabolic syndrome. eGFR was evaluated using the Chronic Kidney Disease Epidemiology Collaboration equation. Serum 25-hydroxyvitamin D (25(OH)D) concentration was used to define vitamin D status as follows: 10 % (*n* 19) had vitamin D deficiency (<16 ng/ml), 43 % (*n* 85) had insufficiency (16–30 ng/ml) and 47 % (*n* 91) had sufficiency (>30 ng/ml). Percentage of body fat (DXA) was significantly associated with vitamin D deficiency independently of age, sex and eGFR. Lower 25(OH)D was associated with higher odds of the metabolic syndrome and dyslipidaemia after adjustment for age, sex and eGFR, but not after additional adjustment for body fat. Hypertension and diabetes were not related to 25(OH)D. Lower serum 25(OH)D was associated with increasing proteinuria and decreasing eGFR even after adjustments for age, sex and percentage of body fat. This study suggests that in RTR of a low-latitude city hypovitaminosis D is common, and is associated with excessive body fat, decreased eGFR and increased proteinuria.

Rosina KTC et al, British Journal of Nutrition Volume 117 (9) 14 May 2017

Take home message

Take home message


thank
you

Proteinuria in pediatric renal transplant recipients

Abstract

Proteinuria has been shown to be an important and potentially treatable risk factor for graft loss. The aim of this study was to evaluate prevalence, etiology, and outcome of proteinuria during the follow-up of children with renal transplantation. We retrospectively reviewed the files of renal transplanted children between 2006 and 2016 in our center. All patients were interpreted with respect to the demographic data and clinical and laboratory features including information about proteinuria. Chi-square test and Mann-Whitney *U* test were used for analysis. Fifty-two children were eligible for the study. Proteinuria was observed in 34 (65%) and nephrotic range proteinuria was detected in 5 (9.6%) patients. Etiology of proteinuria could be identified in 21 patients. Acute rejection and uncontrolled hypertension were the most frequent causes of proteinuria. Proteinuria had resolved during the follow-up in 59% of the patients. We found that children with and without proteinuria had similar glomerular filtration rate at the end of 50 months of follow-up period. Proteinuria seems to be a common complication in renal transplant recipients. Graft functions can be preserved by immediate evaluation of increasing proteinuria, and by fixing treatable causes rapidly and efficiently during the follow-up in majority of the patients.

KEYWORDS

children, proteinuria, transplantation

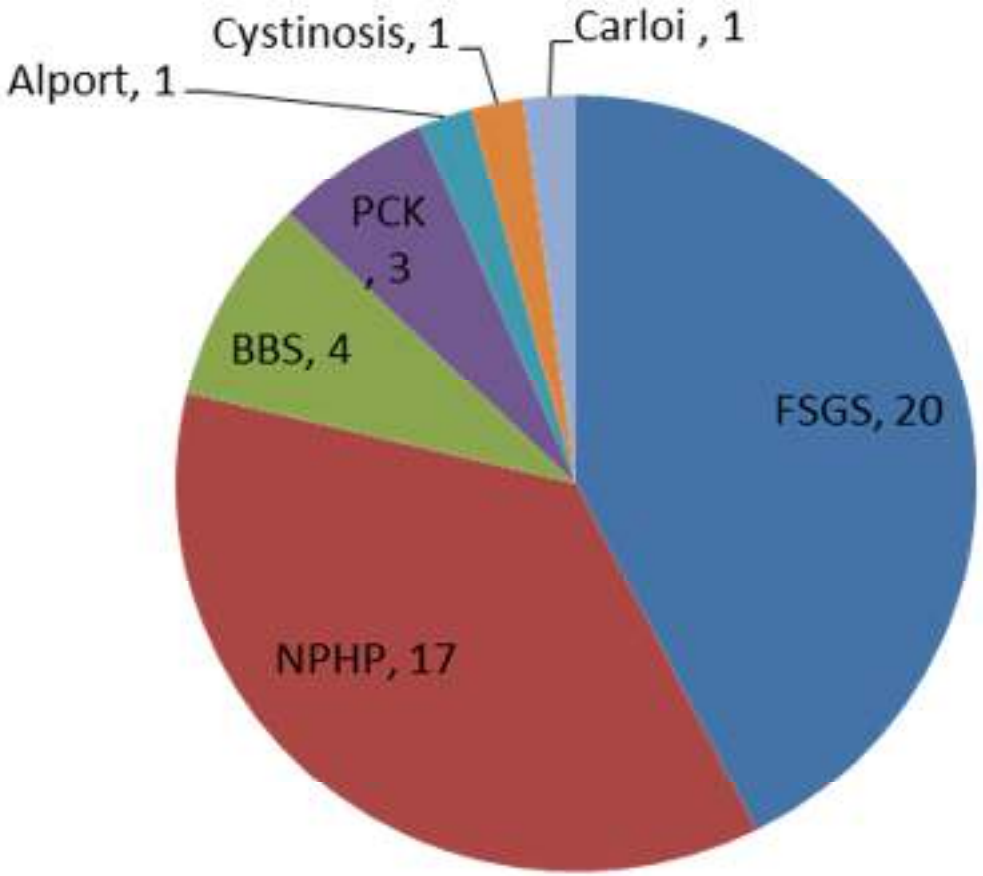
Yilmaz S et al, Pediatric Transplantation. 2017; e13068

Our center experience

- 123 cases were transplanted since May, 2009 till January, 2018
- 83 males / 40 females
- Age range at TX (2-16) years
- Weight range at Tx (9.5-50) Kg

Distribution of inherited nephropathy cases

PEDIATRIC NEPHROLOGY UNIT
(PNU)



PEDIATRIC NEPHROLOGY UNIT
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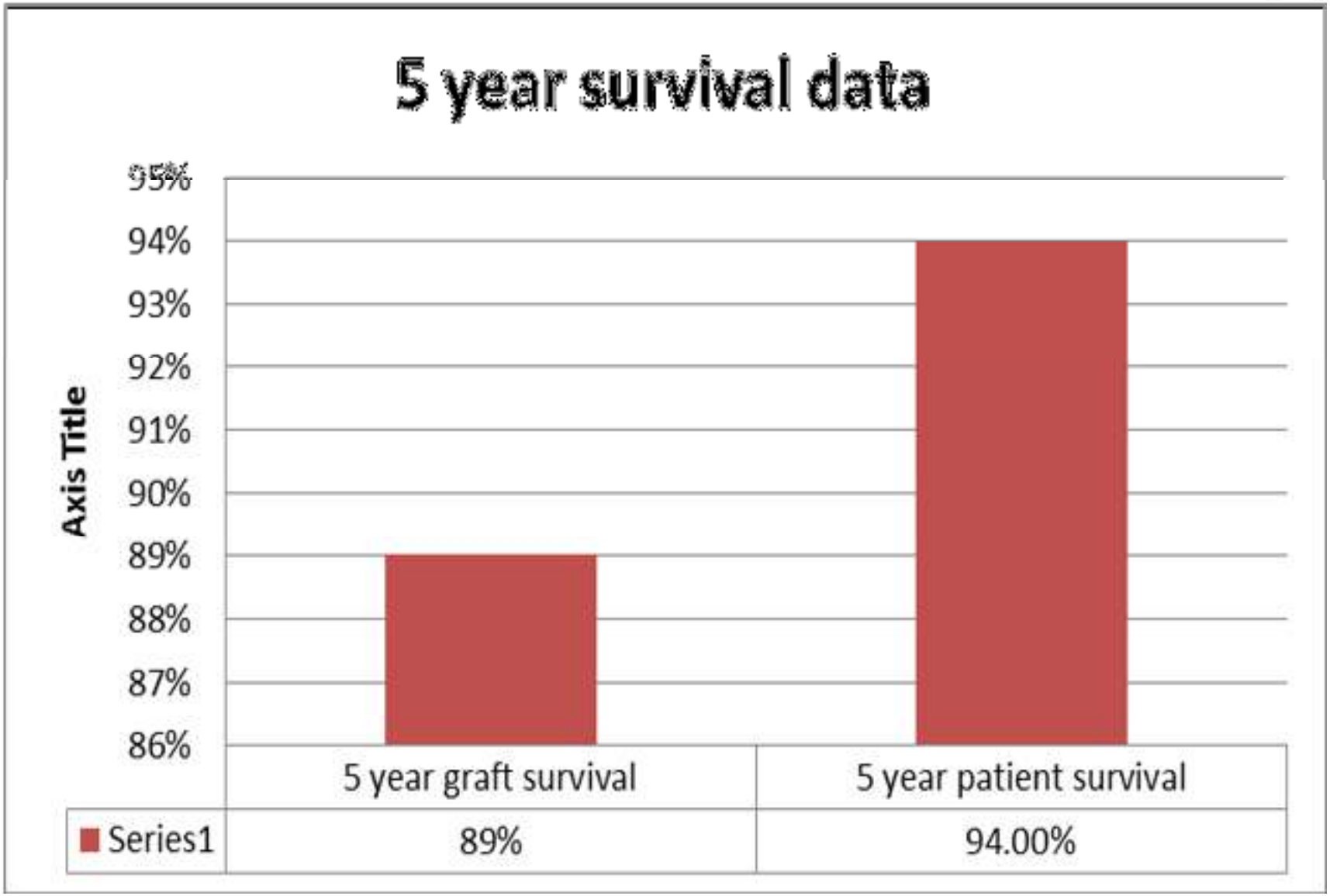
5 year survival data



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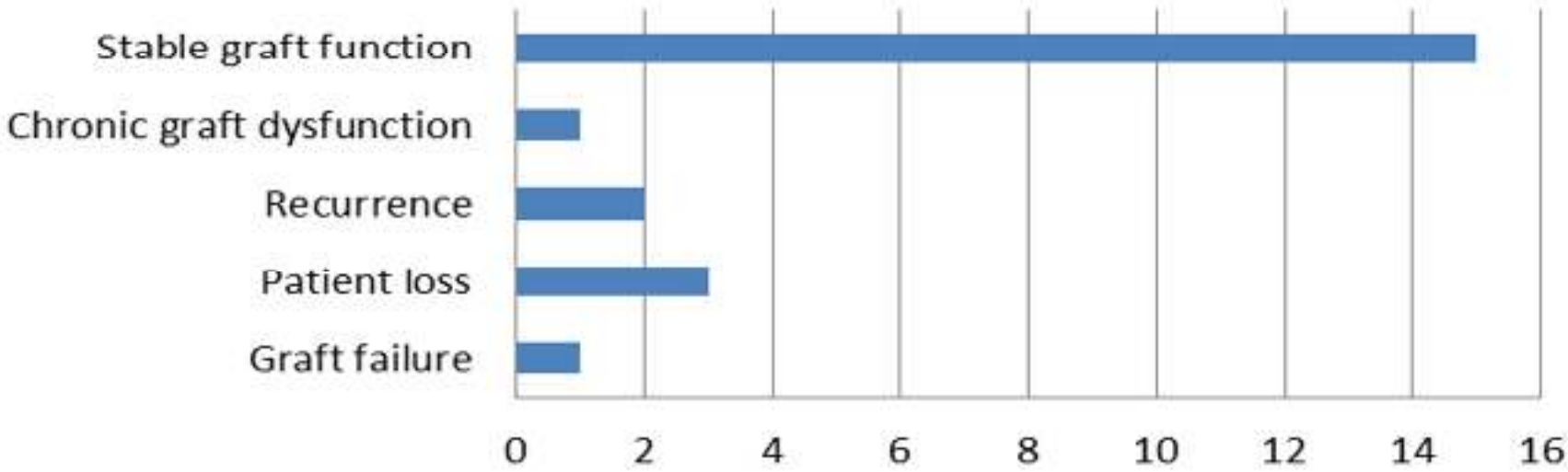


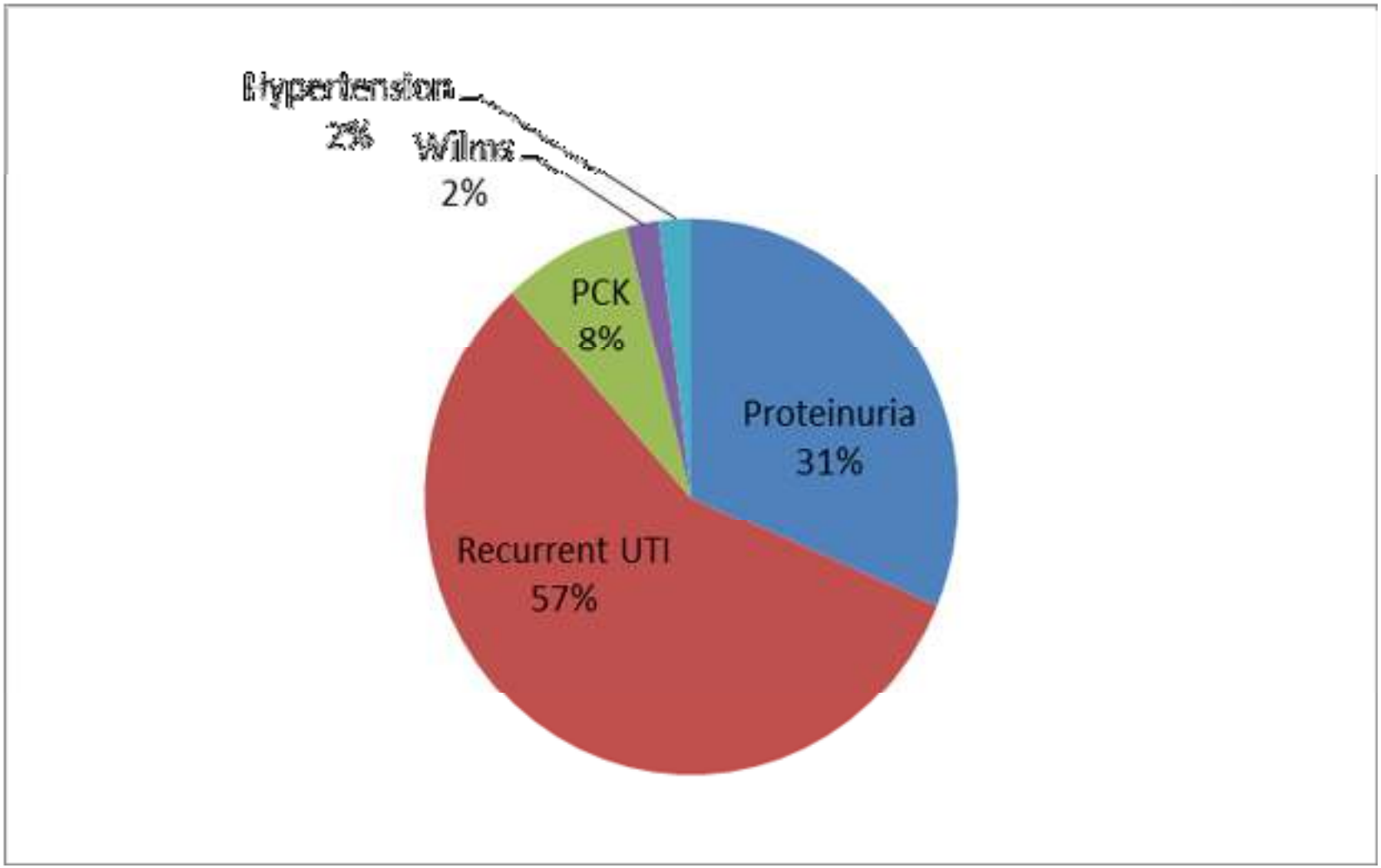
	Graft failure	Patient loss	Recurrence	Chronic graft dysfunction	Stable graft function
Series1	1	3	2	1	15

PEDIATRIC NEPHROLOGY UNIT
(PNU)

Nephrectomy cases

- 51/123 (41.5%) needed native nephrectomy
- Nephrectomy was bilateral in 46 cases and unilateral in 5 cases (2 due to proteinuria and 3 due to unilat.VUR)
- Nephrectomy done pre-transplantation in 49 cases and post-transplantation in 2 cases (1 was bilateral laporoscopic due to resistant hypertension and the other was Rt open nephrectomy due to proteinuria)

PEDIATRIC NEPHROLOGY UNIT
(PNU)



- Proteinuria may be caused by a defective tubular reabsorption of the filtered small proteins or by abnormalities of the glomerular barri
- Tubular proteinuria may result from a huge excretion of low molecular weight proteins that pass through the glomerular barrier and exceed the reabsorption capacity of proximal tubular cells.
- Glomerular proteinuria is usually consequent to podocyte injury with slit

Early Proteinuria After Renal Transplantation and Allograft Outcomes

Table 1. Demographic and Laboratory Data of Patients With and Without Proteinuria

Variable	Proteinuria at Posttransplant Month 3		*P*
	+	−	
Age (y)	17.06 ± 4.92	17.15 ± 4.91	>.05
Age at the time of transplantation (y)	13.85 ± 4.28	13.54 ± 4.32	>.05
Gender (F/M)	22/17	12/16	>.05
Living related donor	24	19	>.05
Deceased donor	15	9	>.05
Immunosuppressive regimen (tacrolimus/cyclosporine)	21/18	9/19	>.05
Acute rejection episode	11	0	<.05
Median creatinine at posttransplant year 3, mg/dL (min–max)	1.02 (0.5–1.91)	0.89 (0.48–10.2)	>.05
Median glomerular filtration rate at posttransplant year 3, mL/min/1.73m^2 (min–max)	71.14 (20.91–223.60)	80,70 (2.00–124.30)	>.05
Graft loss (no. of patients)	3	3	>.05

Gulleroglu K et al, Transplantation Proceedings, 46, 141e144 (2014)

Main physiopathological mechanisms responsible of tubular and glomerular proteinuria

Tubular proteinuria	Glomerular proteinuria
Definition	Definition
Urinary excretion >150 mg/24 h of low molecular weight (<60 kDa) proteins	Urinary loss of proteins with molecular weight exceeding 60 kDa
Etiopathogenesis	Etiopathogenesis
Excessive production of small proteins exceeding the reabsorption capacity of proximal tubular cells (multiple myeloma, tumor lysis, leukemia etc.)	Primary or secondary glomerular diseases that alter the morphology and function of the actin cytoskeleton of podocytes and foot processes eventually leading to a reduced permselectivity and increased passage of proteins into the tubular lumen. The size of filtered proteins may indicate the degree of permselectivity loss (albumin 68 kDa, immunoglobin G 150 kDa)
Congenital proximal tubular defects (Fanconi syndrome, renal tubular acidosis)	
Acquired proximal tubular defects (ischemia-reperfusion-injury, nephrotoxic drugs, acute kidney injury, interstitial nephritis etc.)	

Ponticelli C and Graziani G, Transplant International 25 (2012) 909–917

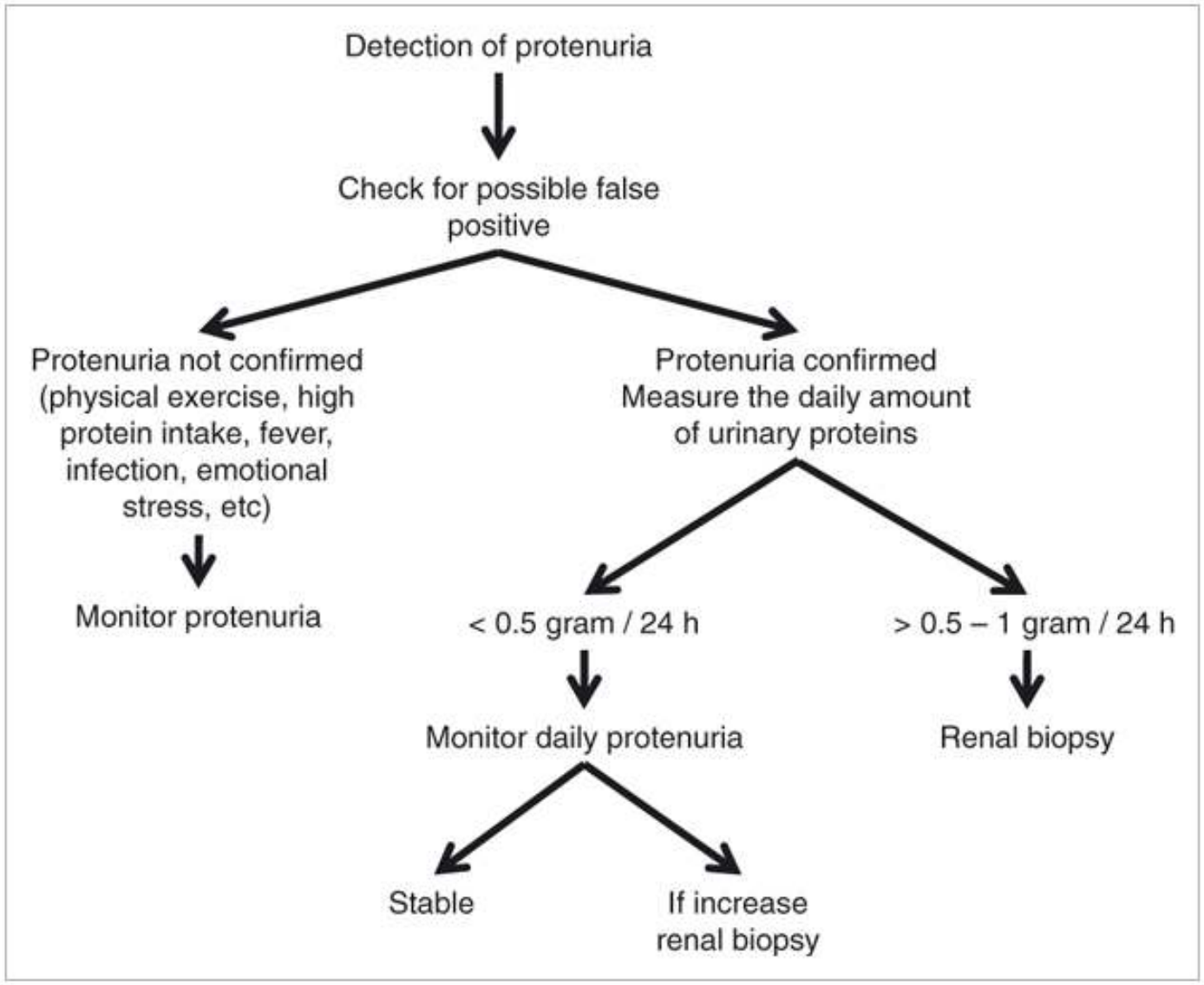
Proteinuria after kidney transplantation

Main causes of tubular proteinuria	Main causes of glomerular proteinuria
Ischemia-reperfusion injury	Recurrent glomerular diseases
Acute kidney injury	*De novo* glomerular or systemic diseases
Acute rejection	Transplant glomerulopathy
mTOR inhibitors	Chronic rejection
CNI	mTOR inhibitors
Aminoglycosides	CNI
Antiviral drugs	Obesity
	Arterial hypertension
	Hepatitis C or B

Table 2. Main causes of proteinuria in kidney transplantation

Ponticelli C and Graziani G, Transplant International 25 (2012) 909–917

Diagnostic approach to posttransplant proteinuria



Ponticelli C and Graziani G, Transplant International 25 (2012) 909–917

National Kidney Foundation®
KDOQI

TOXICITY PROFILES OF IMMUNOSUPPRESSIVE MEDICATIONS						
Adverse effect	**Steroids**	**CsA**	**Tac**	**mTORi**	**MMF**	**AZA**
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

Proteinuria in pediatric renal transplant recipients during the first 60 post-transplant days

Abstract: Although normative values of post-transplant proteinuria have been reported in adults, data for pediatric renal transplant recipients have not been previously published. We hypothesized that pediatric renal transplant recipients achieve normal urinary protein to creatinine (UProt/UCr) ratios (<0.2) by 60 days post-transplant in the absence of early recurrent disease. Retrospective chart review of 108 consecutive pediatric renal transplant recipients at Stanford University was performed. Thirty-two (30%) patients who were eligible had ≥ 1 UProt/UCr ratio obtained during the first 60 post-transplant days. Mean age at transplant was 13.9 ± 4.2 yr. UProt/UCr ratios were grouped by week post-transplant for quantile analysis. Mean weekly UProt/UCr values were not lower than 0.2 until the ninth post-transplant week. No difference in post-transplant proteinuria existed between nephrectomized and non-nephrectomized transplant recipients. Experience with a single patient with proven focal segmental glomerulosclerosis (FSGS) recurrence suggests that normative UProt/UCr data may be useful in early identification of patients experiencing disease recurrence. Univariate correlations demonstrated that UProt/UCr negatively correlated with serum albumin levels (-0.415, $p < 0.0001$) and days post-transplant (-0.531, $p < 0.0001$). Independent of primary diagnosis, proteinuria persists throughout the first 60 days in most pediatric renal transplant patients, decreasing relative to time post-transplant.

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Proteinuria in pediatric renal transplant recipients during the first 60 post-transplant days

Table 2. UProt/UCr values for nephrectomized and non-nephrectomized patients

Week	Recipient	Mean UProt/UCr value (mg/mg)	Median UProt/UCr value (mg/mg)	Patients with UProt/UCr <0.2	*Mean UProt/UCr ± s.d. of all patients/wk
1	Nephrectomized (n = 11)	5.39 ± 11.89	3.0	0	5.2 ± 11.26
	Non-nephrectomized (n = 1)	2.48	2.48	0	
2	Nephrectomized (n = 9)	1.28 ± 0.81	1.03	1	1.25 ± 0.76
	Non-nephrectomized (n = 4)	1.17 ± 0.67	1.17	0	
3	Nephrectomized (n = 11)	0.40 ± 0.34	0.30	4	0.52 ± 0.46
	Non-nephrectomized (n = 5)	0.78 ± 0.59	0.63	0	
4	Nephrectomized (n = 10)	0.40 ± 0.31	0.34	1	0.45 ± 0.29
	Non-nephrectomized (n = 2)	0.33 ± 0.13	0.37	0	
5	Nephrectomized (n = 10)	0.32 ± 0.26	0.25	3	0.32 ± 0.22
	Non-nephrectomized (n = 5)	0.52 ± 0.29	0.15	2	
6	Nephrectomized (n = 13)	0.25 ± 0.14	0.21	7	0.31 ± 0.2
	Non-nephrectomized (n = 5)	0.42 ± 0.26	0.41	2	
7	Nephrectomized (n = 8)	0.32 ± 0.17	0.32	3	0.29 ± 0.15
	Non-nephrectomized (n = 3)	0.25 ± 0.03	0.23	0	
8	Nephrectomized (n = 8)	0.23 ± 0.09	0.19	8	0.23 ± 0.11
	Non-nephrectomized (n = 6)	0.24 ± 0.15	0.22	2	
9	Nephrectomized (n = 3)	0.17 ± 0.04	0.19	3	0.17 ± 0.10
	Non-nephrectomized (n = 3)	0.18 ± 0.16	0.09	1	

Chua AN et al, Pediatr Transplantation 2006: 10: 957–961

Recurrent Disease in Pediatric Renal Transplantation

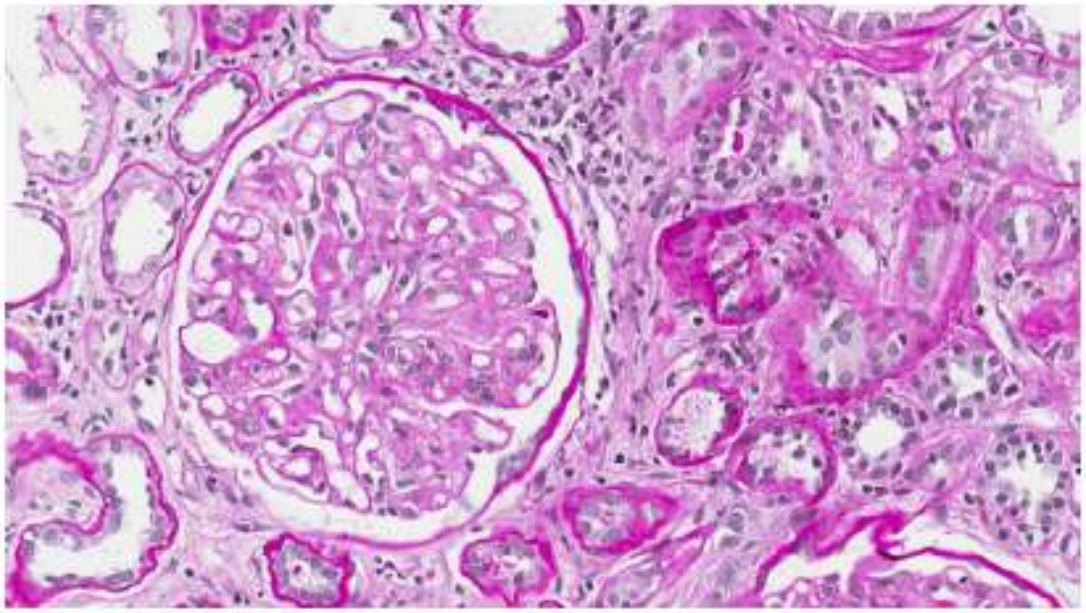
Table 1 Recurrence of primary disease after the first renal transplantation

Primary disease	Recurrence rate (%)	Graft loss to recurrence (%)
Focal segmental glomerulosclerosis	14–50 (average 30)	40–60
Atypical hemolytic uremic syndrome	17 (MCP)–90 (CFH, CFI)	10 (MCP)–86 (CFH, CFI)
Typical hemolytic uremic syndrome	0–1	0–1
MPGN type 1	30–77	17–50
MPGN type 2	66–100	25–61
Lupus nephritis	0–30	0–5
IgA nephropathy (Berger disease)	32–60	3–7
Henoch–Schönlein nephritis	31–100	8–10
Primary hyperoxaluria type 1	90–100	80–100

CFH complement factor H, *CFI* complement factor I, *MCP* membrane cofactor protein, *MPGN* membranoproliferative glomerulonephritis

Cochat P et al, 2013 Current Pediatrics Reports DOI 10.1007/s40124-012-0004-2

A



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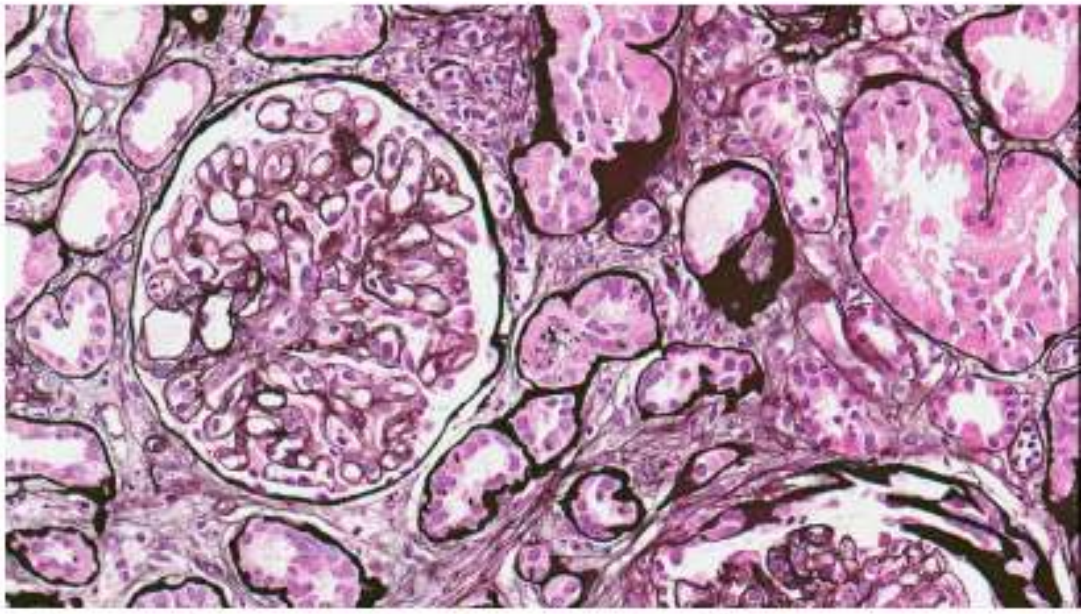

Figure 1: Chronic transplant glomerulopathy with double contours and thickening of glomerular capillary walls, (A) PAS and (B) methamine-silver stain.

Miglinas M,et al, (2013) J Nephrol Ther 4: 145.

Factors Related to Graft Outcome in Pediatric Renal Transplantation: a Single Center Study

	N*	Mean ± SD or n	Range or %
Post-transplant characteristics			
Tx hospitalization (days)		19.3 ± 12.9	7-113
Delayed graft function(DGF)		25	16.6%
Acute rejection			
Yes vs. No		69/82	45.7/54.3 %
Within the first year post Tx		58	38.4 %
Beyond the first year post Tx		23	15.7 %
Time first rejection episode (days)		46 (10-174)§	1-5474
Hemoglobin level at 1 yr (g/dl)	139	11.5 ± 1.4	6.4-14.0
Proteinuria (>1 g/24 h) at 1 yr	140	10	7.1%
Creatinine Clearance at 1 yr (ml/min/1.73 m²)	140	72.1 ± 22.0	14.7-156.5

Herman J and Damme-Lombaerts RV, 2011 www.intechopen.com

National Kidney Foundation®
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RECOMMENDED VACCINES AFTER KIDNEY TRANSPLANTATION

- Diphtheria—pertussis—tetanus
- Haemophilus influenza B
- Hepatitis A*
- Hepatitis B
- Pneumovax
- Inactivated polio
- Influenza types A and B (administer annually)
- Meningococcus (administer if recipient is at high risk)
- Typhoid Vi

*For travel, occupational or other specific risk, and endemic regions.

Consider providing booster polysaccharide pneumococcal vaccination every 3 to 5 years.

CONTRAINDICATED VACCINATIONS AFTER TRANSPLANTATION

- Varicella zoster
- Bacillus Calmette-Guérin (BCG)
- Smallpox
- Intranasal influenza
- Live oral typhoid Ty21a and other newer vaccines
- Measles (except during an outbreak)
- Mumps
- Rubella
- Oral polio
- Live Japanese B encephalitis vaccine
- Yellow fever

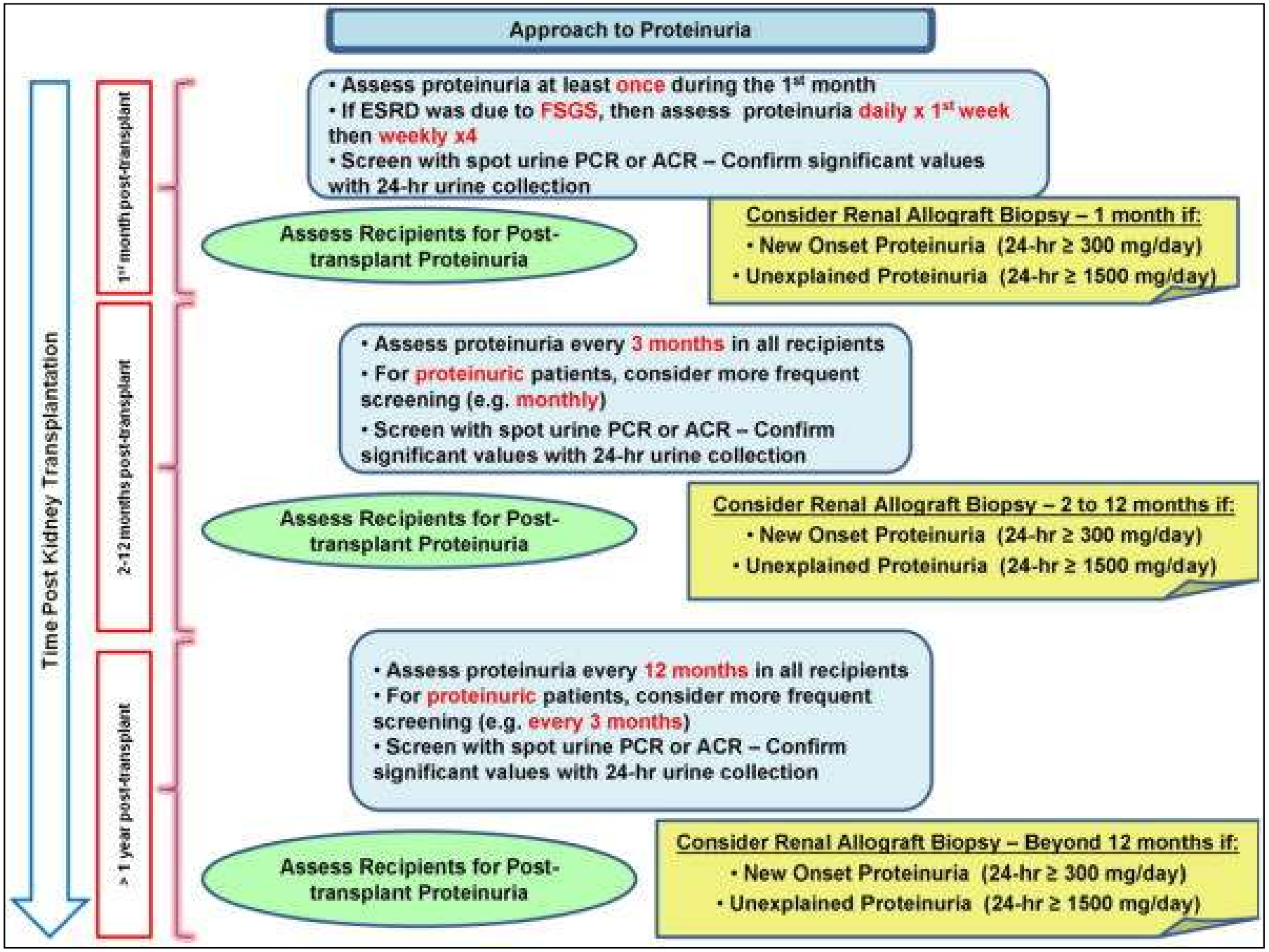
KDOQI Commentary:

It is now standard of care to use vaccinations in KTRs as long as the vaccine does not contain live or attenuated virus. It is also routine to screen for or use prophylaxis to prevent several posttransplant viral infections. Neither revaccination against hepatitis after transplant nor following up hepatitis B antibody titers annually is a common practice in the US.

select guidelines from KDOQI US Commentary on the 2009 KDIGO

- **Common non-specific sign of the renal allograft injury**
- **Marker for allograft pathology**
- **It promotes progression by causing tubular damage**
- **Powerful predictor of graft & patient outcome (even low grade proteinuria)**
- **A target for therapeutic intervention**

Evaluation and Management of Proteinuria After Kidney Transplantation



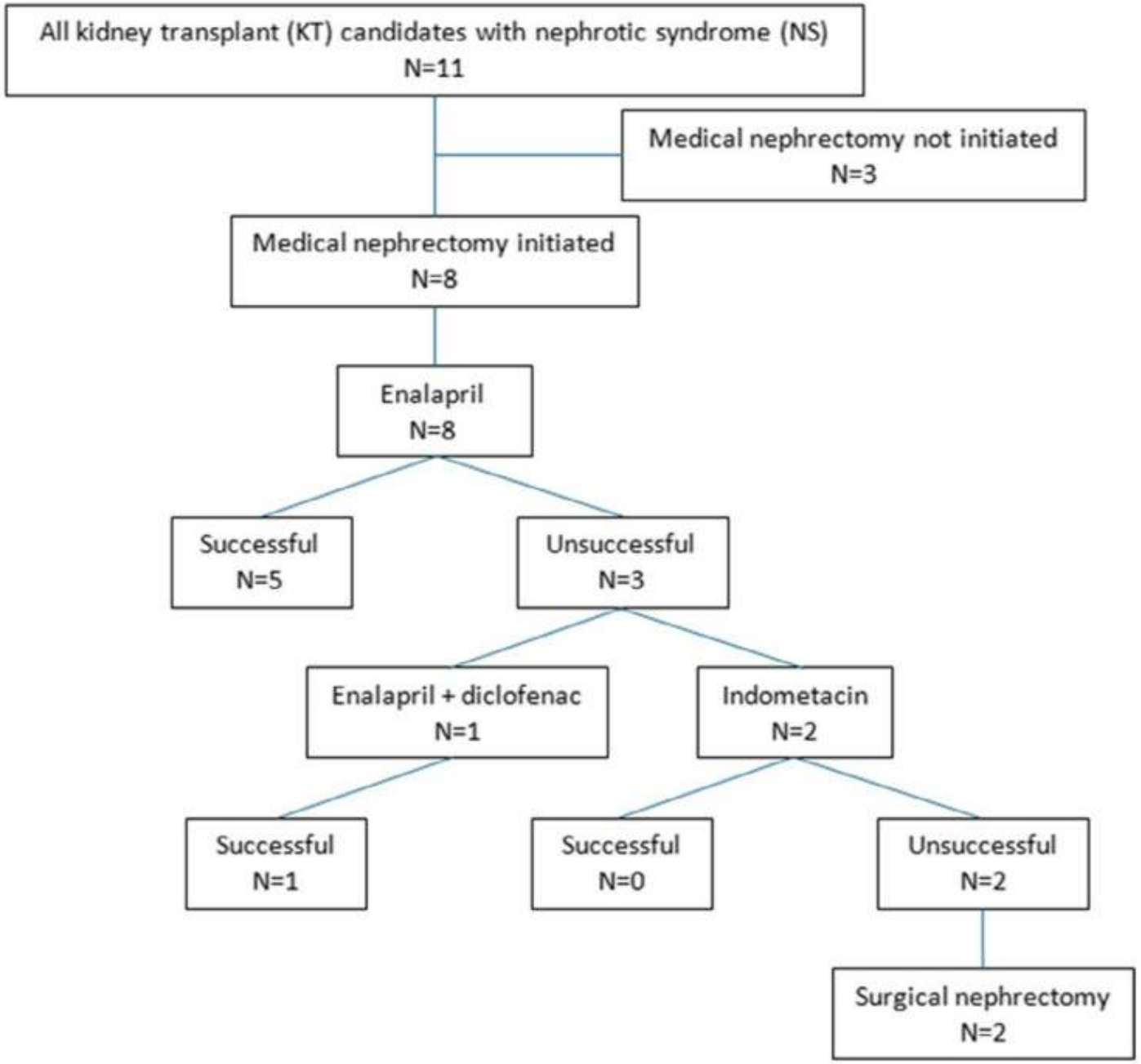
Shamseddin MK, Knoll GA, Clin JASN 2011;6:1786–1793.

Risk factors for post-transplant disease recurrence in Group B (idiopathic SRNS) and Group C (unknown genetic status) individuals, at 8 months of follow-up

Variables	Total	Recurrence, n (%)	No recurrence, n (%)	Univariate analysis *p* value	Multivariate analysis *p* value
Gender					
Male	30 (55.6%)	18 (60%)	12 (40%)	0.4624	0.26990
Female	24 (44.4%)	12 (50%)	12 (50%)		
Age at transplant, *yr*					
≥9	40 (74.0%)	26 (65%)	14 (35%)	**0.01823**	**0.01017**
<9	14 (26.0%)	4 (28.6%)	10 (71.4%)		
HLA-AB matching				0 vs >0	0 vs >0
0	7 (13.5%)	1 (14.3%)	6 (65.7%)	**0.01752**	**0.02465**
1	18 (34.6%)	13 (72.2%)	5 (27.8%)		
2	17 (32.7%)	9 (52.9%)	8 (47.1%)		
3	10 (19.2%)	6 (60%)	4 (40%)		
HLA-DR matching					
0	16 (30.8%)	5 (31.2%)	11 (68.8%)	**0.01763**	0.46309
1	34 (65.4%)	24 (70.6%)	10 (29.4%)		
2	2 (3.8%)	0 (0%)	2 (100%)		
		Recurrence	No recurrence		
Duration of dialysis median, range		2.4, 0.6–9	1.8, 0.1–5	0.06582	0.06994
Time to ESRD median, range		4.6, 0–12	2.7, 0–13	0.2673	0.72323
Donor age median, range		14, 1–63	11, 1–56	0.1609	0.84874

Morello W, et al. Journal of Nephrology **2019**, October
doi.org/10.1007/s40620-019-00660-9

Flow diagram of medical nephrectomy in pediatric patients with ESRD due to nephrotic syndrome in a single-center study



Vos E, et al. Pediatr Transplant. **2020**; 24: e13703
doi.org/10.1111/ petr.13703

clinical characteristics of individual patients with ESRD due to nephrotic syndrome who underwent medical nephrectomy

	1	2	3	4	5	6	7	8
Disease	CNS	CNS	CNS	FSGS	CNS	FSGS	FSGS	CNS
Mutation	NPHS2	NPHS2	NPHS1	–	NPHS2	–	–	NPHS1
Gender (M/F)	M	F	M	M	M	F	M	F
Age at diagnosis	0.8	1.2	0.06	3.0	3.0	3.5	3.7	0.04
Age at start MN (y)	2.9	4.0	2.3	9.4	4.3	5.4	6.2	4.0
Age at KT (y)	3.4	4.4	4.6	10.0	5.7	6.1	–	6.5
RRT mode	PD	PD	HD	HD	HD	PD	HD	PD
Enalapril (mg/kg/d)	+	+	+	+	+	+	+	+
Initial dosage	0.07	0.09	0.09	0.08	0.31	0.11	0.10	0.08
Maximum dosage	0.15	0.40	0.09	0.76	0.37	0.22	0.10	0.08
Indomethacin (mg/kg/d)	–	–	+	–	–	–	–	+
Initial dosage	–	–	1.15	–	–	–	–	1.01
Maximum dosage	–	–	1.15	–	–	–	–	2.02
Diclofenac (mg/kg[a])	–	–	–	+	–	–	–	–
Initial dosage	–	–	–	1.52	–	–	–	–
Maximum dosage	–	–	–	3.05	–	–	–	–
Surgical nephrectomy	–	–	+	–	–	–	–	+
UO before KT	Reduced	Reduced	Anuria	Reduced	Anuria	Reduced	Reduced	Anuria
Serum albumin before MN (g/L)	12	19	11	28	24	17	11	19
Serum albumin before KT (g/L)	30	27	39	33	32	26	–	37
Protein-creatinin ratio after KT[b] (g/10 mmoL)	0.30	0.42	0.25	3.63	0.33	0.40	NA	0.70

Vos E, et al. Pediatr Transplant. **2020**; 24: e13703
doi.org/10.1111/ petr.13703

Effect of medical nephrectomy with ACE inhibitor and/or NSAID in patients with ESRD due to nephrotic syndrome

	Enalapril	Indomethacin	Enalapril and diclofenac
Total (%)	8/8 (100)	2/8 (25.0)	1/8 (12.5)
Urine output			
No difference	1/8	0/2	0/1
Reduced	6/8	2/2	1/1
Anuria	1/8	0/2	0/1
Albumin level (g/L)			
Premedication[a]	18 (11-28)	25 (21-29)	34
Post-medication[a]	31 (21-36)	29 (27-31)	33
Difference pre- and post-medication[a]	12 (2-25)	4 (−2-10)	−1

Vos E, et al. Pediatr Transplant. **2020**; 24: e13703
doi.org/10.1111/ petr.13703

Literature review of medical nephrectomy and renal artery embolization in patients with ESRD due to nephrotic syndrome

Study	Year	N	Disease	Method	Success rate (%)	Side effects
Medical						
Baumelou[17]	1982	1[a]	Membranous nephropathy	Indomethacin (150 mg/day)	1/1	–
Hagerty[18]	1989	1[a]	Type 1 MPGN	Naproxen (500 mg/day)	1/1	–
Pomeranz[14]	1995	1	Finnish CNS	ACEi (max 5 mg/kg/day) + indomethacin (max 4 mg/kg/day)	1/1	–
Solak[13]	2010	1[a]	NS secondary to amyloidosis	ACEi (80 mg/day) + indomethacin (150 mg/day)	0/1	No effect
Maeda[19]	2011	1[a]	Membranous nephropathy	Indomethacin (max 1000 mg/day)	0/1	No effect
Sallam[12]	2012	1[a]	FSGS	NSAID (high dose)	0/1	Gastrointestinal
Vos (current)	2018	8	FSGS, CNS	ACEi, ACEi + diclofenac, indomethacin	6/8	Low blood pressure, elevated transaminases
Total		14			9/14 (64.3)	
Embolization						
Capozza[11]	2007	1	Massive proteinuria		1/1	Flank pain, (fever)
Solak[13]	2010	1[a]	NS secondary to amyloidosis		1/1	–
Maeda[19]	2011	1[a]	Membranous nephropathy		1/1	Fever, elevated LDH, WBC, CRP
Sallam[12]	2012	1[a]	FSGS		1/1	Fever, flank pain, leukocytosis
Total		4			4/4 (100)	

Vos E, et al. Pediatr Transplant. **2020**; 24: e13703
doi.org/10.1111/ petr.13703

Recurrent diseases in the kidney transplant

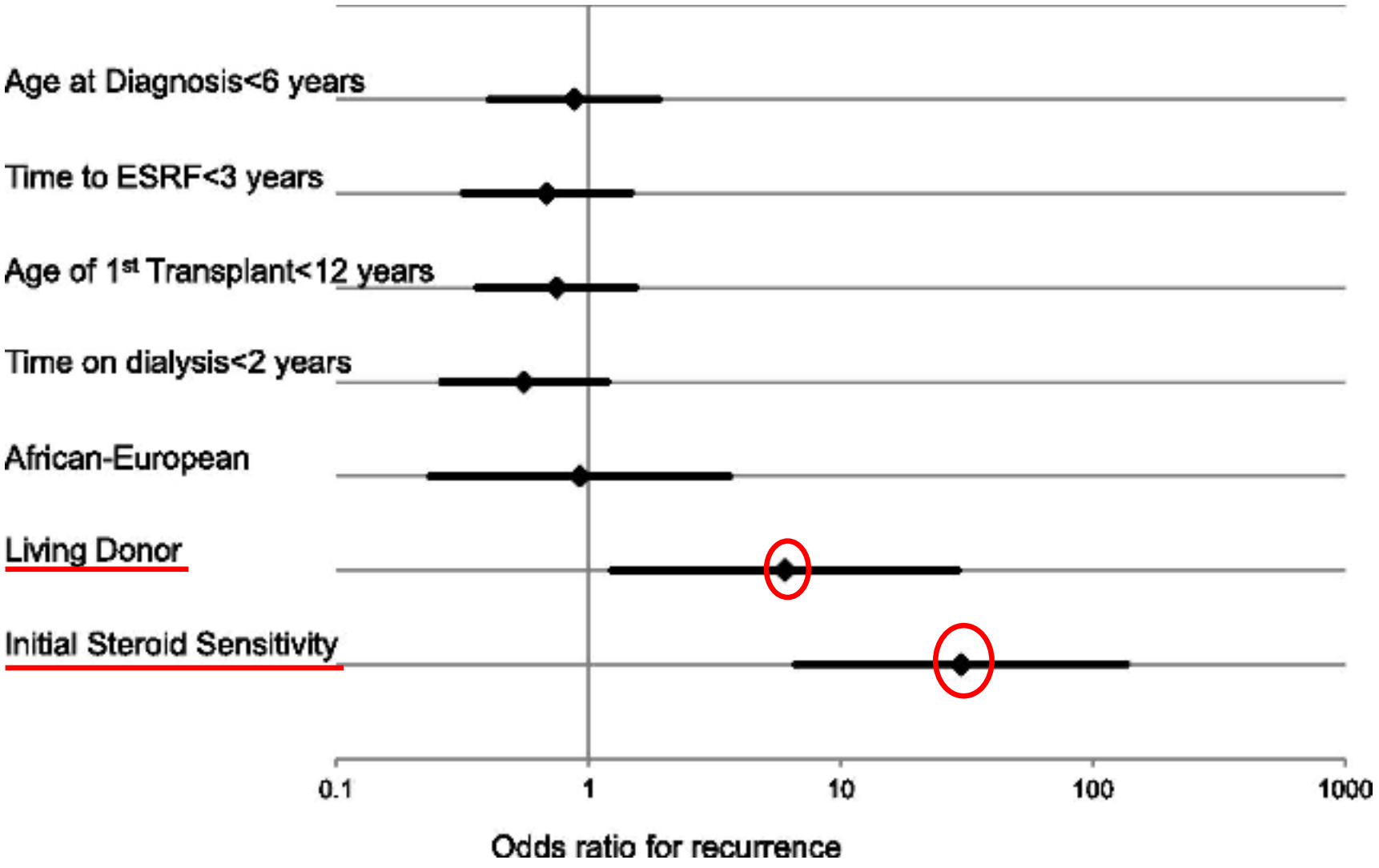
Ramos EL, and Tisher CC, AJKD 1994 Jul;24(1):142-54.
doi: 10.1016/s0272-6386(12)80172-7

Abstract

Virtually all diseases affecting the native kidney recur in the kidney transplant with the exception of Alport syndrome, polycystic kidney disease, hypertension, chronic pyelonephritis, and chronic interstitial nephritis. Fortunately, in the majority of patients, recurrence of the original disease has minimal clinical impact, with

The primary renal diseases that commonly recur include membranoproliferative glomerulonephritis type II, IgA nephropathy, and focal and segmental glomerular sclerosis. The most common systemic disease that recurs is diabetic nephropathy. Living-related transplantation should be used with caution in patients with the hemolytic uremic syndrome, recurrent focal and segmental glomerular sclerosis, and membraneous glomerulonephritis. Fabry disease and primary hyperoxaluria type I are no longer absolute contraindications to kidney transplantation.

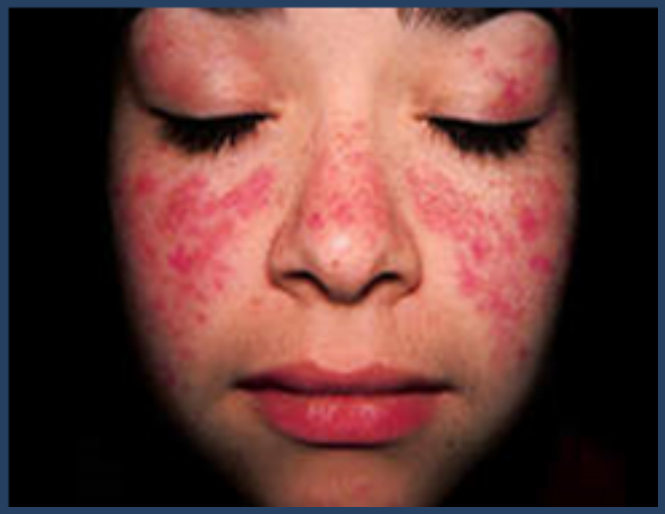
Initial Steroid Sensitivity in Children with Steroid-Resistant Nephrotic Syndrome Predicts Post-Transplant Recurrence



Forest plot of ORs for recurrence in nongenetic/nonfamilial cases.

Wen Y. Ding et al. JASN 2014;25:1342-1348

Juvenile SLE Nephritis

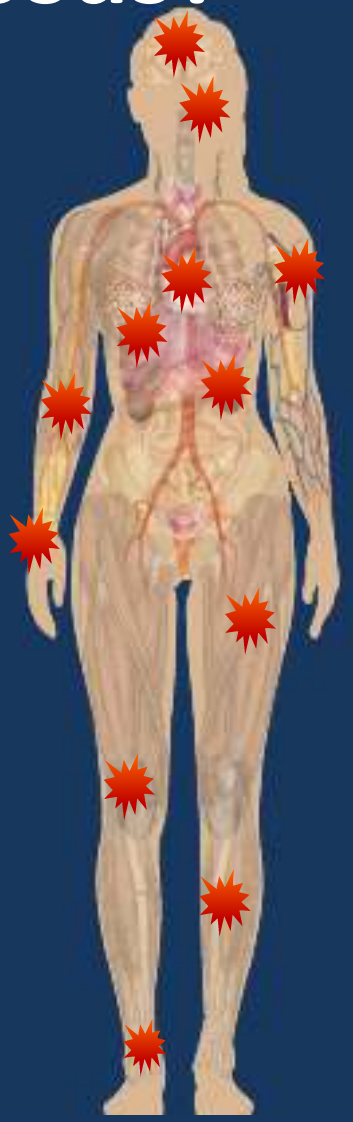


16th Congress of The Arab Society of Nephrology and Renal Transplantation
22nd Annual International Conference of Jordan Society of Nephrology and Renal Transplantation (JSNRT)
7th International Pediatric Nephrology Association (IPNA) Teaching Course in Clinical Nephrology

Issa Hazza Alkhatatbeh MD,FRCP
Consultant Pediatric Nephrologist
5-7June 2024

What Is Systemic Lupus Erythematosus?

A chronic multisystem autoimmune connective tissue disorder that manifests with a broad spectrum of clinical phenotypes, and can presented in childhood.



Barsalou et al. An update on childhood-onset SLE.Curr Opin Rheumatol. 2013.

WHY JSLE IS A CHALLENGE FOR PEDIATRICIAN?

- heterogeneity of its clinical manifestations.
- severe morbidity including mortality.
- susceptibility to relapse- and remission.
- diagnosis remains difficult.
- limited awareness among the public and even doctors .

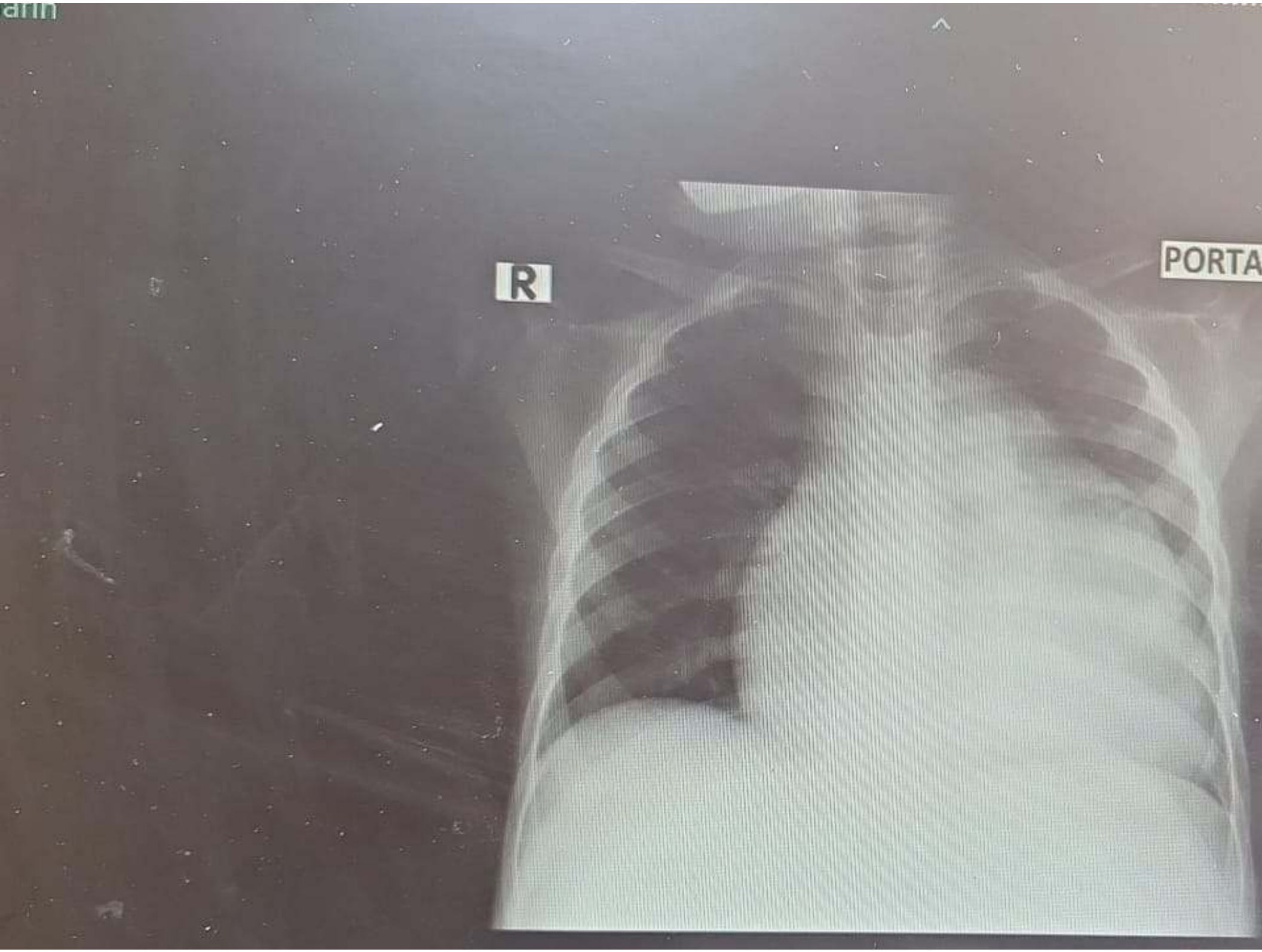
Erken b. Marmara Medical Journal 2015 ,Early-onset neurolupus: A challenge for pediatricians

disease with 1000 faces

Symptoms vary from person to person.
mimic other illnesses.
can attack any tissue .

Case1

- Dalal is an 8yr old female patient, with 2 months H/O shortness of breath seen by a paediatrician diagnosed her as chest infection, received antibiotics no improvement ,she was referred to a ped.cardiologist diagnosis was severe pulmonary hypertension with pulmonary artery thrombosis, started her on warfarin and aspirin.
- Dalal condition was not improved so she was seen by another ped. cardiologist who confirm the diagnosis with heart failure lasix was added and referred her to a paediatric rheumatologist 27/8/2023.
- Workup :SLE –ANA+++
- APAbs+++
- C3,C4↓
- Urine +2 abumin,RBCs↑ PCR1.4
- KFT normal
- Kidney bx was not done
- Admitted to hospital several times.3 months later died of chest infection and heart failure


R
PORTA

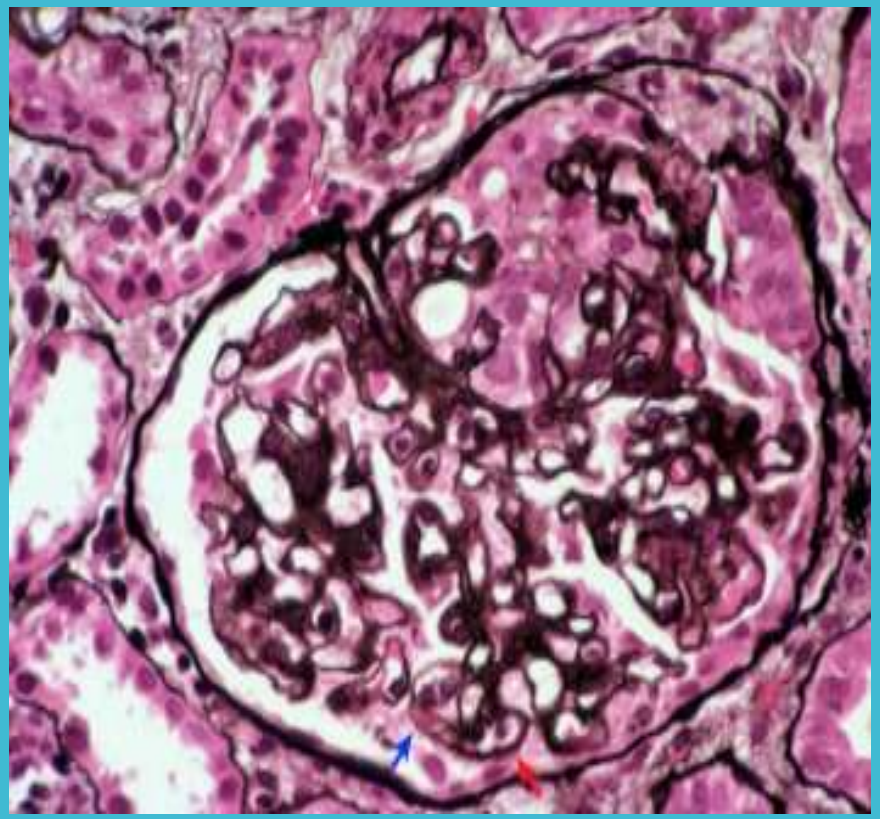
Case2

Yara is a 13 year old female patient, previously healthy, was found incidentally to have thrombocytopenia with plt count 39, referred to hematologist who ordered full lab workup, among labs SLE workup was done (ANA, Anti-dsDNA, C3,C4), initially, all labs were negative and plt count remained low, after 6 months of follow up, ANA became +ve, so she was referred to a paediatric Rheumatologist who diagnosed her to have SLE, and started her on maintenance hydroxychloroquine since October/2021.

3months after diagnosis, upon follow up she started to have new onset proteinuria ,Jan/2021 urine protein +3. kidney biopsy was done .

investigations

- Upon admission, labs showed
- CBC **HB 11.3 MCV 68 PLT 53** WBC 5.9 N 62 L 29 M 8
- **ESR 37**
- Blood film decreased platelets with large forms
- KFT Na 136 K 4 U 16 Ca 8.5 Cro.4
- LFT ALT 11 AST 13 GGT 18 TP 5.8 ALB 3.4 G 2.4
- Urine analysis WCC 2 RCC 6 PH 7 SG 1015 **Protein +3 spot protein 98 spot Creatinine 0.9 Pr:Cr ratio 5.8**
- APS IgM/IgG negative
- Anticardiolipin IgM/IgG negative
- C3 170, C4 39 (normal)
- ANA 1/1200



EPT. OF PATHOLOGY & LABORATORY MEDICINE

مستشفى الأردن
JORDAN HOSPITAL

دائرة المختبرات والأنسجة المرضية

DEPARTMENT OF PATHOLOGY & LABORATORY MEDICINE

Order No : P1003 –22 Specimen Date: 23/3/2022
Patient No : 228828 Order No: 8360734 Room No: 165
Patient Name : يارا محمد عماد بشير صالح
Age : 12 years Sex: female
Doctor :عيسى خطاطبه

Origin of Tissue: Kidney biopsy.
Brief Clinical History: Admitted as a case of suspected SLE. Had thrombocytopenia, nephrotic range proteinuria, recurrent episodes of abdominal pain and nausea. Positive ANA.
Pre-operative diagnosis:
Post-operative diagnosis:

Pathology Report

Gross Exam:

1) Specimen is received fixed in formalin, labeled with patient name and consists of one soft tissue needle biopsy fragment measuring 1.5 cm in length. Totally submitted in one cassette.
2) Specimen is received fresh in normal saline for immunoflourescence studies.

Microscopic Exam:

Sections reveal 11 glomeruli in the submitted core, all of which show mild uniform thickening of capillary loops with minimal increase of mesangial cells in some glomeruli. No wire loops, segmental or global sclerosis, necrosis or crescents seen. The tubules, intersitium and blood vessels appear normal. Special stains are non-contributory.

Immunoflourescence studies:

15 glomeruli are present. They reveal peripheral granular deposits of IgG (3+) in capillary loops. Negative for IgA, IgM, C3, C4 and fibrinogen.

Diagnosis:

Kidney biopsy:

Membranous lupus nephritis (Class V).

...n University Hospital
...ic Pathology
...026

Consultants
M. Shomaf, M.D | N. Abu Shahin, M.D | H. Awad, FRC Path
M. Al-Abbadi, M.D | M. Hajeer, FRC Path | A. Mansour, MD
F. Obeidat, M.D | T. Al-Adily, M.D | Maram Abdaljaleel, M.D

Patient's Name: يارا محمد عماد بشير صالح
Age/Sex : 12 years/ Female
Hosp. No. :
Ward : م. الاردن

Specimen No. : E37-22
Date of Specimen:
Date of Report : 10/04/2022
Ref. Consultant :

Nature of Specimen: Kidney, biopsy

Clinical Data: Admitted as a case of suspected SLE. Had thrombocytopenia, nephrotic range proteinuria, recurrent episodes of abdominal pain and nausea.

Report:

Macroscopic:

1 core of renal cortical tissue received in gluteraldehyde, measuring 0.1x0.2 cm for electron microscopy.

Electron microscopic description:

1 micron-thick, toluidine blue-stained slides, containing sections of two viable glomeruli, are examined by transmission electron microscope.

The GBMs display irregularities in thickness due to the presence of multiple sub epithelial immune deposits. The overlying podocytes show cytoplasmic swelling and microvillous transformation of the foot processes. The mesangium appears expanded by matrix and similar immune deposits. No evidence of endocapillary proliferation, necrosis, thrombosis or crescents.

Interpretation:

The EM findings in correlation with the provided light microscopic and immunofluorescence report are compatible with early membranous nephropathy of secondary etiology; in keeping with the current diagnosis of membranous lupus nephritis class V.

Consultant
N. Abu-Shahin, M.D

Resident

L.D

ارسلت بـ ١٢/٤/٢٠٢٢

Case 3

- 11 years old previously well, presented to the emergency department with sudden onset of recurrent seizures, hypertensive emergency, acute kidney injury with rapid deteriation in KFT .

- Relative history: the patient has been having symptoms of dark urine, facial puffiness and myalgia for the past 2 months treated with Ibuprofen pills she also had previous H/O URTI two weeks ago plus 2 protein and plus 4 blood in urine , with cbc showing Hb of 9.8gm/dl . Without further investigation. She had no rash, but had personality changes elicited by disinterest with her usual activities and being irritable.

- Family hx is significant for a second degree relative who underwent renal transplant for hyper IgD syndrome

- **Physical exam and Hospital course:**

At first encounter :

- **Vitals**

BP	HR	RR	O2 sat	Temperature
150/100	113	18	97	37.4

- She was conscious alert oriented to place time and person, with return to baseline after each seizure attack, she had normal general appearance , no rash, no skin discoloration , with normal s1 and s2 , and good air entry bilateral, normal muscle tone and power.

Soon after presentation her BP reached a maximum of 237/160

She developed status epileptics and was intubated .

Day 1 to 6 of admission:

On midazolam and phentanyl infusion.
Started on Levetirecitam and phenytoin.
 bluish discoloration of the right index finger was noted, BP around 150/ 85, Heart rate mean 130.

- **RENAL:** developed anuria by day 4 , started on Hemodialysis.

- **cbc:** pancytopenia, was started on antibiotics.

C3	**Less than30**
C4	**Less than 16**
ANA	**1:640 (homogenous)**
DsDNA	**1:640**
ANCA	**C-anca (negative) P-anca (borderline)**
Anti cardiolipin igG/igM	**15/19 elevated**
Anti-B2 glycoprotien igG/igM	**14/16 elevated**
Anti RNP	**Negative**
Anti Mi2 alpha	**poistive**
Anti DFS70	**poistive**
Anti Histones	**+2 poistive**
Anti RO/LA	**negative**
ASO titer	**800**

	30/4	6/5
urea	75	126
Creatinine	1.97	4.6

Management:

- Received 3 doses pulse methylprednislone.
- pulse Cyclophosphamide.
- Prostacycline for 5 days.
- Hemodialysis.
- Allopurinol.
- LMW Heparin .
- Renal Doppler U/S normal.

Day 6 to 13 of admission:

CNS: no regain of consciousness, intact brainstem reflexes, no seizures , EEG (consistent with encephalopathy.

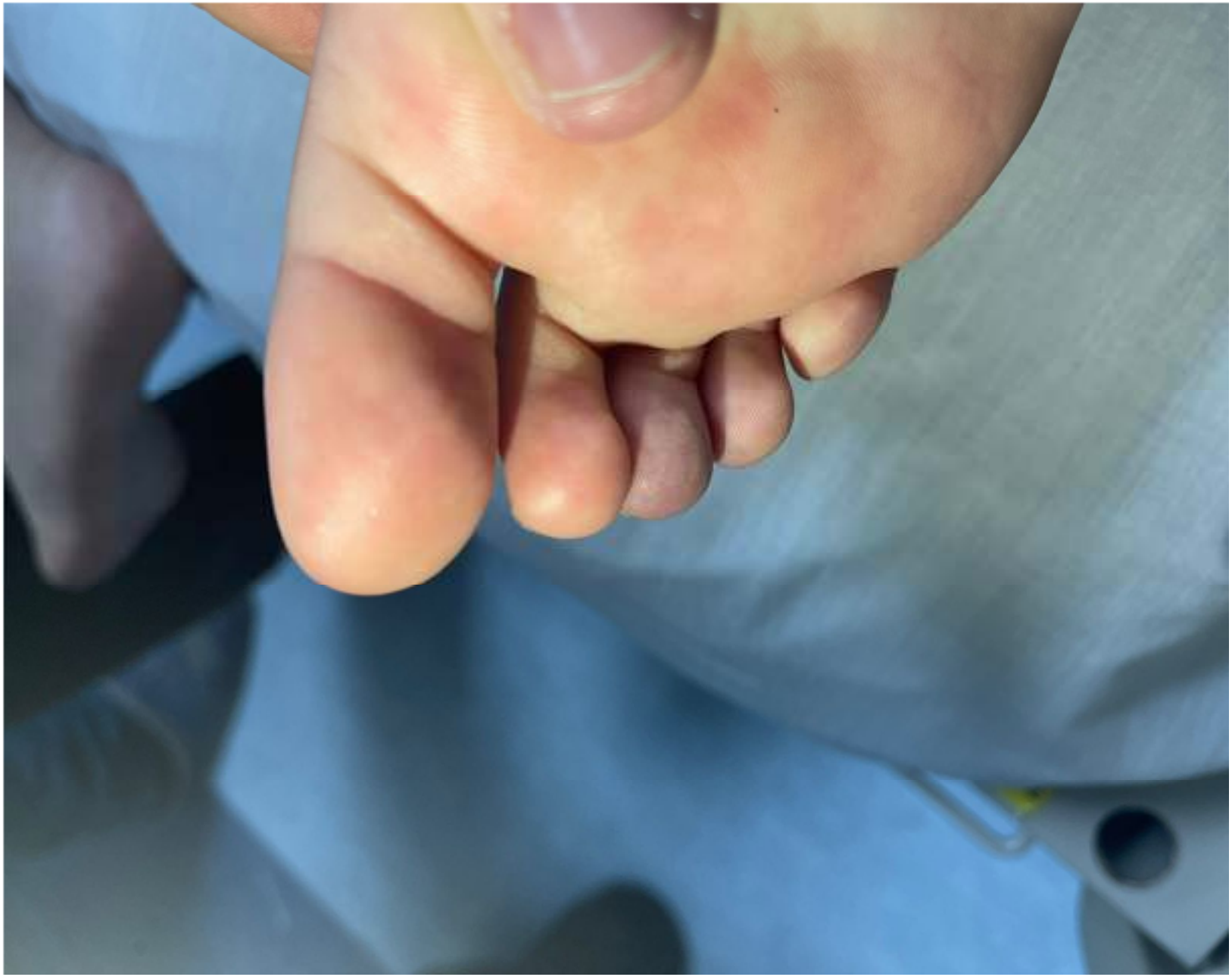
CVS: Echo showed septal hypertrophy , diastolic dysfunction with intact cardiac index.

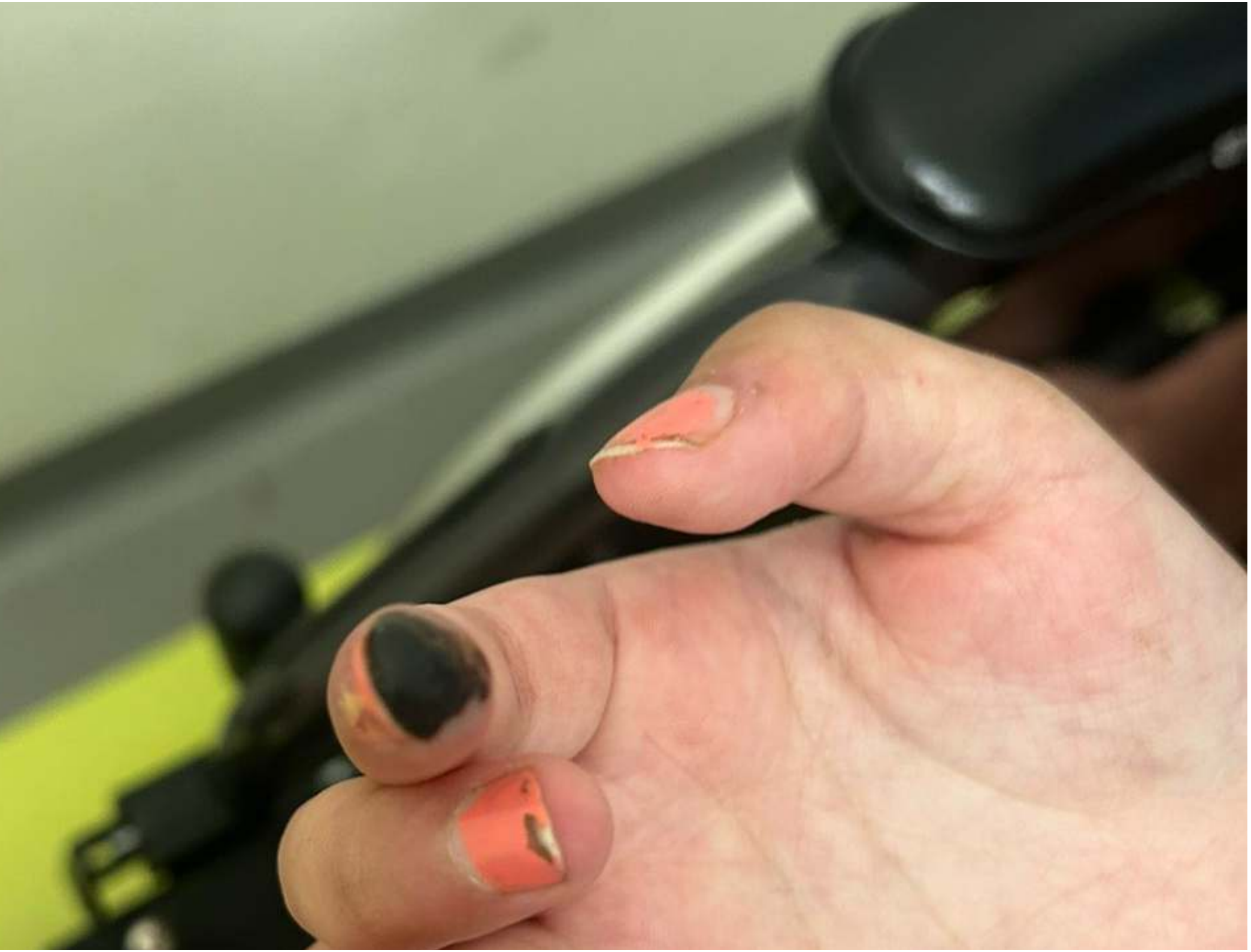
Renal: on hemodialysis, anuria.

CBC: Pancytopenia, received G-CSF.

Vascular: developed bluish discoloration of the toes. And Rt. index finger

- Started on plasmapheresis (6 sessions)



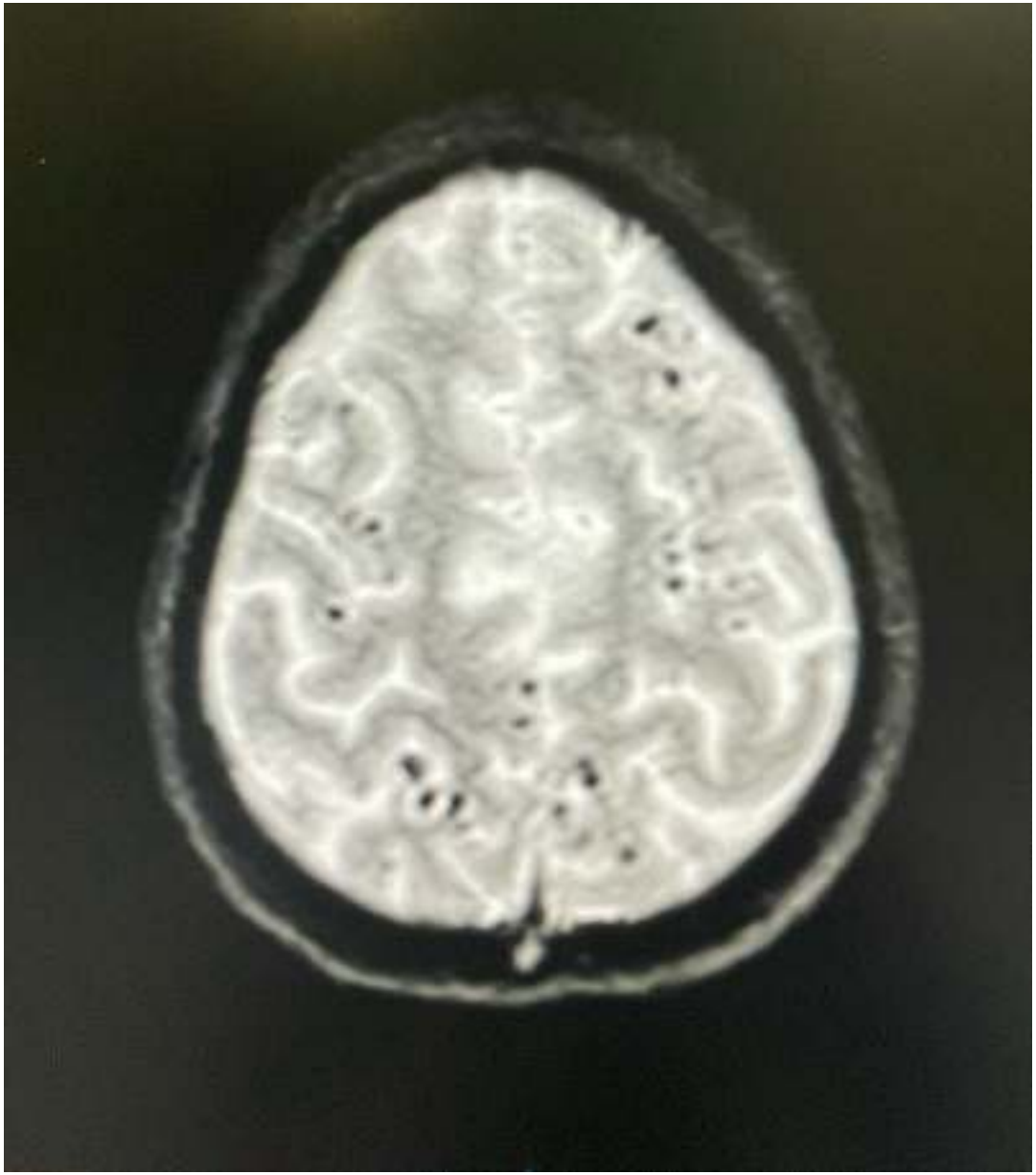


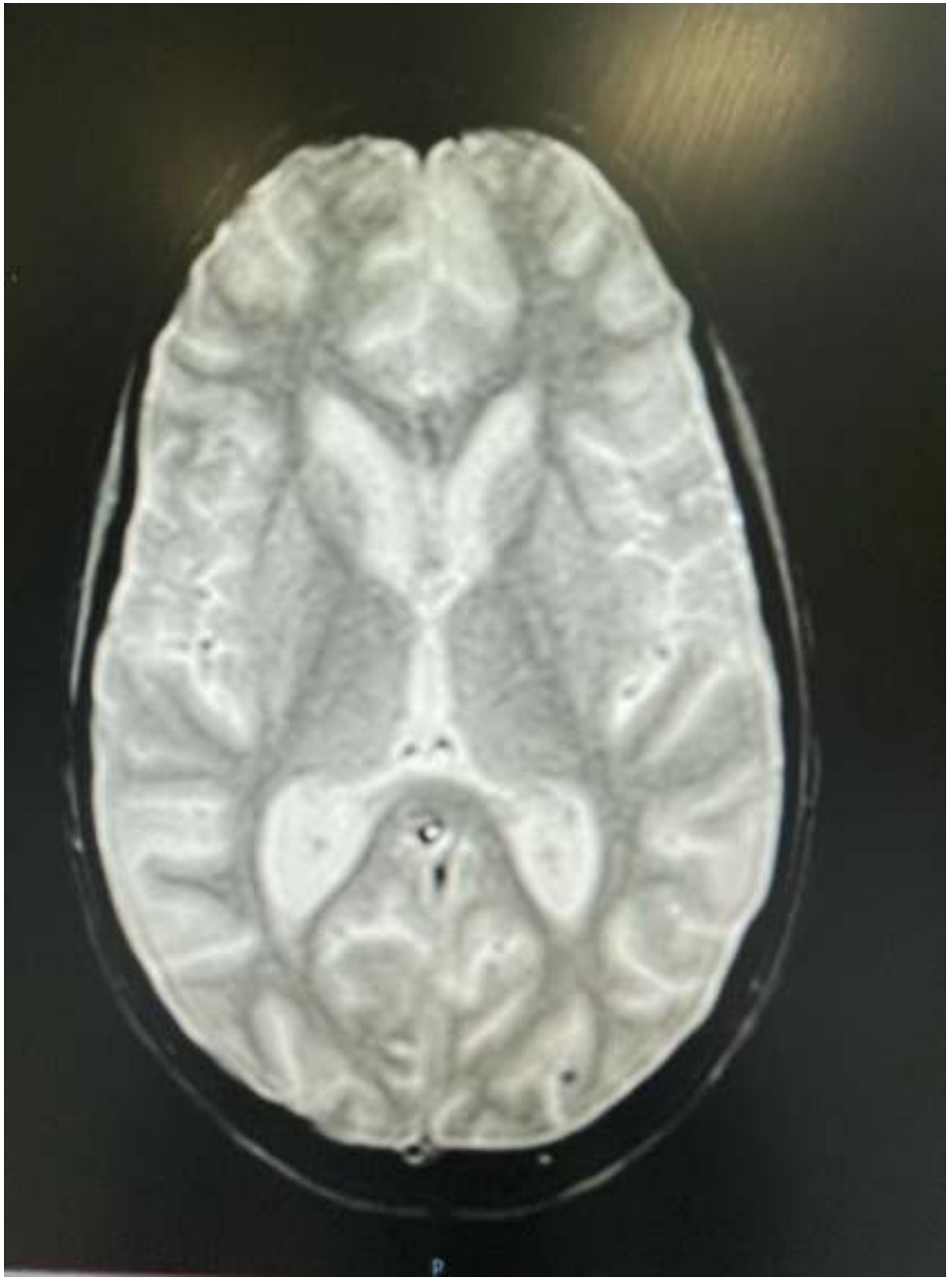
Day 14 of admission :

- the patient was successfully extubated, started on chest physiotherapy , occupational and physical physiotherapy.
- MRI showed active lesions of vasculitis , micro-hemmorrhages, and changes consistent with chronic hypertension.

P/E:

- alert and aware to surrounding knows her parents.
- unable to swallow or talk .
- Absent deep tendon reflexes in the lower extremities, intact sensation, intact upper lower extremities reflexes.





Day 15 to discharge:

- The patient received Rituximab one dose and IVIG (one dose).
  - Was continue on Mycophenolate mofetil and Hydroxychloroquin,and steroid.
  - Her condition improved she started to tolerate feeding and speak small sentences.
  - Uses both of her upper extremities (power 4/5), intact cerebellar exam. Able to sit unsupported , lower extremity weakness (power 2/5) and absent reflexes.
  - Bluish discoloration of the toes progression, was started on Warfarin.
  - Her BP was controlled with Nifdipine 10 mg by three and Bisoprolol 2.5 mg by 1.
- 2 weeks after discharge she was readmitted with febrile uti ,kft were normal ,dialysis discontinued.

- incidence: 2.22 per 100,000 /USA
- SLE prevalence: 9.73 per 100,000 children ages 3 to 18 years.

- M Brunner. Update on differences between childhood-onset and adult-onset SLE. Arthritis Res Ther 2013

Twenty per cent of SLE cases are diagnosed in childhood, and 50–80% of adolescents with SLE will develop kidney involvement (lupus nephritis) , at some point in their disease course

~55% of patients have lupus nephritis (LN) at onset

J Pediatr 2008;152:550-556.

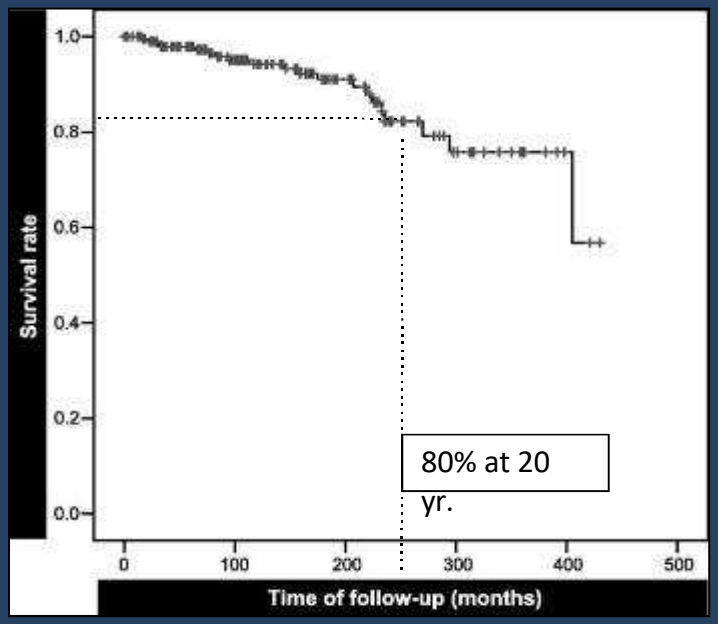
5-year renal survival rates in children with cSLE have ranged from 77% to 93%.
Children with LN have 19-times higher risk of dying compared with age-matched general populations.
There is 22% mortality during the 5-year period since the initiation of renal replacement therapy, with cardiopulmonary compromise and infections accounting for 47% of all causes of death

Rheum Dis Clin North Am. 2016 Aug 11

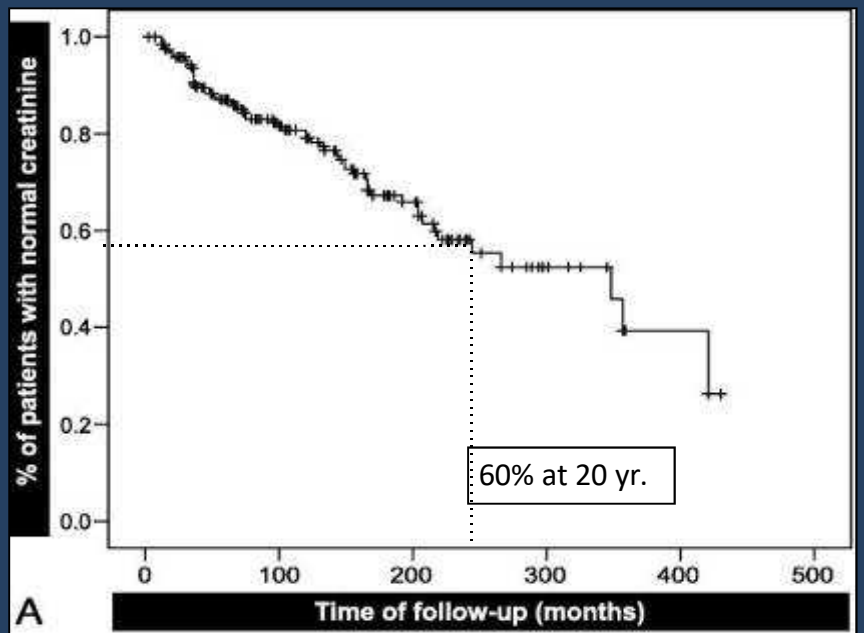
Lupus nephritis outcomes (adult)

670 patients with systemic lupus erythematosus (SLE) consecutively followed from 1970 until 2006

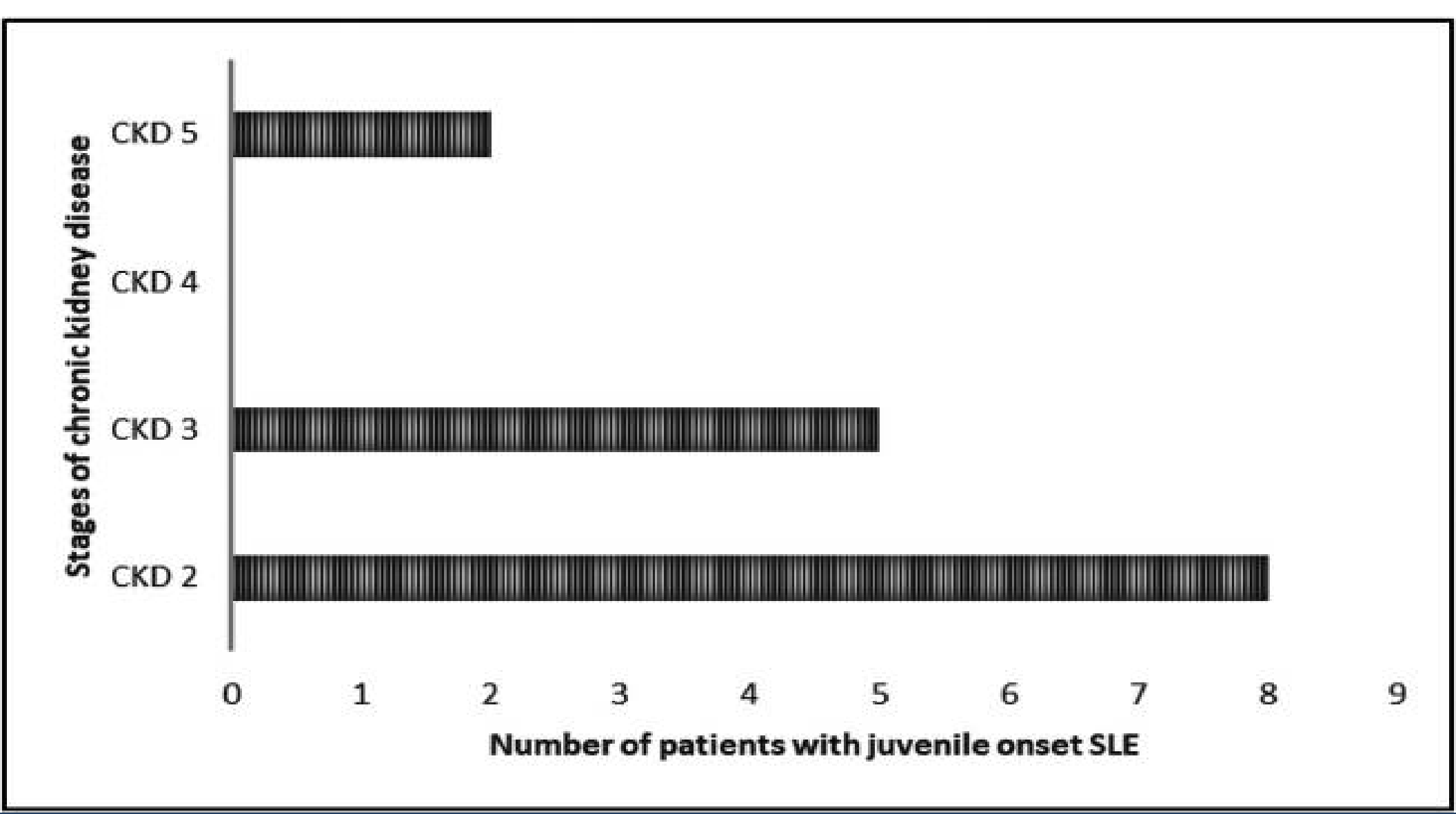
Survival



Survival with preserved renal function



Sisó et al, *Medicine* 2010



the incidence of chronic kidney disease (CKD) was 3.8% (15/399 children) after a median follow-up time of 6.6 years (range 0–21 years). The stages of CKD are shown demonstrating that the majority of children had CKD stage 2 (8/15; 53%, 8/399; 2% of entire cohort), followed by CKD 3 (5/15; 33%, 5/399; 1% of entire cohort), none had CKD 4 (0/15; 0%, 0/399; 0%) and 2 patients had CKD 5 (2/15; 13%, 2/399; 0.5% of entire cohort) UK JSLE Cohort Study Pediatr Nephrol. 2021; 36(6): 1377–1385

Lupus nephritis in children and adolescents: results of the Italian Collaborative Study ,ndt, 2013-06-18

the predictors of Stage III CRF .
Younger age was associated with a higher probability of developing CRF both in univariate (P = 0.0001) and in multivariate analysis (P = 0.003).
class IV LN was significant risk factors for developing CRF (P = 0.042).

Table 4.
Predictors of stage III CRF

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
General characteristics at onset						
Female gender	0.81	0.30–2.15	0.670			
Age at the onset of nephropathy (years)	0.84	0.76–0.91	0.0001	0.86	0.78–0.95	0.003
Acute renal failure	2.32	1.07–5.04	0.033	1.83	0.77–4.36	0.175
Nephrotic range proteinuria (>40 mg/m^2/h)	1.88	0.87–4.07	0.109			
Hypertension (>95th percentile)	1.84	0.84–4.04	0.130			
Hypocomplementemia (C3 < 80 mg/dL)	0.59	0.25–1.39	0.226			
Number of ACR criteria	0.86	0.66–1.06	0.219			
Treatment score	0.73	0.44–1.19	0.208			
Delay-SLE	3.74	1.50–9.34	0.005	3.59	1.29–9.98	0.014
WHO classification						

Spectrum of Pediatric Systemic Lupus Erythematosus at Queen Rania Al-Abdullah Hospital f

Mohammed Abu-Shukair MD*, Zeyad Habahbeh MD*, Mohammad Almutereen MD*, Raed Zyoud MD*, Hiffa Bindahaman MD*, Gazi Saliteh MD**, Fareed Haddad MD^, Adel Alwahadneh MD*, Issa Hazaa MD**

- 25 patients from the pediatric Rheumatology unit at Queen Rania Al-Abdulla Hospital for children, who met four or more of the revised American College of Rheumatology classification criteria for Systemic lupus Erythematosus were reviewed. Results: Renal involvement was found in 40% of cases. (10pts) Kidney biopsy was done for seven patients with renal manifestations. Three had class IV, two class III and two class I World Health Organization nephritis stage classification. three patients developed end stage renal disease. 12%

JUVENILE VS ADULT SLE

Increased need for corticosteroid.

Children tend to die during acute SLE phase

Adults tend to die secondary to complications

have more aggressive disease.

worse outcomes.

Onset in childhood carries a higher risk of nephritis.

More anti-dsDNA, and hemolytic anemia.

- Pediatr Clin N Am 65 (2018)

Lupus Nephritis

- *The American College of Rheumatology (ACR) criteria for the diagnosis of LN require the presence of persistent proteinuria defined as a spot urine protein/creatinine ratio of >0.5 gm or greater than 3+ on a urine test strip, and/or cellular casts including red blood cells, hemoglobin, granular, tubular or mixed*

The most common initial manifestation of nephritis is microscopic hematuria (79%), followed by proteinuria, including nephrotic syndrome (55%). Decreased GFR and hypertension are also seen (50% and 40%, respectively) .
acute renal failure as a presenting manifestation of nephritis is rare (1.4%)

INDICATIONS FOR RENAL BIOPSY IN PATIENTS WITH CSLE

- *Increased serum creatinine without compelling alternative causes, such as sepsis, hypovolemia, or medication.*
  Confirmed proteinuria of 1.0 g per 24 h .
  Combinations of the following.
  (1) Proteinuria: 0.5 g per 24 h plus hematuria,
  (2) Proteinuria: 0.5 g per 24 h plus cellular casts.

Pathological assessment of kidney biopsy

The use of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system is recommended with assessment of active and chronic glomerular and tubulointerstitial changes, and of vascular lesions associated with anti-phospholipid antibodies/syndrome

Histopathology classification of lupus nephritis according to the criteria established by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) in 2003 revised in 2018

HISTOPATHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS

Class I

Minimal Mesangial Lupus Nephritis

- Deposition of imune complexes detectable by immunofluorescence techniques.

Class III

Focal Lupus Nephritis

- Active or inactive focal, segmental or global endo/extracapillary glomerulonephritis involving <50% of all glomeruli.
- Manifestations include active lesions (A), chronic inactive lesions (C) or active and chronic lesions (A/C)

Class V

Membranous Lupus Nephritis

- Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy, with or without mesangial alterations.
- It can occur in combination with class III or IV and it can manifest advanced sclerosis.

Class II

Mesangial Proliferative Lupus Nephritis

- Mesangial hipercelularity of any degree or mesangial matrix expansion with immune deposits detectable by light microscopy.

Class IV

Diffuse Lupus Nephritis

- Active or inactive diffuse, segmental or global endo/extracapilarry glomerulonephritis involving ≥50% of all glomeruli. Subendothelial diffuse immune deposits, with or without mesangial alterations, are common.
- This class is also divided in: diffuse segmental (IV-S), when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G), when ≥ 50% of the involved glomeruli have global lesions.
- It can also manifest A, C or A/C lesions.

Class VI

Advanced Sclerosis Lupus Nephritis

- Lupus Nephritis with terminal prognosis.
- 90% of the glomeruli in global sclerosis.

Active Lesions	*Chronic Lesions*
1. Endocapillary hypercellularity, with or without leukocyte infiltration and with substantial luminal reduction	*1. Glomerular sclerosis (segmental, global)*
2. fibrinoid necrosis	*2. Fibrous adhesions*
3. Rupture of glomerular basement membrane	*3. Fibrous crescents*
4. Crescents (cellular or fibrocellular)[e]	*4. Tubular atrophy*
5. Subendothelial deposits identifiable by light microscopy (wireloops)	
6. Intraluminal immune aggregates (hyaline thrombi)	
NIH Activity Index 0–24	*NIH Chronicity Index 0–12*

RISK FACTORS TO POOR OUTCOME OF LN

Male gender
Non-Caucasian race
Non adherence to treatment
Presence of antiphospholipid or anti-dsDNA antibodies
Persistent hypocomplementemia or proteinuria
Nephrotic syndrome at presentation,
Failure to adequately respond to therapy by 3 months
Flare of LN
Diagnosis with proliferative LN, especially in the setting of a high
Degree of histologic activity and damage.

treatment challenges

- Treatment vary between clinicians and often based on: adult-derived trials or studies, anecdotal case series in children, and individual clinician experience.

The SHARE initiative

The ultimate goals of treatment in LN are long-term preservation of renal function.
prevention of disease flares.
avoidance of treatment-related harms.
and improved quality of life and survival

Aim for complete renal response with UPCR <50 mg/mol and normal or near-normal GFR .

Indications and goals of immunosuppressive treatment in lupus nephritis (LN)

Initiation of immunosuppressive treatment should be guided by a diagnostic renal biopsy.
Immunosuppressive agents are recommended in:
class IIIA or IIIA/C nephritis
class IVA or IVA/C nephritis
class V nephritis if proteinuria exceeds 1 g/24 h despite the optimal use of renin-angiotensin-aldosterone system blockers

European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association, EULAR/ERA-EDTA revised recommendations (2019)

EULAR/ERA_EDTA Recommendations for the management of adult and pediatrics with lupus nephritis

- Initial treatment for class III–IV LN: Mycophenolate mofetil (MMF) or low-dose IV cyclophosphamide plus glucocorticoids
- Alternate option for class III–IV LN: Combination therapy of MMF with a calcineurin inhibitor (CNI), especially tacrolimus, particularly in patients with nephrotic-range proteinuria
- To reduce cumulative glucocorticoid dose: Intravenous pulses of methylprednisolone (total dose 500–2500 mg, depending on disease severity), followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months

- Initial treatment for pure class V disease with nephrotic-range proteinuria: MMF in combination with methylprednisolone followed by oral prednisone
- Alternate options for pure class V:
  I.V cyclophosphamide or a CNI, especially tacrolimus, as monotherapy or in combination with mMMF/mycophenolic acid (MPA)

- In all LN patients: Hydroxychloroquine (HCQ) should be coadministered at a dose not to exceed 5 mg/kg/day and adjusted for the GFR, in the absence of contraindications

- Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in patients with complete clinical response. HCQ should be continued long-term.
- Continuation, switching to or addition of CNIs, especially tacrolimus, can be considered in pure class V LN at the lowest effective dose and after considering nephrotoxicity risks
- Patients in whom initial therapy fails should be switched to one of the alternative initial therapies or to rituximab

HOW LONG SHOULD A PATIENT BE MAINTAINED ON IMMUNOSUPPRESSION?

- The 2023 EULAR update recommends that treatment for LN should be continued for at least 3 years.
- glucocorticoids should be withdrawn as soon as sustained remission is achieved.
- The EULAR 2023 update recommends a maintenance dose of ≤5 mg/day

- *The EULAR recommend repeated kidney biopsy to guide reduction and withdrawal of immunosuppression, when patients are in remission for at least 2 years .*
  In the case of limited/no evidence of histologic activity (National Institutes of Health Activity Index of ≤1), reducing or stopping glucocorticoids might be attempted if such agents are used to maintain remission. Other immunosuppressants might be reduced/withdrawn over time

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

- In Patients with active proliferative lupus nephritis combination therapy with belimumab (either with cyclophosphamide or mycophenolate (1b/A)) or calcineurin inhibitors (especially voclosporin(adult) or tacrolimus, combined with mycophenolate, 1b/A) should be considered

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

- Following renal response, treatment of LN should continue for at least 3 years (2b/B); patients initially treated with mycophenolate alone or in combination with belimumab or a calcineurin inhibitor should remain on these drugs (1a/A), whereas mycophenolate or azathioprine should replace cyclophosphamide for those initially treated with cyclophosphamide alone (1a/A) or in combination with belimumab (1a/A)

Belimumab

- Belimumab, a fully humanized monoclonal antibody which inhibits B-lymphocyte stimulator, is the 1st targeted biologic agent licensed for the treatment of SLE to date.

GlomCon edu

Newer Therapies for Lupus Nephritis

An overview of therapeutic targets, status of trials, FDA approval

Targeted biological agents available and in ongoing phase II and III trials of SLE

TULIP-LN1

Phase 2 RCT, n=147,
Class III/IV±V LN,
1:1:1 (Anifrolumab- Basic Regimen (BR) vs Intensified Regimen (IR) vs placebo)
At 52 weeks
*No difference in 24 hr UPCR (PE)
*CRR numerically higher with IR
*More herpes zoster in BR+IR

Approved for adults with moderate to severe SLE with SOC, iv, July 2021

NOBILITY

Phase 2 RCT, n= 125,
Class III/IV LN,
1:1 (Obinutuzumab vs placebo)
At 104 weeks
*Δ19% for CRR(↑ from 12% at week 52)
*92% were B-cell depleted at 52 weeks
*Δ10% for need of rescue therapy
*No safety signals

REGENCY

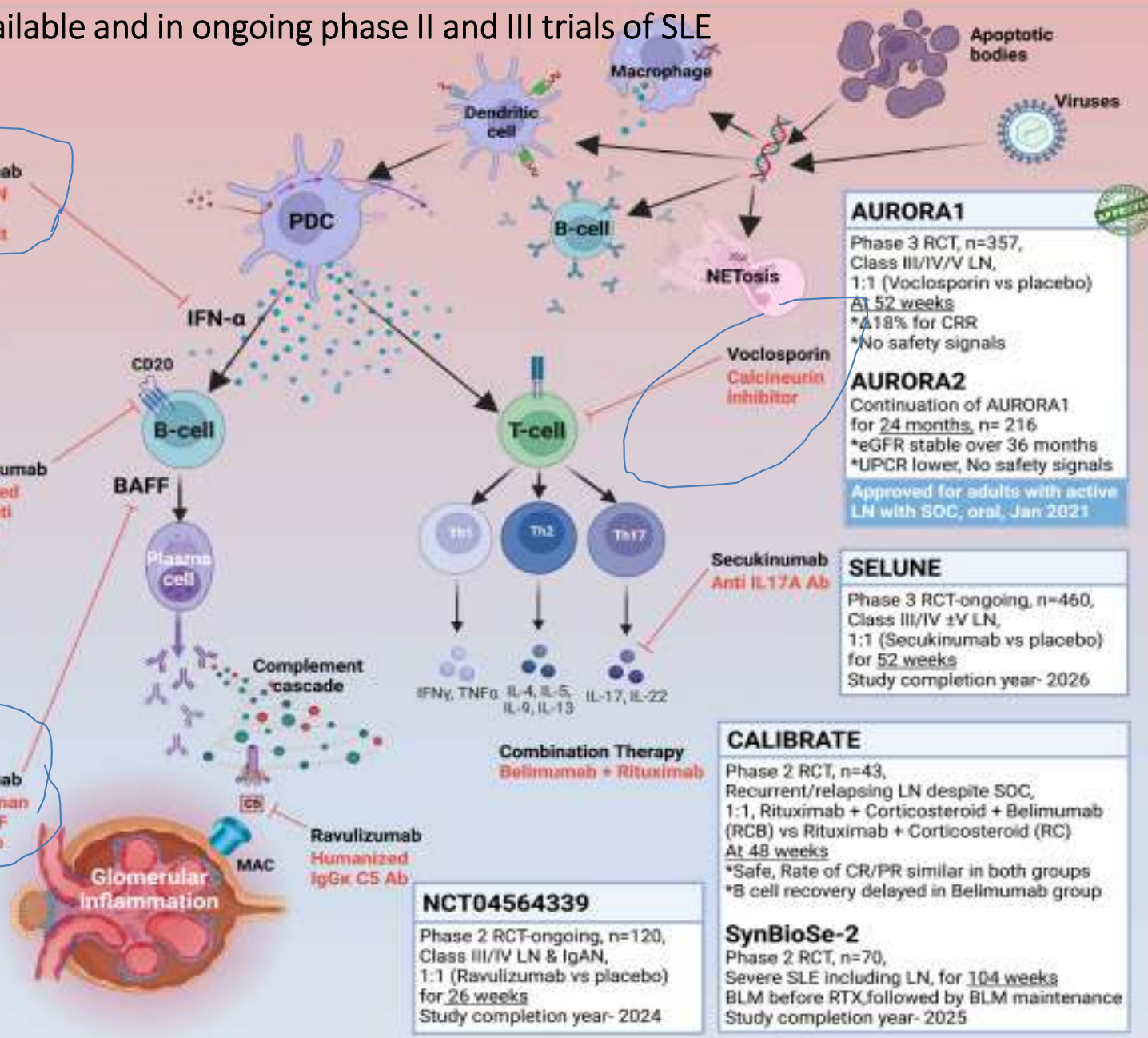
Phase 3 RCT- ongoing, n= 252,
Class III/IV±V LN for 76 weeks
Primary completion year- 2024

Breakthrough therapy designation for LN, Sept 2019

BLISS-LN

Phase 3 RCT, n= 448,
Class III/IV/V LN,
1:1 (Belimumab vs placebo)
At 104 weeks
*Δ11% for Primary Efficacy Renal Response
*Δ10% for CRR, No safety signals

Approved for active LN with SOC,iv & sc, Dec 2020



AURORA1

Phase 3 RCT, n=357,
Class III/IV/V LN,
1:1 (Voclosporin vs placebo)
At 52 weeks
*Δ18% for CRR
*No safety signals

AURORA2

Continuation of AURORA1 for 24 months, n= 216
*eGFR stable over 36 months
*UPCR lower, No safety signals

Approved for adults with active LN with SOC, oral, Jan 2021

SELUNE

Phase 3 RCT-ongoing, n=460,
Class III/IV ±V LN,
1:1 (Secukinumab vs placebo)
for 52 weeks
Study completion year- 2026

CALIBRATE

Phase 2 RCT, n=43,
Recurrent/relapsing LN despite SOC,
1:1, Rituximab + Corticosteroid + Belimumab (RCB) vs Rituximab + Corticosteroid (RC)
At 48 weeks
*Safe, Rate of CR/PR similar in both groups
*B cell recovery delayed in Belimumab group

SynBioSe-2

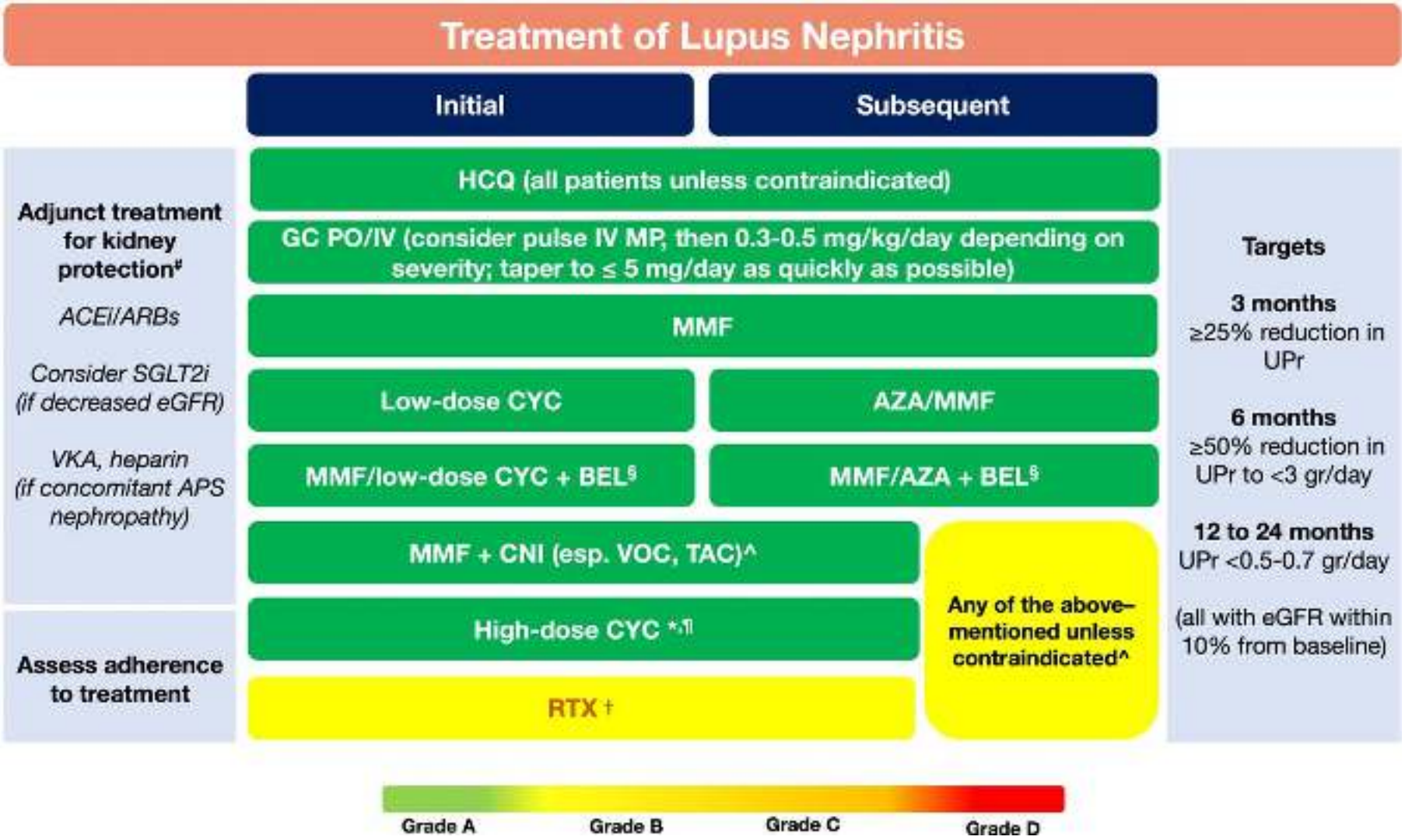
Phase 2 RCT, n=70,
Severe SLE including LN, for 104 weeks
BLM before RTX,followed by BLM maintenance
Study completion year- 2025

NCT04564339

Phase 2 RCT-ongoing, n=120,
Class III/IV LN & IgAN,
1:1 (Ravulizumab vs placebo)
for 26 weeks
Study completion year- 2024

- BEL should always be given in combination with MMF or low- dose CYC as initial therapy, and with MMF or AZA as maintenance therapy.
  CNIs should be given in combination with MMF.
  Particularly recommended in the presence of poor prognostic factors: reduced eGFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation.
  Extension of high- dose CYC to subsequent phase refers to severe LN cases, in which bimonthly or quarterly CYC pulses may be given following six monthly pulses.

Treatment of lupus nephritis.



Antonis Fanouriakis et al. Ann Rheum Dis 2024;83:15-29

ARD

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis
September 16, 2020
N Engl J Med 2020;383:1117-1128

- A total of 448 patients underwent randomization (224 to the belimumab group and 224 to the placebo group). At week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (43% vs. 32%; odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3; P=0.03) and a complete renal response (30% vs. 20%; odds ratio, 1.7; 95% CI, 1.1 to 2.7; P=0.02). The risk of a renal-related event or death was lower among patients who received belimumab than among those who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P=0.001). The safety profile of belimumab was consistent with that in previous trials

- Refractory disease — Rituximab is a therapeutic option in children with severe SLE refractory to conventional therapy.

Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis

- Results: Out of 233 reports, we selected 26 for analysis, which described 300 patients with a mean follow-up of 60 weeks. The complete or partial response criteria were met by 87% of patients with LN class III, 76% with class IV and 67% with class V, respectively. Mixed classes responded in 76% of patients. RTX induced complete responses in 60% (type III), 45% (type IV), 40% (type V) and 24% (mixed types), respectively.

- Conclusions: Our systematic review of existing evidence suggests that RTX effectively induces remission of LN in patients who have not achieved remission with standard therapies.

- Nephrol Dial Transplant. 2013 Jan;28(1):106-11. Epub 2012 Jul 3.

ReumatolClin.2016;12(4):210–21RituximabinLupusNephritis:ANon-systematicReview5

Characteristics of the Observational Studies With Rituximab.

Author/year	Population	No. of patients (mean age [years])	Treatment-naïve patients (%)	Protocol of RTX administration	Mean follow-up period	Main outcomes (*P* value)
Melander et al.[13] 2009[a,b]	III-V LN according to biopsy	20; 95% W (25.6)	10	375 mg/m^2 × 4 in 90% of patients	22 months	CR: 35%; PR: 25%
Terrier et al.[12] 2010[c]	SLE, 31% con LN; 19% class III and 52.4% class IV (95% biopsy)	42	24	Dose in LN patients of the registry not reported	16.6 months	CR: 45% (.0001); PR: 29% (.004)
Condon et al.[11] 2013[d]	III-V LN according to biopsy	50; 78% W (45)	58	1 g × 2 (with 0.5 g MPS)	40.75 months	CR: 72%; PR: 18%

CR, complete remission; GFR, glomerular filtration rate; LN, lupus nephritis; MPS, methylprednisolone; PR, partial remission; RTX, rituximab; SLE, systemic lupus erythematosus; UPC, urinary protein to creatine; W, women.

a Retrospective observational study.

Plasma exchange therapy in systemic lupus erythematosus

- Therapeutic plasma exchange (TPE) : this therapeutic option is helpful when treatment with other agents fails or in presence of leucopenia and psychosis, but it has been profiled as an effective therapeutic option especially for patients with SLE with thrombotic thrombocytopenic purpura and catastrophic antiphospholipid syndrome

Systemic Lupus Erythematosus (SLE) Therapy: The Old and the New Rheumatol Ther. 2020 Sep; 7(3): 433–446

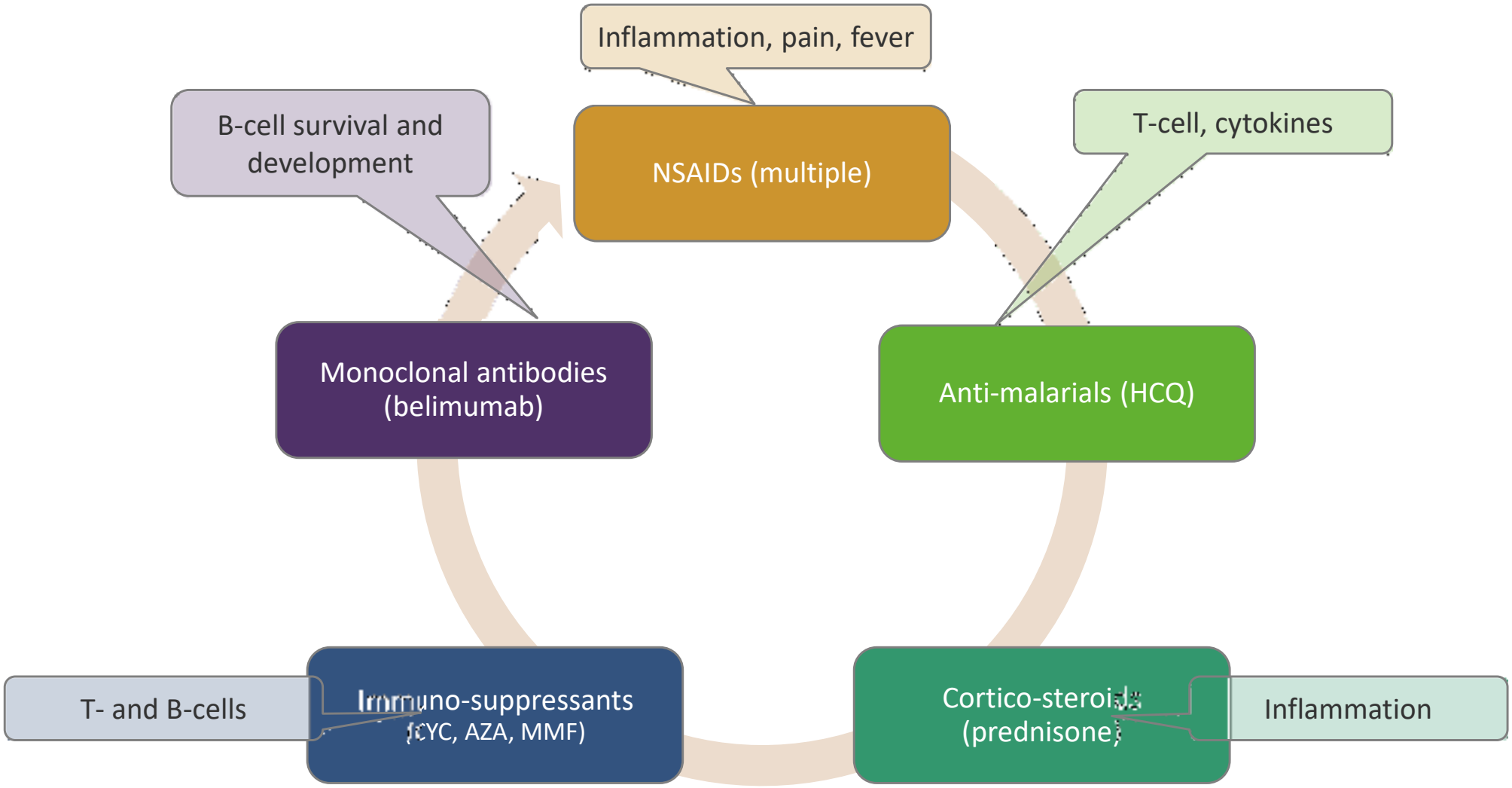
Indications for plasma exchange in systemic lupus erythematosus
Lupus 2005;14(11):871-7

- Acute life-threatening manifestations
  Severe therapy-resistant manifestations
  Refractory SLE renal disease
  Diffuse alveolar hemorrhage,
  Neuropsychiatric SLE, thrombotic
  Thrombocytopenic purpura, catastrophic
  Antiphospholipid syndrome,
  Hyperviscosity syndrome and
  Cryoglobulinemia

IVIG

- Intravenous immunoglobulins (IVIGs), represent a valid therapeutic option for those patients with SLE with:
  concomitant infections
  for those who have contraindications or are refractory to conventional therapies.
  in cases of neurological or hematological involvement, IVIGs can be given as first-line therapy .
  Despite being used since the 1980s, IVIG therapy is still considered to be experimental without any clear indications.

- Systemic Lupus Erythematosus (SLE) Therapy: The Old and the New Rheumatol Ther. 2020 Sep; 7(3): 433–446



Maidhof W, et al. *P T.* 2012 Apr; 37(4): 240-246.

THANK YOU

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Anaemia in Pediatric chronic kidney disease

Dr : Jawaher Thiab Albderat

Paediatric Nephrology consultant

The Head of pediatric Nephrology Department

Queen Rania Children Hospital-KHMC

Outline

- Definition of anemia
- The prevalence of anemia
- The impact of anemia
- Pathophysiology of anemia
- Causes of anemia
- Management of anemia

Definition of CKD

Structural and / or Functional Abnormalities of the Kidneys for > 3 months and manifested by either:

- **Kidney Damage with or without decreased GFR as defined by:**
  - **Pathological Abnormalities**
  - **Markers of Kidney Damage including:**
    - **Abnormalities in the composition of Blood (high serum creatinine)**
    - **Abnormalities in the Urine (Proteinuria/Hematuria)**
    - **Abnormalities in Imaging Tests (small or hydronephrotic kidneys and solitary kidney)**
- **GFR < than 60 ml/min 1.73 sq.m; With or Without Kidney Damage.**

Historical Background of Anemia

- **Richard Bright in 1836 first observed that anemia was a complication of renal failure.**
- **Robert Christison further described renal anemia.**
- **Miyake in 1977 purified and identified erythropoietin.**
- **Escbach in December 2, 1985: first human use of EPO.**
- **The human EPO gene was isolated in 1985**

Definition of Anemia

Anemia is a condition in which the number of RBCs or their oxygen-carrying capacity is insufficient to meet physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status (WHO).

Haemoglobin cut offs to define anaemia in people living at sea level

Age or gender group	Hb below: (g/litre)
Children	
6 months to 5 years	110
5 to 11 years	115
12 to 14 years	120
Non-pregnant females >15 years	120
Men >15 years	130

NCGC, AMCKD Update, June 2015

Table 1 Definitions of anemia in children with kidney disease [22, 23, 65]

KDOQI (2006)		
Age group (years)	**5th percentile Hemoglobin level (g/dL)**	
	Boys	**Girls**
1–2	10.7	10.8
3–5	11.2	11.1
6–8	11.5	11.5
9–11	12.0	11.9
12–14	12.4	11.7
15–19	13.5	11.5
KDIGO (2012)		
Age group (years)	**Hemoglobin level (g/dL)**	
0.5–5	< 11.0	
5–12	< 11.0	
12–15	< 12.0	
≥ 15 and adult	< 13.0 (males) < 12.0 (females)	
RA (2017)		
Age group (years)	**Hemoglobin level (g/dL)**	
< 2	Hb 10.5 g/dL	
≥ 2	Hb 11 g/dL	

Prevalence of Anaemia

Anaemia is a common disorder

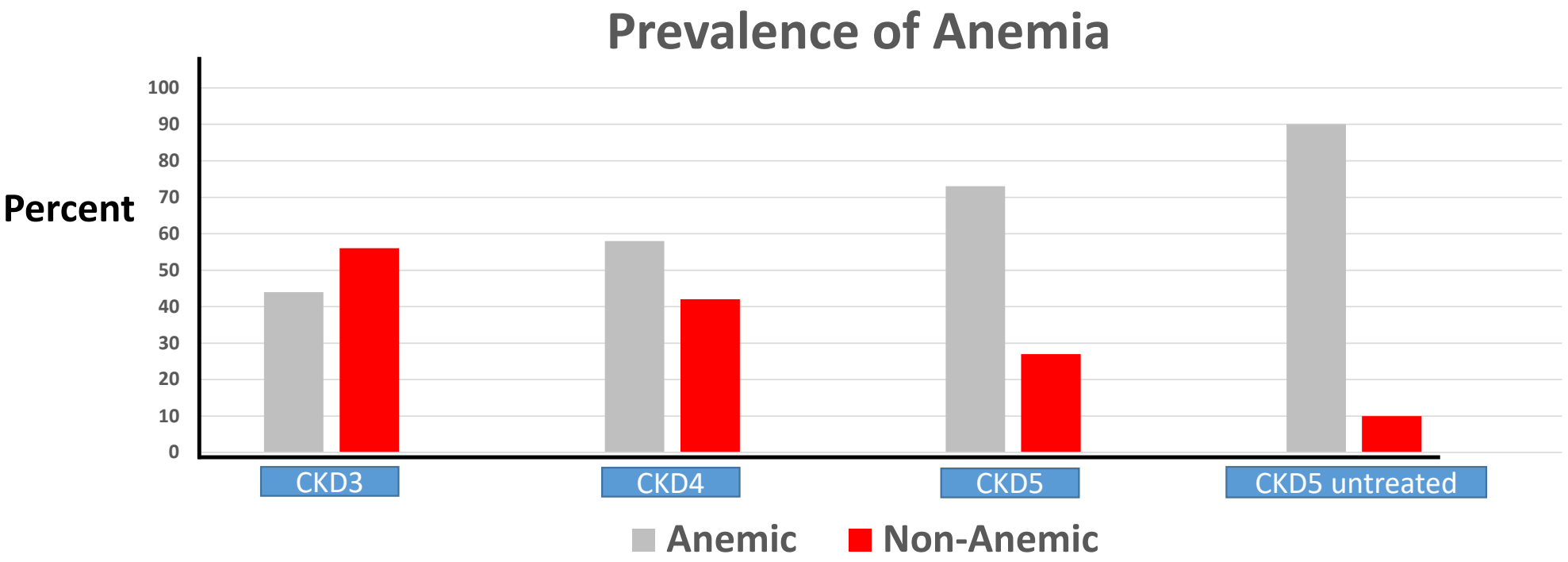
According to WHO:

- 30% of the world's population have anaemia.

- Anaemia in CKD population:
  - 9-54% of pre-dialysis CKD Patients
  - 80–90% of dialysis patients
  - 20 -30 % of Kidney transplant patients

Gates B Colbart. April 13. 2020

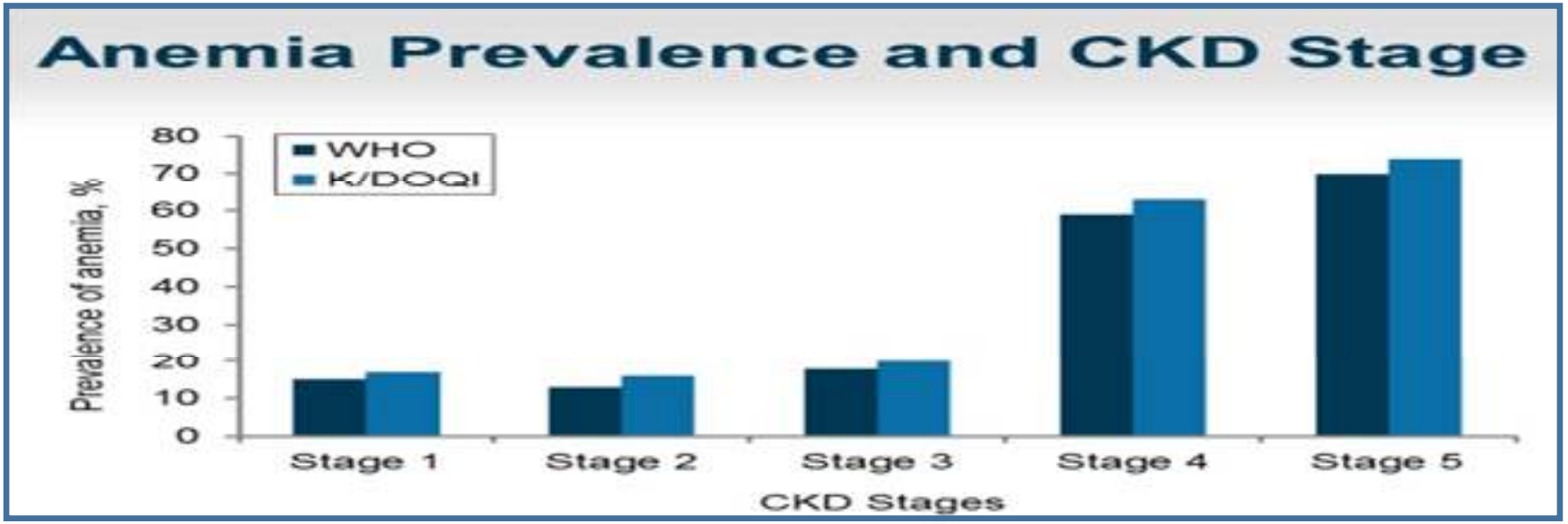
Anemia & CKD
Medicare Data 2018



BMC Nephrol, 2018

Anemia in CKD

- Anemia Begins at a GFR < 60 mL/min, and is more common in diabetics compared to non-diabetics.

- 

- Almost 70% of CKD patients starting dialysis are anemic (Hct < 30%).

Hemoglobin Decline in Children with Chronic Kidney Disease: Baseline Results from the Chronic Kidney Disease in Children Prospective Cohort Study

Jeffrey J. Fadrowski,[*] Christopher B. Pierce,[†] Stephen R. Cole,[†] Marva Moxey-Mims,[‡] Bradley A. Warady,[§] and

Clin J Am Soc Nephrol. 2008 Mar; 3(2): 457–462.
doi: 10.2215/CJN.03020707

Data from the Chronic Kidney Disease in Children (CKiD) cohort study have shown that median hemoglobin levels decline as the measured glomerular filtration rate (GFR) decreases below a level of 43 ml/min/1.73m2

Anaemia in CKD

- The anaemia of CKD begins when the GFR falls below 35 ml/min/1.73m2.
- It is a normochromic, normocytic , with a low reticulocyte count.

- Anaemia due to CKD is associated with:
  - increased hospitalisation and mortality[1–3]
  - increased burden of cardiovascular disease[4] ,LVH&Ventricular dysfunction
  - reduced quality of life[5]
  - Increased mortality with stroke

Dis 2009;54:498–510; [3]Roberts et al. *Nephrol Dial Transplant* 2006;21:1652–62; [4]Silverberg. *Nephrol Dial Transp* 2003;18(Suppl 2):ii7–ii12; [5]Perlman et al. *Am J Kidney Dis* 2005;45:658–66
S[1]Riva et al. *Haematol* 2009;94:22–8; [2]Servilla et al. *Am J Kidney* C-LBN-DARBEPOETI-00010 May 2018

Other Effects of Anemia in CKD

- Acceleration of progression of kidney disease by oxygen deprivation.
- Increased risk of bacteremia (11% increased risk for every 1g/dl fall in Hgb).
- Detrimental effects on brain and cognitive functions.

Benefits of Anemia Correction
Target Hgb/Hct

- ↑ Quality-of-life
- ↑ Exercise capacity
- ↓ Cardiac output
- ↓ Angina
- ↓ LVH
- ↓ Bleeding tendency
- ↑ Brain / cognitive function
- ↓ Depression
- ↑ Sleep patterns

- ↑ Sexual function
- ↑ Endocrine function
- ↑ Immune function
- ↑ Muscle metabolism
- ↓ Hospitalizations
- ↓ Transfusions
- ↑ Nutrition

Macdougall et al., Lancet 1990; 335: 489-493

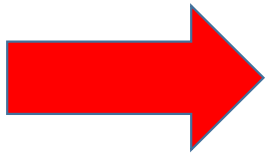
Benefits of treatment of anaemia

- Anaemia may contribute to decreasing progression of CKD.
- Amelioration of left ventricular hypertrophy (LVH).
- Improved quality of life and decreased hospitalization .
- Reduced need for transfusion, with its risks of infection and HLA sensitization.

Koshy SM , Geary DF,(2008),Anaemia in children with chronic kidney disease. Pediatr Nephrol.

Symptoms of Anemia in CKD

- Fatigue
- Exhaustion (decreased energy)
- Weakness
- Impaired concentration
- Decreased cognition
- Respiratory distress
- Tachycardia



Leads to

- Impaired quality of life
- Diminished physical capacity

Ludwig et al. *Semin Oncol.* 2001;28(suppl 8):7-14

MEDICAL SCIENCE

Long-term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin

IAIN C. MACDOUGALL NEIL P. LEWIS MICHAEL J. SAUNDERS
DENNIS L. COCHLIN M. ENID DAVIES R. DAVID HUTTON
KEITH A. A. FOX GERALD A. COLES JOHN D. WILLIAMS

The long-term cardiorespiratory effects of recombinant human erythropoietin treatment were investigated in ten haemodialysis patients by means of maximum exercise testing, lung function tests, echocardiography, chest X-ray, and rheological assessment over 12 months. There were significant rises in exercise time (mean [SD] 13·2 [5·5] to 20·0 [6·2] min), maximum oxygen consumption (19·1 [7·0] to 25·0 [6·7] ml.min^{-1}.kg^{-1}), and anaerobic threshold (11·7 [3·6] to 15·4 [4·8] ml.min^{-1}.kg^{-1}) after 2 months of erythropoietin treatment. The improvements were maintained but not augmented on repeat testing after 4, 8, and 12 months of therapy. Carbon monoxide treatment rose from 15·5 (2·9) to 18·6 (3·7) ml.min^{-1}.mm Hg^{-1}. There was a substantial reduction in exercise-induced cardiac ischaemia (eight patients had significant ST segment depression before erythropoietin, only one after 2

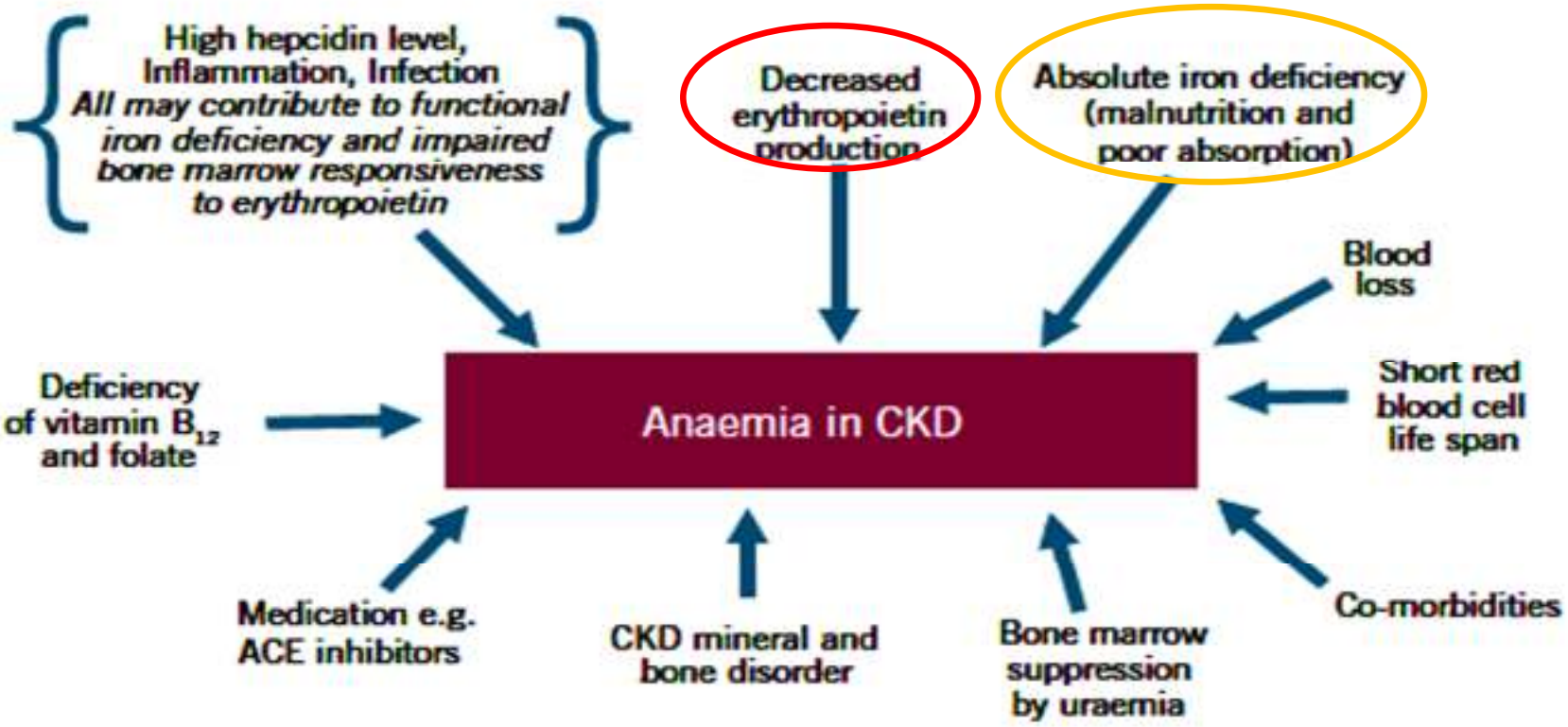
age and sex. Various factors may contribute but the main determinant seems to be chronic anaemia.[1]

Longstanding severe anaemia has profound effects on the cardiovascular system, resulting in a rise in cardiac output, a fall in peripheral resistance owing to compensatory vasodilation secondary to tissue hypoxia, and reduced blood viscosity.[3,4] In addition, the reduction in oxygen-carrying capacity of the blood impairs oxygen delivery to the myocardium, thus exacerbating myocardial ischaemia in people who are already predisposed to coronary artery disease as a result of abnormal lipoprotein profiles and other factors.[5,6] The anaemia of end-stage renal failure has an important role in the development of left ventricular hypertrophy in patients on long-term dialysis,[2,7] which, in turn, seems to be an important, independent determinant of their survival.[8]

Acute correction of uraemic anaemia by red cell transfusion is followed by a return to normal cardiac output and total peripheral resistance.[9] It is likely, therefore, that

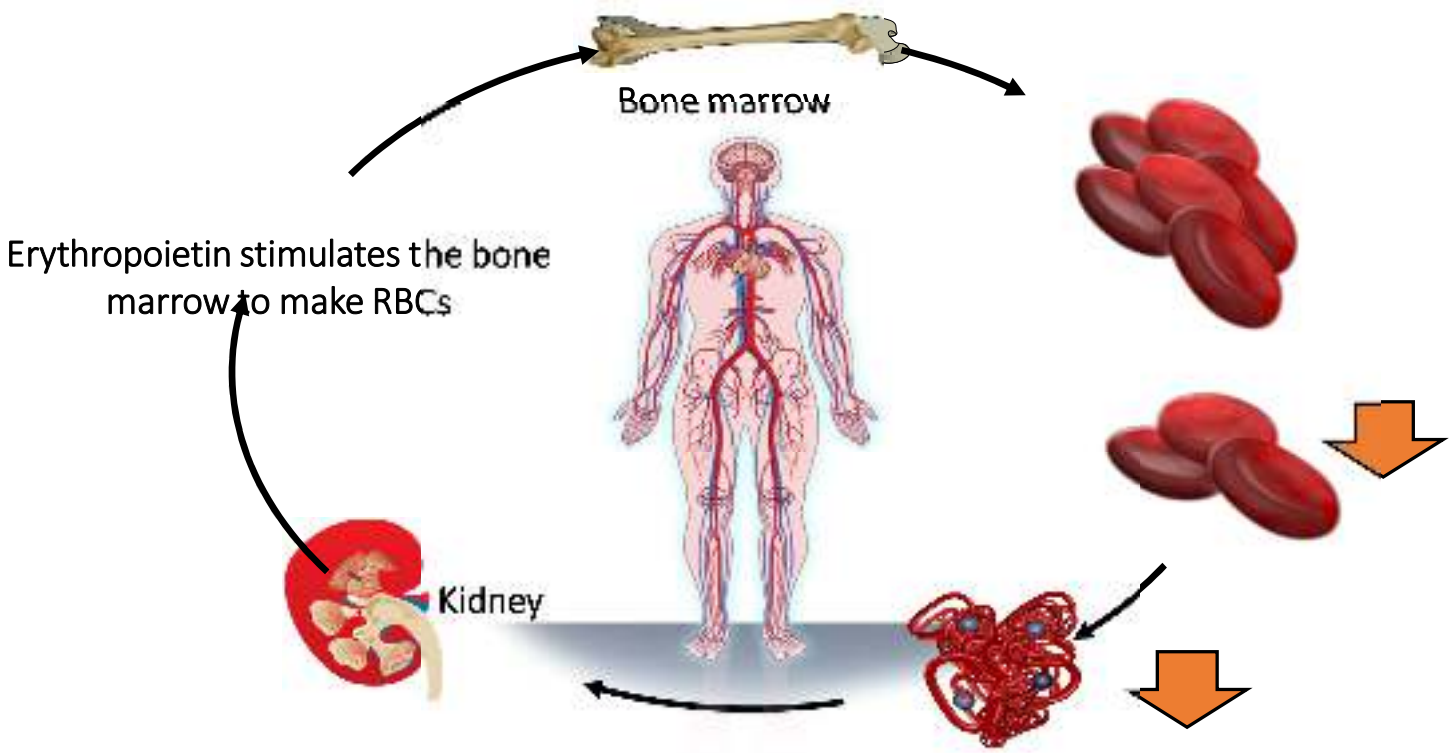
Macdougall et al., Lancet 1990; 335: 489-493.

Etiology of Anemia in CKD



Agarwal AK, J A Med Dir Assoc 2006

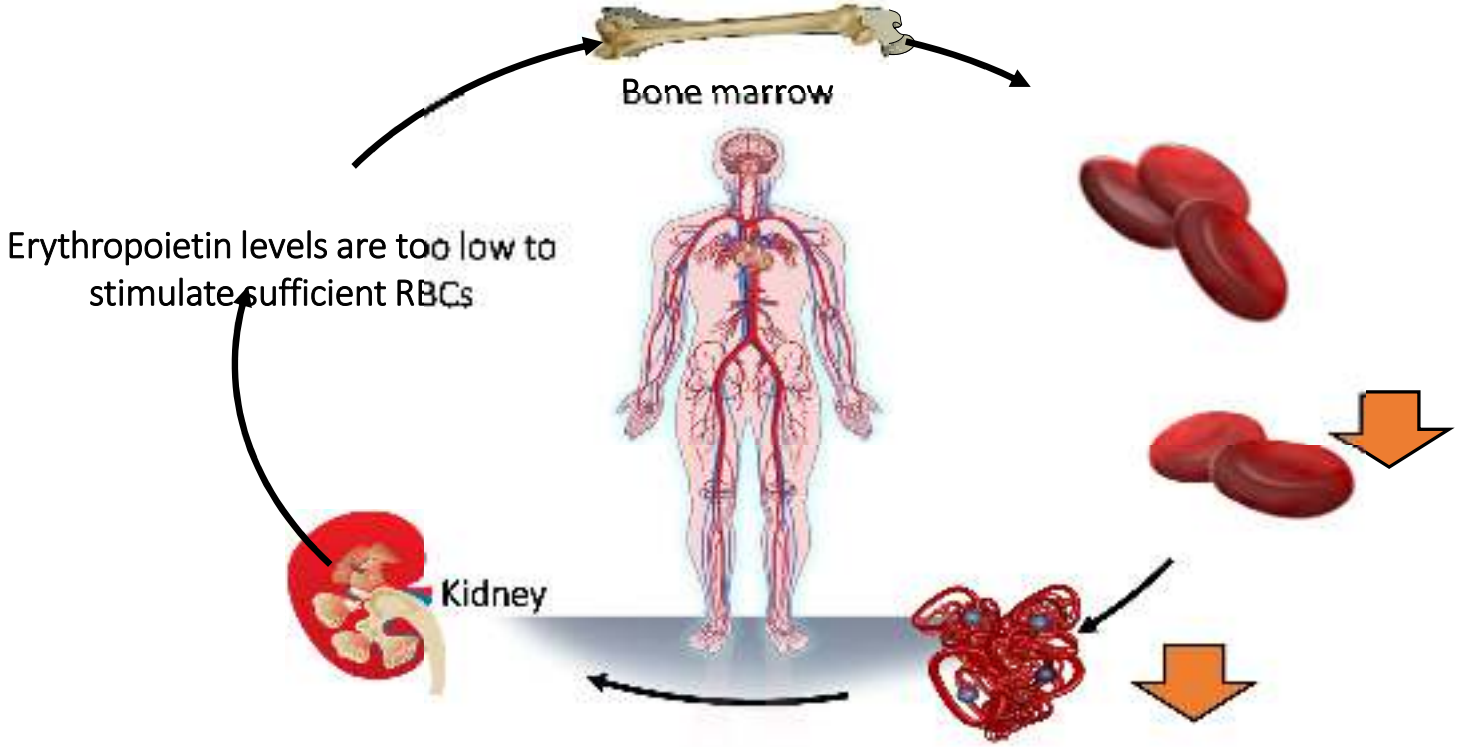
In Healthy Individuals the Kidneys Produce and Release Erythropoietin When an Increase in RBCs Is Needed



Hb = hemoglobin; RBC = red blood cell.

Adapted from: Guyton AC, et al. *Textbook of Medical Physiology.* 2006:419-428.

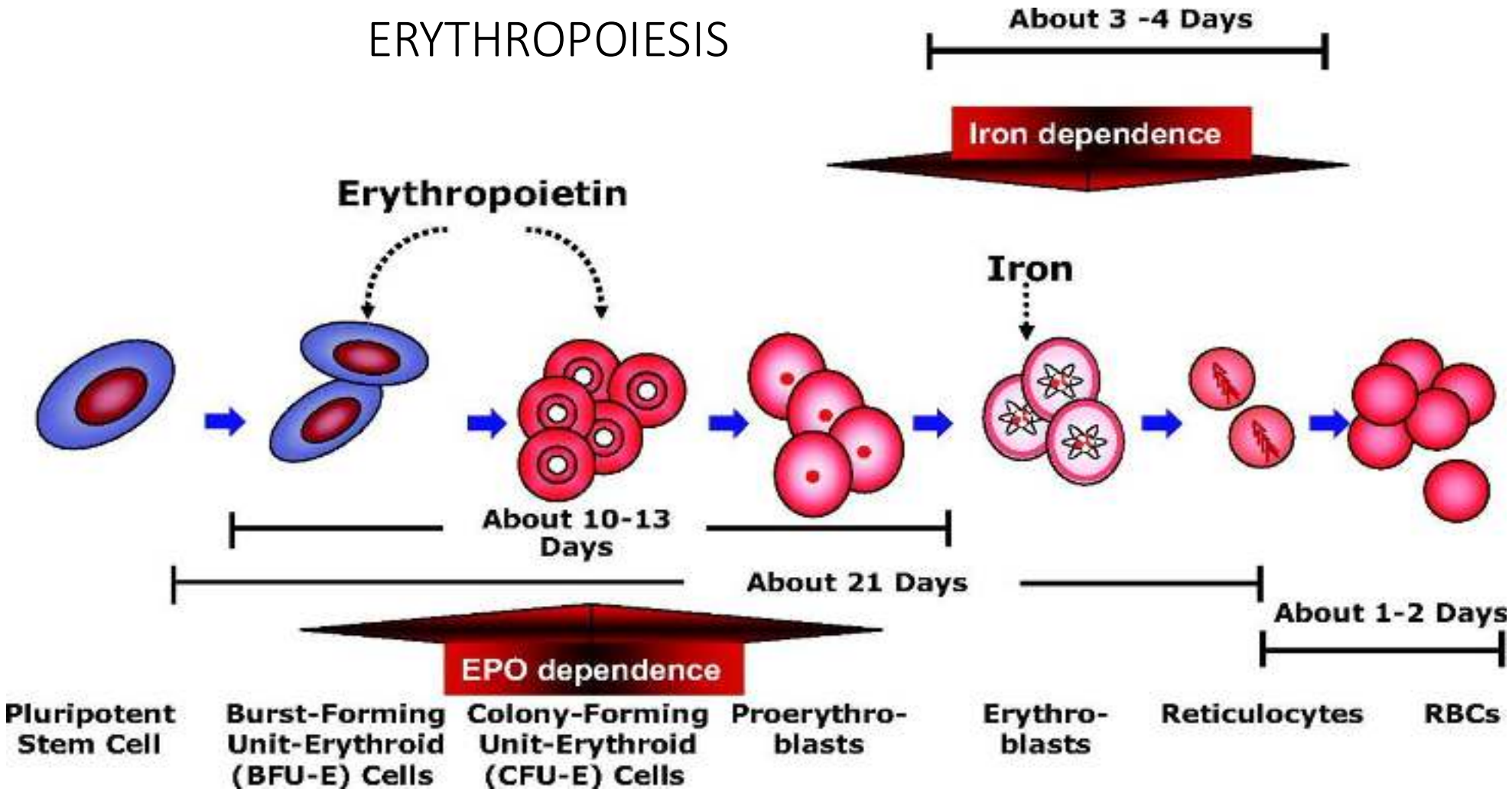
In Patients With CKD, Inadequate Production of Erythropoietin Results in Anemia



CKD = chronic kidney disease; Hb = hemoglobin; RBC = red blood cell.

Adapted from: Guyton AC, et al. *Textbook of Medical Physiology.* 2006:419-428.

ERYTHROPOIESIS



Iron Metabolism, Iron Deficiency, Thrombocytosis, and the Cardiorenal Anemia Syndrome Anatole Besarab and al. *The Oncologist* September 1, 2009 vol. 14 no. Supplement 1 22-33

ERYTHROPOIETIN :

- Hemopoietin.
- 30.4 kDa Glycosylated peptide , plays a role as a growth factor that sustains the survival of erythroid progenitor cells.
- Primary site of production is the liver in the fetus and kidney after birth.
- 90% produced in the peritubular interstitial fibroblasts like cells of kidney , 10% in the liver
- Produced in response to low oxygen tension in the tissues of the kidneys.

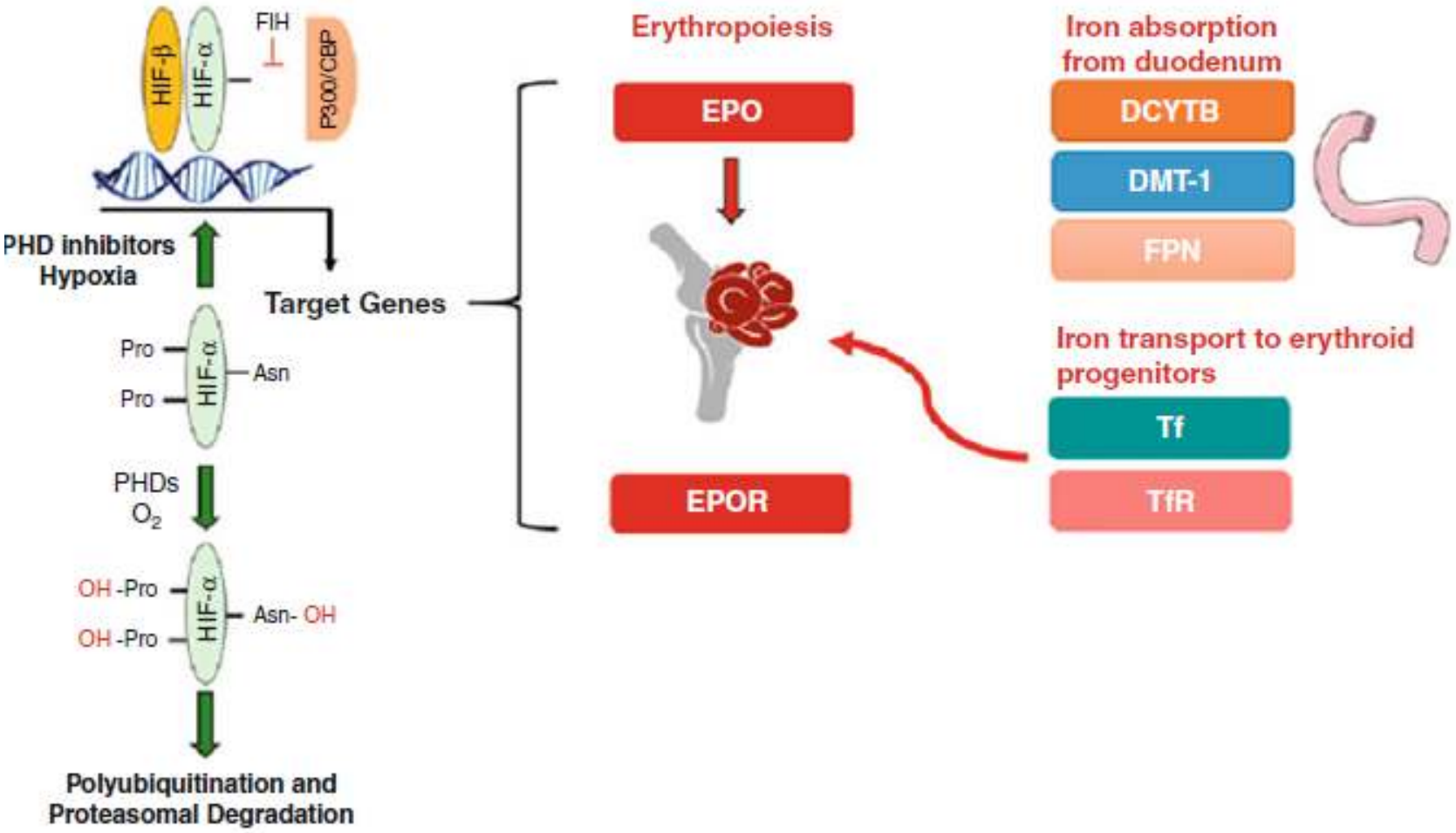
Erythropoietin

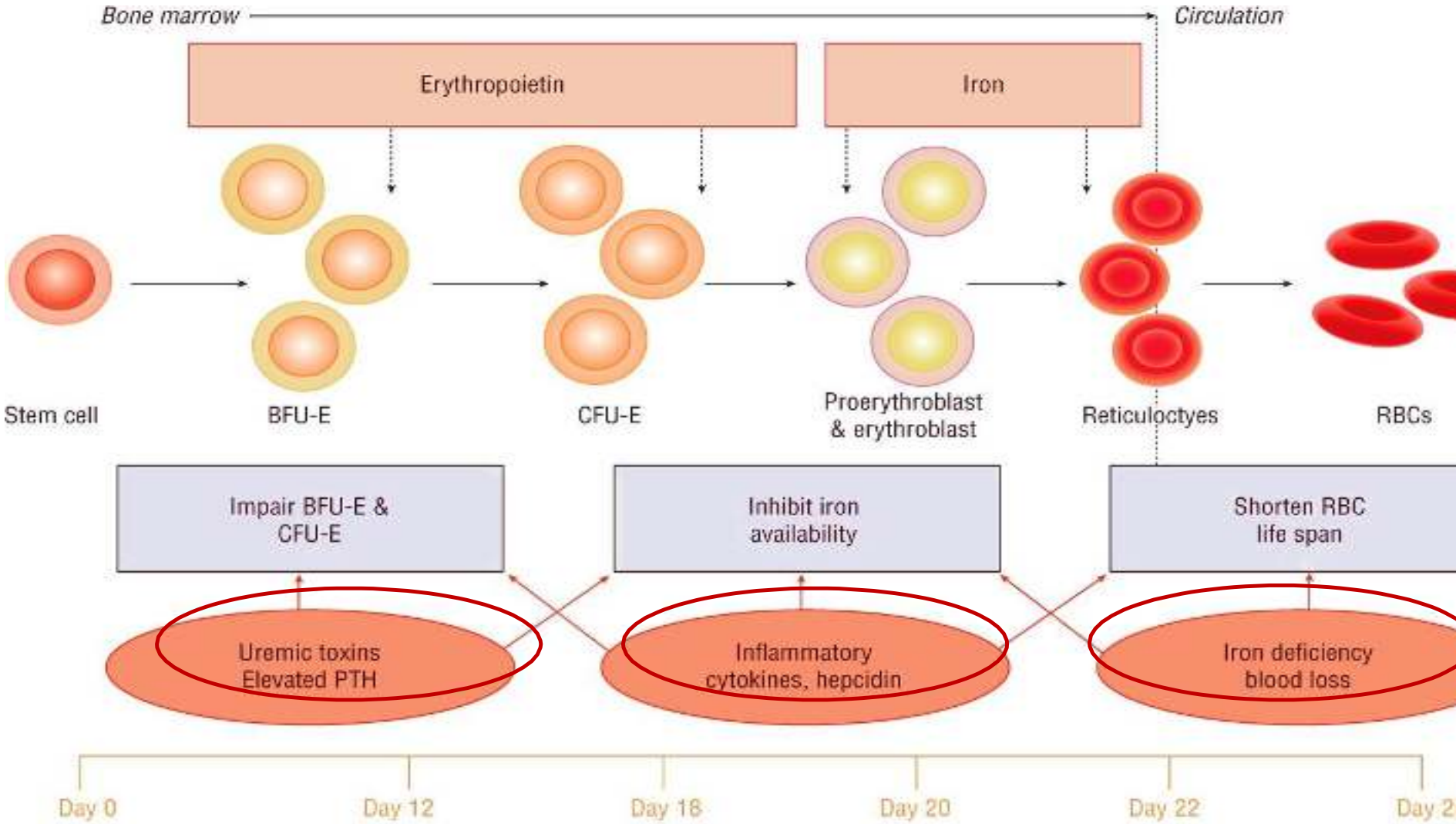
- Secreted EPO (165 amino acids) binds to EPO receptors on the surface of bone marrow erythroid precursors, resulting in their rapid replication and maturation to functional red blood cells.

- This stimulation results in a rapid rise in erythrocyte counts and a consequent rise in blood oxygen.

- Altered levels of EPO or mutations in EPO receptors are linked to changes in the hematocrit.

- Kidney failure leads directly to anemia due to low EPO levels and hence reduced hematopoiesis.


HIF-β
HIF-α
FIH
P300/CBP
PHD inhibitors
Hypoxia
Target Genes
Pro
Pro
HIF-α
Asn
PHDs
O_2
OH -Pro
OH -Pro
HIF-α
Asn- OH
Polyubiquitination and
Proteasomal Degradation
Erythropoiesis
EPO
EPOR
Iron absorption
from duodenum
DCYTB
DMT-1
FPN
Iron transport to erythroid
progenitors
Tf
TfR



Red blood cell development in uremia: Time to mature

Hepcidin Regulates the Ferroportin-Based Movement of Iron

The iron-regulatory protein hepcidin has emerged as the key regulator of iron homeostasis

Hepcidin is produced in hepatocytes and regulates both intestinal iron absorption and body

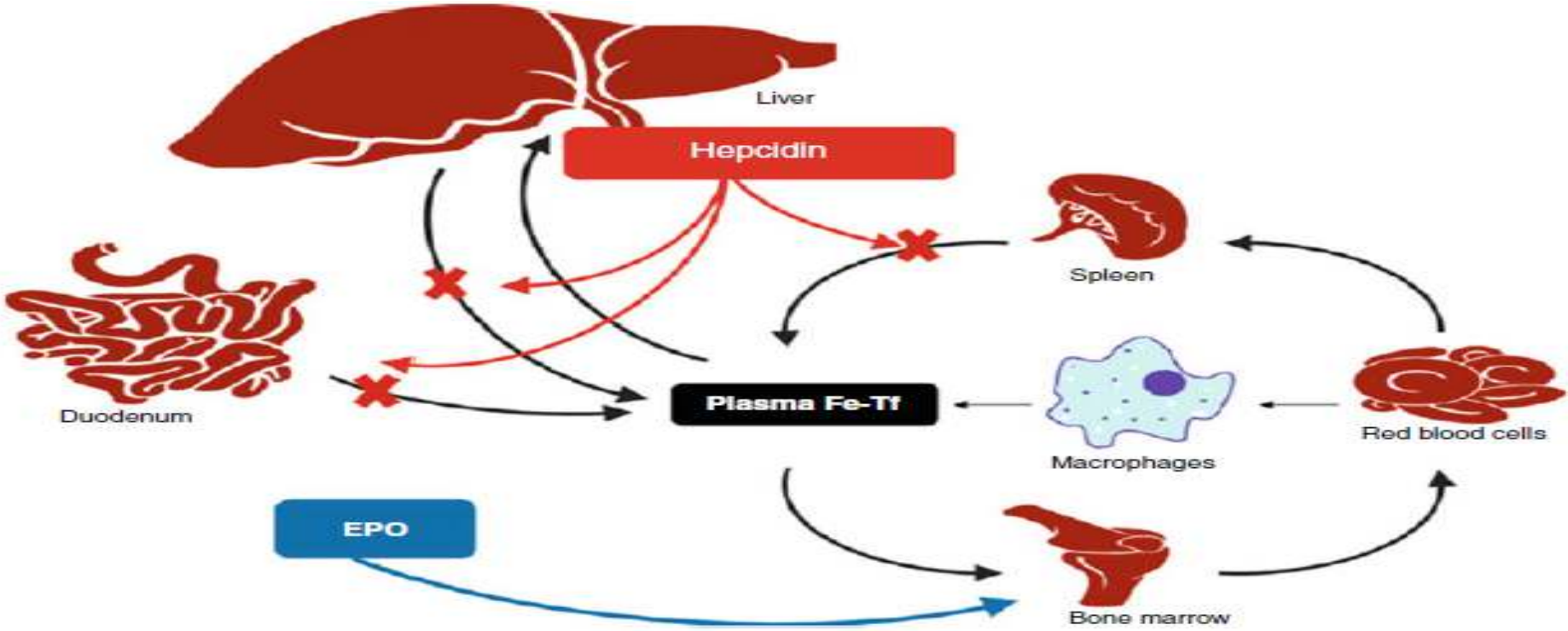
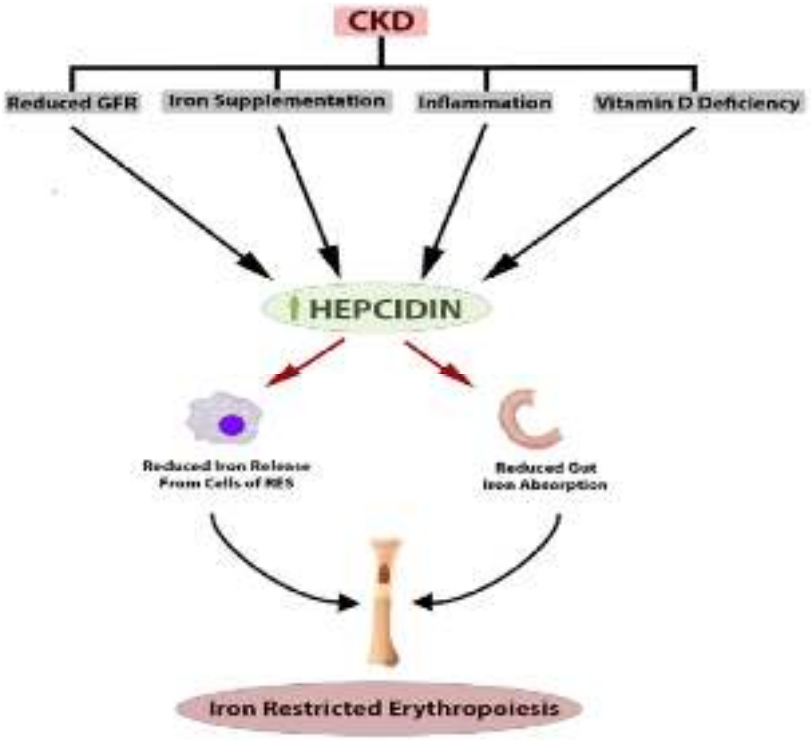
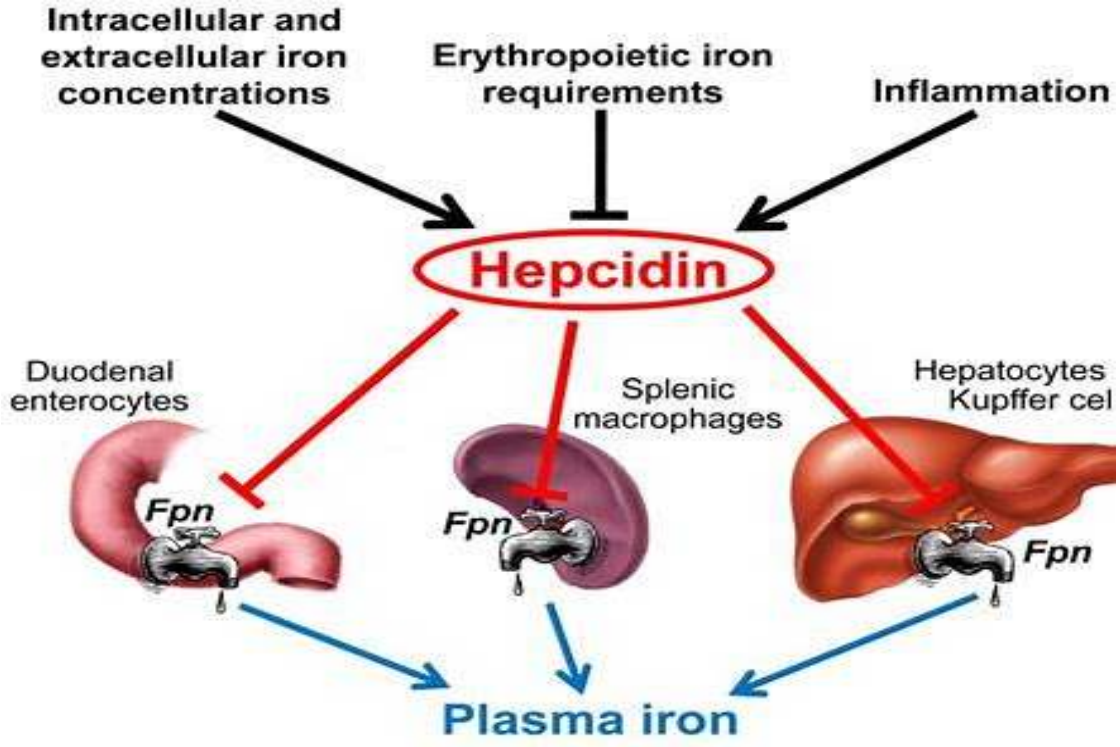


Fig. 3 Iron metabolism is a tightly controlled process [4]. (Reprinted with permission). Iron metabolism is a tightly regulated process. Iron is absorbed in the gut and bound to soluble transferrin. Iron is then moved to storage in the bone marrow and used for erythropoiesis. Additional stores are repleted by macrophage uptake of iron from RBC destruction. EPO induces RBC production, leading to the mobilization of iron stores from the bone marrow. Hepcidin, which is produced by the liver and often stimulated by inflammation, leads to decreased iron uptake from the gut and decreased mobilization of iron stores. Fe-Tf, iron-bound transferrin

Fpn: Ferroportin is a transmembrane protein that transports iron from inside the cell to the outside. Is the only known iron exporter

Is secreted primarily by hepatocytes in the circulation





Hemoglobin Independent Benefits of Iron

- Iron deficiency impairs
  - Physical Performance
  - Thermoregulation
  - Cognition
  - Immune function

- Iron deficiency also is associated with
  - Restless legs syndrome (RLS)
  - Reduced Aluminum absorption (animal data)

Agarwal R, Am J Nephrol 27: 565-571, 2007

Iron deficiency

- The second major cause of anaemia of CKD.
- ***absolute iron deficiency*** occurs when iron stores are depleted as a result of loss or decreased intake.
- ***functional iron deficiency*** occurs when there is a need for a greater amount of iron to support hemoglobin synthesis than can be released from iron stores. (Besarab A, Frinak S, 1999 An indistinct balance: the safety and efficacy of parental iron therapy. J Am Soc Nephrol 10:2029-2043.)
- Iron deficiency is common in HD patients due to chronic blood loss from repeated blood sampling, surgical intervention, blood loss through the use of dialyzers and tubing , shortened red blood cell life span.

Iron Deficiency in CKD Patients

➢ **Absolute:**

TSAT<20% (TSAT = Serum iron / TIBC x 100)

Ferritin level <100 ng/mL

For CKD patients (TSAT ~~20% & Ferritin level ~~ 500 ng/mL)

- **Hemodialysis population:**
  - Blood losses into the dialyzer, dialysis tubing, venipuncture
  - Losses of 3-9 mL of blood / 3-9 mg of iron/day
  - **Normal daily intake of Iron is 1 mg**

- **Predialysis CKD** population & Peritoneal Dialysis patients:
  - Iron deficiency related to anorexia, decreased intake, chronic GI bleeding, non-steroidal ingestion, menstruation and pregnancy in women.

Iron deficiency

- Daily blood loss in predialysis pediatric CKD patients is about 6 ml/m2.
- HD patients have GI blood losses about 11 ml/m2 daily , and further HD – associated blood loss of 8 ml/m2 per treatment.
- Treatment with iron demands more iron for hemoglobin synthesis
- High Fe availability can decrease the required dose of EPO in both adult and children and maximize the response to ESAs. (Gillespie RS ,Wolf FM, 2004 . IRON THERAPY IN PEDIATRIC HEMODIALYSIS PTS. Pediatr Nephrol 19 .
- Serum ferritin reflects body Fe stores and need to be kept betweeb 100- 500 microgram /L .
- Transferrin saturation TSAT is a marker of the amount of Fe available to support Hb synthesis , should be > 20%.

Evaluation

- S.ferritin, TSAT , the most commonly utilized biomarkers of stored iron.
- Limited sensitivity and specificity , Acute phase reactant.
- (Ret-He) content reflects iron availability for incorporation into reticulocyte over the previous 2-4 days.
- % HRC , percentage of hypochromic red blood cells% another marker of iron status to assess iron availability for incorporation into red cells

EVALUATION

Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia *(Not Graded)*:

- **Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count**
- **Absolute reticulocyte count**
- **Serum ferritin level**
- **Serum transferrin saturation (TSAT)**
- **Serum vitamin B12 and folate levels**

EVALUATION

Frequency of testing for anemia

1.1.1: For CKD patients without anemia (as defined in Recommendation 1.2.1 for adults and Recommendation 1.2.2 for children), measure Hb concentration when clinically indicated and (*Not Graded*):

- at least annually in patients with CKD 3
- at least twice per year in patients with CKD 4–5ND
- at least every 3 months in patients with CKD 5HD and CKD 5PD

1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (*Not Graded*):

- at least every 3 months in patients with CKD 3–5ND and CKD 5PD
- at least monthly in patients with CKD 5HD

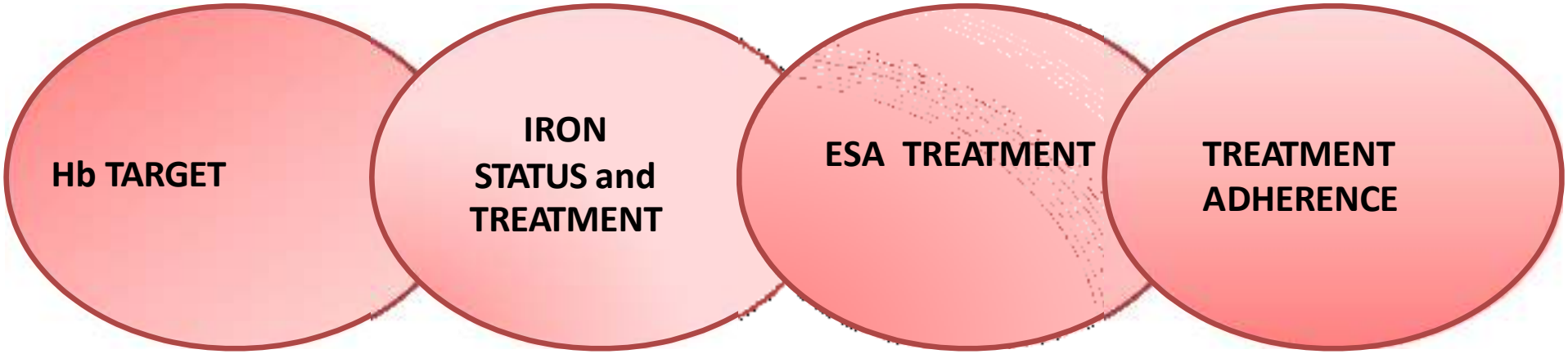
KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease

For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is <20% and ferritin is <100 ng/ml (<100 microg/l). (1D)

For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 microg/l). (1D

ANEMIA MANAGEMENT in CKD

HOW to MAKE it OPTIMAL?



Definitions

- The Hgb target is the intended aim of ESA therapy for the individual CKD patient.

- Achieved Hgb is the result of ESA therapy.

➢ Achieved Hgb results vary considerably from the Hb target.

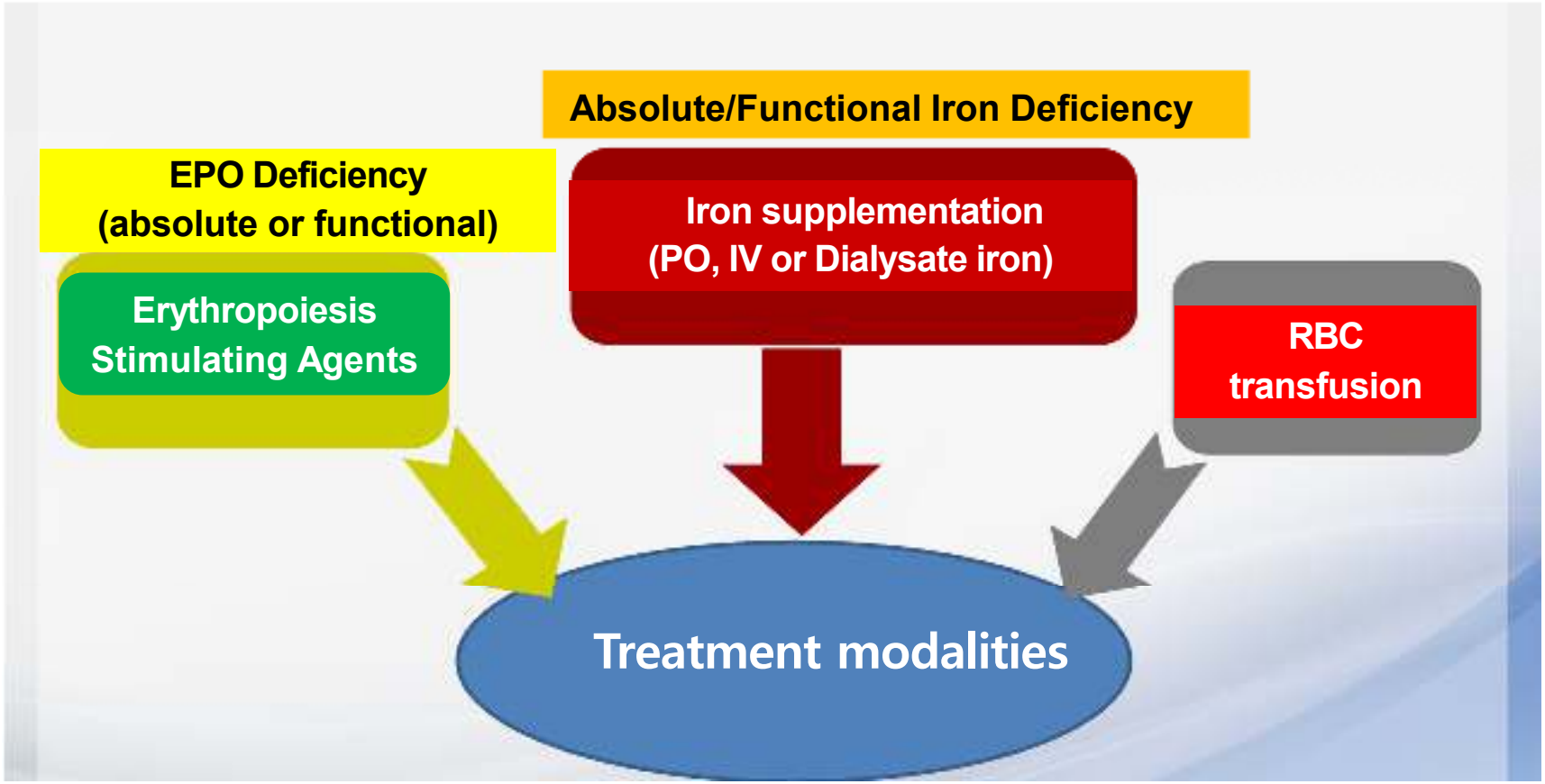
Hb target concentration in ESA maintenance therapy: KDIGO guidelines[1]

- In CKD patients:
  - Generally Hb concentration ≤11.5 g/dL
  - Some patients improved QoL when Hb >11.5 g/dL
  - High bleeding frequency: Hb concentration 11.5-13 g/dL may be justified: lower transfusion needs
  - Risk-Benefit consideration for Hb >11.5 g/dL

  → Individualized therapy necessary

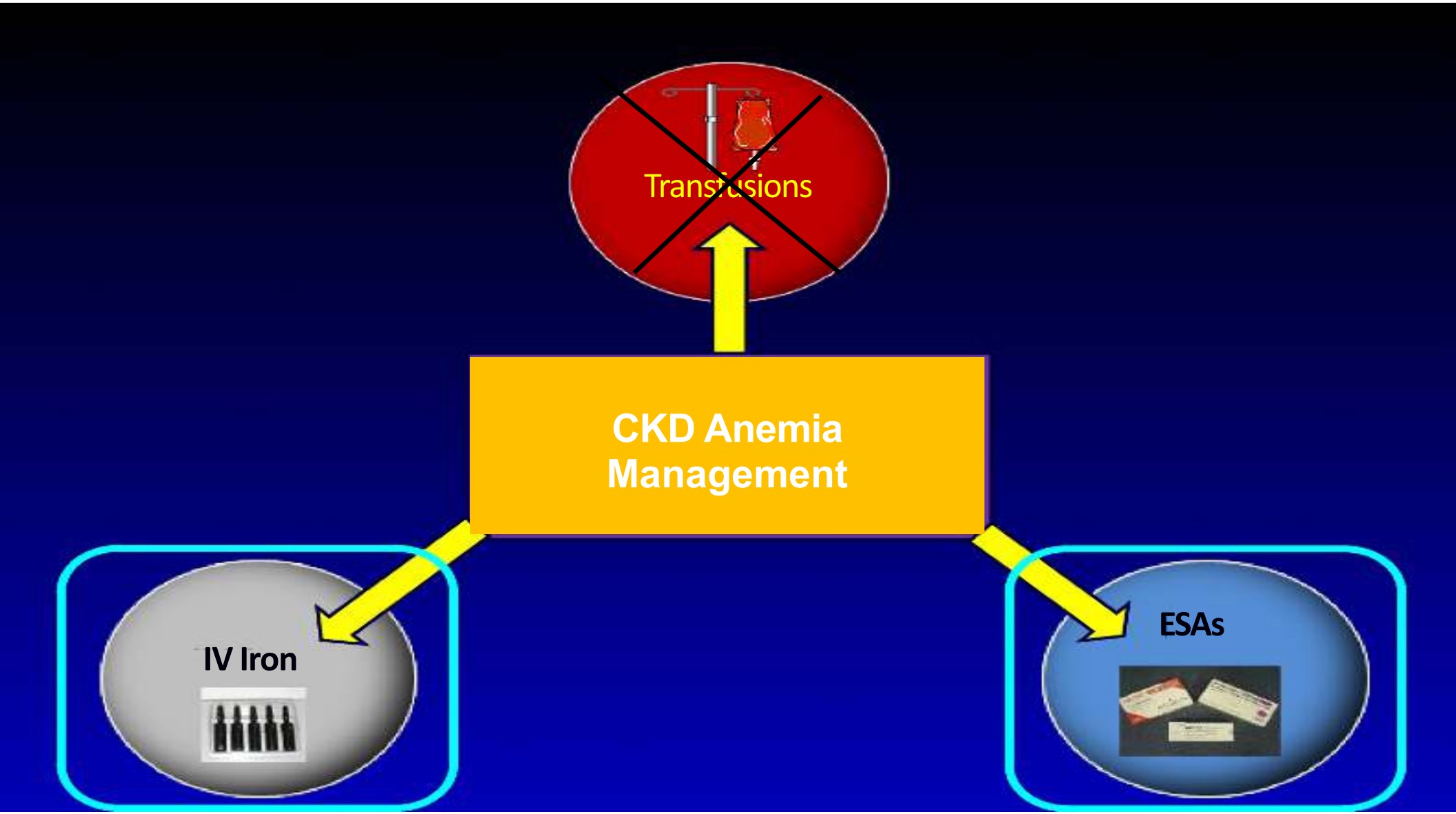
[1]KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int;* Suppl. 2012;2:279–335.

Available Treatments for Anemia in CKD



Before rhEPO

- Transfusion associated problems
  - Hepatitis B
  - Other blood borne viral infections
- Decreased transplant success
  - Sensitization of the patient to possible kidney transplant
- Iron Overload Syndromes
  - Hemochromatosis
    - **Characteristic skin pigmentation change, yellowish-green (90%)**
    - **Iron deposition in**
      - **Liver (95%), DM (65%), Arthropathy (25-50%), Heart (15%)**
    - **CHF in 10%, especially young people**
    - **Death**


Transfusions
CKD Anemia Management
IV Iron
ESAs

Oral vs Parenteral Iron

- Oral iron is not as effective as parenteral iron in hemodialysis, peritoneal dialysis, and CKD patients

- Causes include:
  - Iron malabsorption (the use of phosphate binders).
  - Lack of patient compliance due to GI effects.
  - Recently, ORAL Ferric Citrate as Phosphate Binder is available.

Intravenous versus Oral iron in CKD

Risks of IV iron

- Inflammation
- Oxidative stress
- Cytotoxicity
- Endothelial dysfunction
- Anaphylaxis
- Hemosiderosis
- Bacterial infections
- Cardiovascular events
- Mortality

Benefits of IV iron

- Better bioavailability
- Rapid efficacy
- No compliance issue
- Greater Hgb increase
- Reduced ESA needs
- Reduced transfusion needs

Drüeke T, kidney Int. 2015: 88,673–675.

Intravenous iron

Iron carbohydrate complexs

- Iron dextran
- Iron sucrose
- Ferric gluconate
- Iron isomaltoside 1000
- Ferric carboxymaltose
- Ferumoxytol

Intravenous Iron :Advantages

- Bypasses GI absorption
- increase treatment adherence
- Fewer administration required to reach target Hb
- May delay /avoid need for ESA therapy

Oral Iron: Advantages

Widely used and ease of administration

Relatively inexpensive, frequent dosing can increase cost

Avoid need for oupatient visit

New formulation available

IV iron and hypersensitivity reactions

True anaphylaxis is extremely rare, < 1:200,000 administrations

Common occurrence: complement –activated related pseudo-allergy (CARPA) ….(Fishbane reaction)……frequency: 1:100-250 …. Characterized by **transient flushing and truncal myalgia(pains in the back and chest) with joint pains….**The sx abate spontaneously over a few minutes and don't usually recur on re-challenge

IRON SUPPLEMENTATION

- Oral iron is initiated at a dose of 2-6 mg/kg/day
- Inadequate response to Rx; requires reevaluation.
- IV iron is indicated if:
  - Adequate iron stores can't be maintained with maximum oral dose.
  - Compliance is questionable.
  - HD
- Preparations: Dextran, Sucrose, and Sodium ferric gluconate.
- Adverse effects: hypersensitivity reactions, most resolve within 1-2 hr.
- Patients should receive 3 infusions per week at the close of HD sessions for the first ten sessions. Subsequently, once weekly.

International Society of Nephrology, Protocols in Pediatric Nephrology:2013 ,199-200.

IRON SUPPLEMENTATION

❖ Monitoring:

- TSAT & Ferritin should be evaluated every 3-4 months to detect overdosing.
- Therapy with iron should be withheld for 3 months if TSAT > 50% &/ or Ferritin > 800 ng /ml.

- When therapy resumed, the dose should be 33-50%.

International Society of Nephrology, Protocols in Pediatric Nephrology:2013 ,199-200.

Table 18.15 Dose of IV iron according to ferritin and TSAT levels

	Ferritin (micrograms/L)	TSAT	Dose	Maximum single dose
Maintenance dose	>100 and <500	>20%	2 mg/kg/dose given every 2 weeks	100 mg
Accelerated dose	<100	<20%	7 mg/kg/dose × 1 dose for first week then 2 mg/kg/dose given once every 2 weeks	200 mg 100 mg
No treatment	>500	>50%		

IV IRON ADMINISTRATION

Intravenous iron therapy in patients with chronic kidney disease: recent evidence and future directions.

Macdougall IC. Etal

Clin Kidney J. 2017 Dec;10 (Suppl 1):i16-i24

In this article, the implications of the findings from RCT are discussed :

- The Ferinject Assessment in Patients with Iron
  •Deficiency Anaemia (FIND-CKD)
- Randomized Trial to Evaluate IV and Oral Iron in Chronic Kidney Disease (REVOKE)

They have added to the clinical evidence base in support of the efficacy and short-term safety of IV iron therapy in patients with CKD-ND and CKD-5D

Iron study , ferritin

- TSAT < 20%
- Ferritin < 100 ng/ml

Iron deficiency anemia

TSAT <20%

Ferritin > 100 ng /ml

Functional iron deficiency

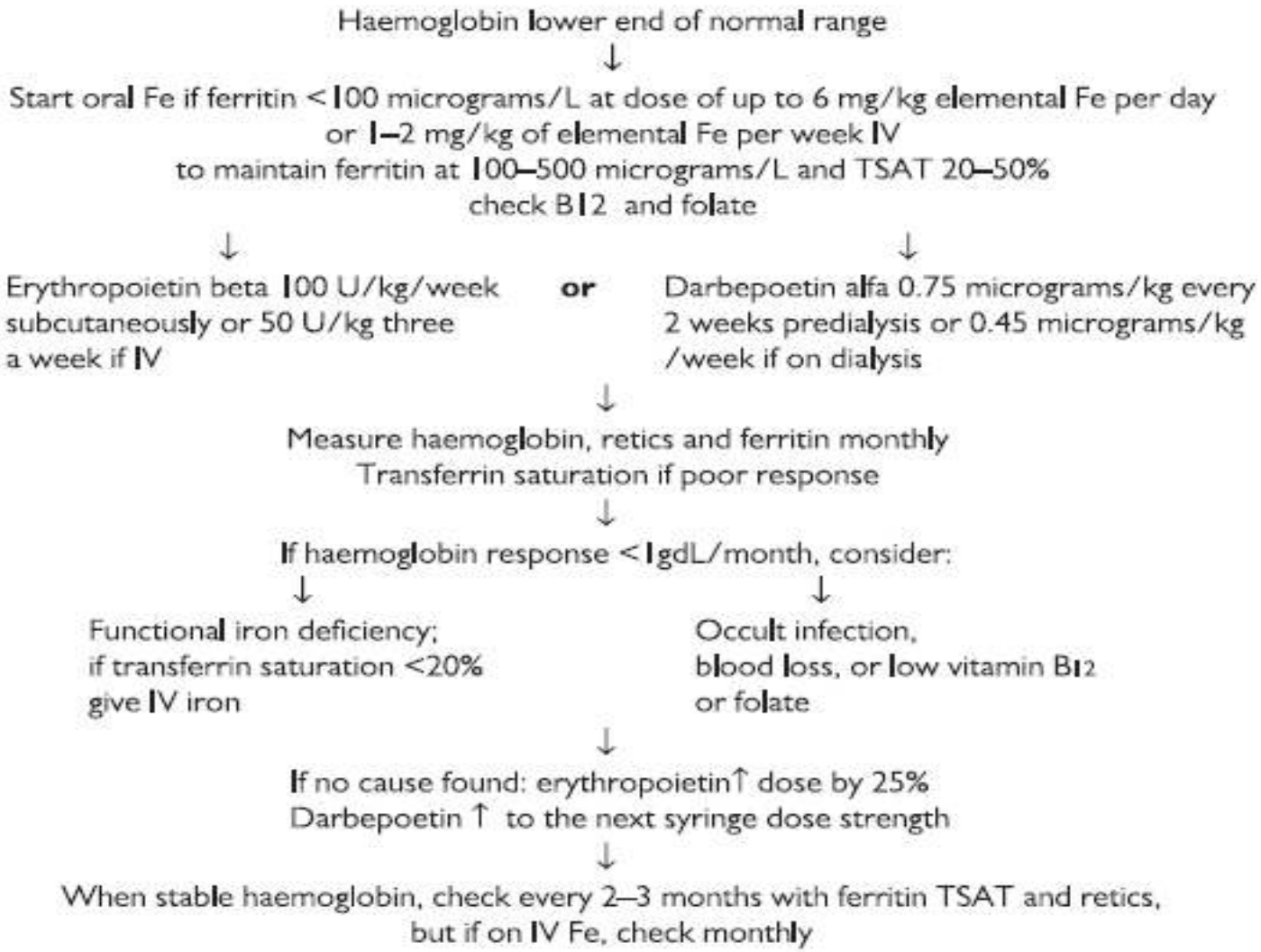


Fig. 18.7 Commencement of an ESA.

Anaemia in CKD-ESAs

- Erythropoiesis stimulating agents (ESAs)[1]:
  - Mimic the action of physiological erythropoietin
  - Stimulate red blood cell production
  - Can correct anaemia

- Types of ESAs[2]:
  - Short-acting ESAs (since 1989)
    - administration 1-3x per week
  - Long-acting ESAs (since 2001)
    - less frequent administration of up to 1x per month
    - Third generation ESA

    Continuous erythropoietin receptor activator (Mircera)

[1]Jelkmann. *Transfus Med Hemother* 2013;40:302-9; [2]Hörl. *Drugs* 2013;73:117-30.

Currently Available ESAs

Recombinant human erythropoietin
Short Acting 1-3 /week, since 1989

- Epoetin alfa
- Epoetin beta
- Epoetin theta

Longer-acting ESA
up to 1/month since 2001

- Darbepoetin alfa
- CERA

Biosimilars

- HX575
- Epoetin zeta

***Biosimilar* EPO's**

- SEP
- EPO infusion protein
- HCP inhibitors
- HIF-PH inhibitors
- EPO gene therapy
- EPO-mimetics

Elliott S, et al. Nat Biotechnol. 2003;21(4):414-421. *kidney international, 2006(70) s14-s16*
Jelkmann. Transfus Med Hemother 2013;40:302-9; Hörl. Drugs 2013;73:117-30

Darbepoetin alpha

- Hyperglycosylated derivative of EPO with a longer half –life.
- Available in the following strengths --20,40,60,80,100,150,300,500 microgram as prefilled syringes or a disposable injection pen device.

- Conversion from EPO beta:

  weekly EPO dose (u)/240=weekly darbepoietin alpha dose (micro)

Benefits	Risks
• Reduces the risk of transfusions	. Seizures
• Improves the symptoms of anemia	• Arterial hypertension
• Improves quality of life	• Vascular access thrombosis
	• Cancer progression?

Cases A, Egocheaga MI, Tranche S, Pallarés V, Ojeda R, Górriz JL, et al. Anemia en la enfermedadrenal crónica: Protocolo de estudio, manejo y derivación a Nefrología. Nefrologia. 2018;38:8–12.

ESA DOSING

Lower initial ESA doses if:

- Higher baseline Hb concentrations
- History of CVD
- Patients with a history of thrombo-embolism or seizures
- Patients with high blood pressure

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl* 2012; 2: 279–335

Dose of ESAs

- The initial dose of ESA should be in the lower range (25u/kg 3x/ week) in patients with:
  - **History of thrombosis,**
  - **Uncontrolled hypertension,**
  - **Fits**
  - **or recent history of Cancer.**

- Titrate the weekly dose of ESA up or down by about 25% as needed every month by dose reduction or less frequent injection.

Table 3 Erythropoiesis stimulating agent dosing guide for initiation in children

	Starting Dose	Interval	Route
Epoetin alfa/beta	20–50 IU/kg	3 times per week	SC or IV
Darbepoetin alfa	0.45 μg/kg 0.75 μg/kg	Weekly Every 2 weeks	SC
CERA	4 μg per each prior weekly dose of: 125 IU epoetin 0.55 μg darbepoetin	Every 4 weeks	SC or IV

IU international units; SC subcutaneously; IV intravenously; CERA continuous erythropoietin receptor activator

DOSE ADJUSTMENT

- If the Hb is increasing and approaching 11.5 g/dl, the dose should be reduced by approximately 25%.

- If the Hb continues to increase, doses should be temporarily withheld until the Hb begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose.

- If the Hb increases by more than 1.0 g/dl in any 2-week period, the dose should be decreased by approximately 25%.

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease.
Kidney Int Suppl 2012; 2: 279–335

ESA Hyporesponsiveness

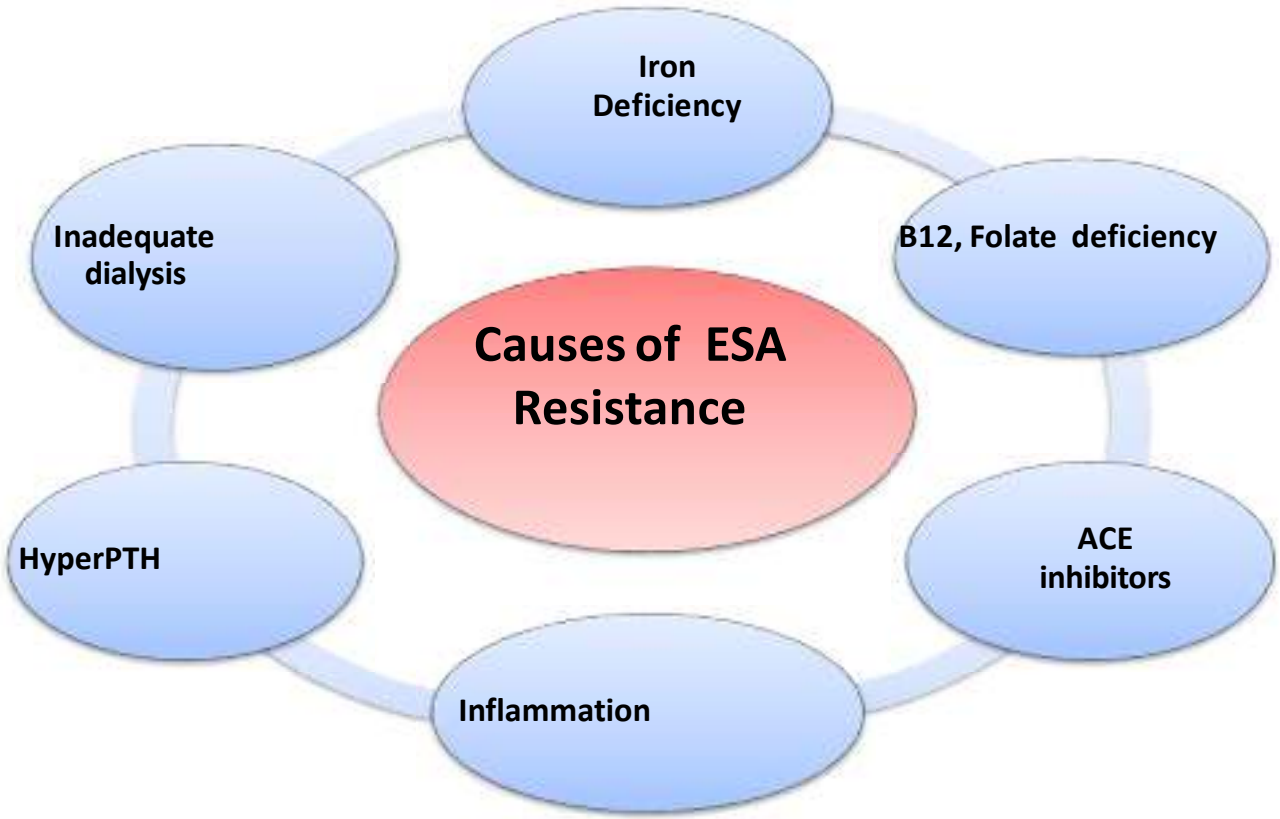
- KDIGO defines ESA hyporesponsiveness as no increase in Hb concentration from baseline after firs month of weight based dosing.

- Acquired ESA hyporesponsiveness as requirement for 2 increase in ESA doses up to 50% beyond the dose required to maintain a stable Hb concentration.

OR

Persistant Hb deficit after 3 months of high –dose ESA treatment (rHuEPO in excess of 400 unit/kg weekly or darpepoeitin alfa in excess of 1 Mg/kg weekly)

CAUSES OF ESA RESISTANCE



International Society of Nephrology, Protocols in Pediatric Nephrology:2013 ,199-200.

Newer Anaemia Therapies

- **Peginesatide**
- **HIF stabilization**
- **Hepcidin modulation**
- **GATA-2 inhibition**
- **Erythropoietin Gene therapy**
- **Epo delivery systems**

HIF-PHI

- Inhibit the action of prolyl-hydroxylase, lead to high level of HIF
  (Roxadustat, daprodustat , vadadustat , molidustst)
- Increase endogenous EPO
- Improve iron availability
- decrease hepcidine level

Consider use of HIF-PHI in hemodialysis patients :

- Patient preference for oral treatment
- Home hemodialysis
- Hypersensitivity or unavailability of IV iron
- ESA hyporesponsiveness or intolerance
- Chronic inflammatory states (CRP >3mg/l)

Potential advantages of HIF-PHI (Roxadustat) compared to ESAs therapy in CKD population

- Convenience of oral treatment
- Needle –phobia or unable to self-administer ESA
- ESA hyporesponsiveness or intolerance
- Better in chronic inflammatory states
- Hypersensitivity or unavailability of iron therapy
- Exposure to lower circulating levels of ESA
- Has proved efficacy and safety on NDD-CKD,HD,PD
- Use with caution in HD patients: with retinal disorders, vascular access with a high risk of thrombotic complication ,history of cured malignancy or without recurrence for at least 5 years,also in kidney transplant recepients

HIF-PHI

Avoid or use with extreme caution in:

- Patient with CV or thrombotic event in previous 3 months
- History of malignancy in the last 5 years
- Polycystic kidney disease
- Idiopathic pulmonary arterial hyperension
- Untreated proliferative diabetic retinopathy, macular degeneration and retinal vein occlusion

Thank you

Prevention of Chronic Kidney Disease in Children

Kamal Akl MD

Professor of Pediatrics & Pediatric Nephrology

The 7th IPNA Teaching Course in Clinical Nephrology

June 2024 Amman-Jordan

Objectives

- To review causes of Childhood CKD in Jordan
- To review preventive measures
- Prevention is cheaper than management

CKD in Jordan

- **Incidence** :
- Jordan :10.7 new cases / million-child population / year
- vs Kuwait :38.2/million children/year
- **Prevalence**:
- Jordan 51 / million population/year
- vs Kuwait: :55 /million children/year

- Hamed R . J Nephrol 2002
- Al-Eisa A et al. Pediatr Nephrol 2005

CKD in Jordan in Children

- Incidence & prevalence not accurate because:
- CKD definition
- Under-estimated
- Age group covered
- No proper Registry in developing countries
- Harambat J et al. Pediatr Nephrol Pediatr Nephrol 2023

Causes ESRF in Jordan

- CAKUT 45.8%
- Glomerulopathies 26.2%
- Heredofamilial 23.2%

- Akl,K et al West Indian Med J 2015

ESRF in Jordan

- **CAKUT:**
- Neurogenic Bladder 16.8%
- Reflux Nephropathy 12.7%
- Posterior Urethral Valve 4.0%

ESRF in Jordan

- Glomerulopathies:
- FSGS 10.2%

- Heredofamilial Disorders:
- Oxalosis 8%
- Cystic disease 7.2%

Prevention of CKD

- **ESRF** = Tip of the iceberg
- **----------**
- **CKD**

- **----------**
- **High Risk for CKD**

- Pecoraro C. Ital J of Peds 2015

Prevention of CKD

- **Primary Prevention-** Best

Reduce Exposure

- **Secondary Prevention**

Prevent Deterioration

- **Tertiary Prevention**

Delay Complications

Penido M et al Uro Nephrol Open Access J 2020

Prevention of CKD in Children

- Before pregnancy
- Antenatal Preventive measures
- Postnatal preventive measures

- Vijayakumar M et al Indian J Nephrol 2007

Risk factors for CKD in adults

- DM
- HTN
- Obesity

- Xie Y, et al Kidney Int 2018

CKD Risk Factors in Children

- Unlimited
- May start before birth: Fetal and perinatal programming of Kidney Disease in adults

- Barker DJP 1990
- Terstappen F et al Nephrol Dial Transplant 2020

Identification of risk factors for CKD in Children

- LBW & prematures
- Spinal cord problems
- Renal dysplasia/Hypoplasia
- Prolonged NICU stay
- FH of CKD/genetic kidney disease
- Obesity

Past history of Glomerulopathies /HUS

Bladder diseases(NB, NNNB, Lower Urinary Tract Dysfunction)

Penido M et al 2020

CAKUT Diagnosis

- Antenatal Ultrasound
- Physical Examination Clues
- Imaging Workup for UTI
- Incidental Finding
- On investigation of a syndrome with nephro-urologic involvement:-Importance of Genotype-Phenotype

Physical Examination Clues to CAKUT

- **Inspect :**
- Facies: if dysmorphic
- Smile: if inverted /like crying
- Ears: difference in size and abnormalities
- Nose: bifid
- Chest: supernumerary nipples
- Abdomen: muscles; bladder
- Lumbosacral area: dimples, hair tufts, gluteal cleft
- Hands and feet: syndactyly, polydactyly, digit fusion or absence

- Akl K JMJ 2016

Physical Examination Clues to CAKUT (continued)

- Anal Position Index(API)

- Unpublished data from AlBashir Gov Hospital & Dr Ibrahim Shatat

Spina Bifida

- Prevention Should Start Before Birth

- Filler G, et al Int Urol Nephrol 2008

Spina Bifida

- A major cause of Neurogenic Bladder in childhood
- Renal involvement in 30%-40%

- Muller T et al. Curr Opin Urol 2002

Spina Bifida

- Importance of early assessment and followup
- Newborn: US, MCUG, Urodynamics
- US Q 3 months in first year; Q 6 months in second year; then Q 1 year

Spina Bifida

- Early CIC(<1 year)-> less urinary tract deterioration than late initiation(>3 years old)

Kochakarn W et al Asian J Surg 2004

Anticholinergics

Early Diagnosis of Primary VUR

- Antenatal US
- During investigation for UTI especially in the first 2 years of life
- Sibling Screen

Acute Kidney Injury

- AKI increases risk for long- term incident Chronic Kidney Disease

Hessey E . Can J Kidney Health and Dis 2019

Prevention of AKI

- **Helpful measures**
- Fluid administration in Hypovolemia

- Nephrotoxic medications adjustment

- **Unhelpful**
- Low dose dopamine
- Loop diuretics
- Fenoldopam

Don’t undestimate PSAGN

- Childhood post-streptococcal glomerulonephritis as a risk factor for chronic kidney disease in later life

- Med J of Australia 2001

APSGN

- Nephrotic range proteinuria with hypoalbuminemia 22.9%

  more frequent than previously reported

IMAJ 2016

Neonatal AKI

- Under-Recognition of Neonatal Acute Kidney Injury and lack of followup

- Roy JP et al Am J Perinatol 2022

Nephrolithiasis

- Loss of kidney function in Nephrolithiasis

- Keddis M et al .Curr Opin Nephrol Hyperten 2013

Don’t underestimate Urinary Incontinence

- Daytime wetting

- How far to investigate Nocturnal Enuresis

Nocturnal Enuresis

- Nighttime wetting is not a benign condition in every child

- Yalmaz AC et al , Pediatr Nephrol 2018

NICU Graduates

- Low Birth Weight
- Number of Nephrons (Berram JF et al Pediatr Nephrol 2011)
- Telomere integrity
- Hormonal factors
- Genetic factors
- Epigenetics
- Penido M et al 2020

Intrauterine Exposure

- Aminoglycoside , Steroids -> Reduction in number of nephrons
- ACEi, NSAIDS -> Renal Tubular Dysgenesis, Fetal Anuria, Neonatal Death
- CMV-> CNS
- Obesity in pregnancy-> renal dysplasia, congenital renal and NTD

SGLT2s Inhibitors

- Slows CKD Progression in Adults
- EMPA-Kidney trial
- Insufficient data in children
- US FDA and EU approved Empagliflozin for children >10 years with type 2 diabetes
- Boehringer Ingelheim & Eli Lilly 2023

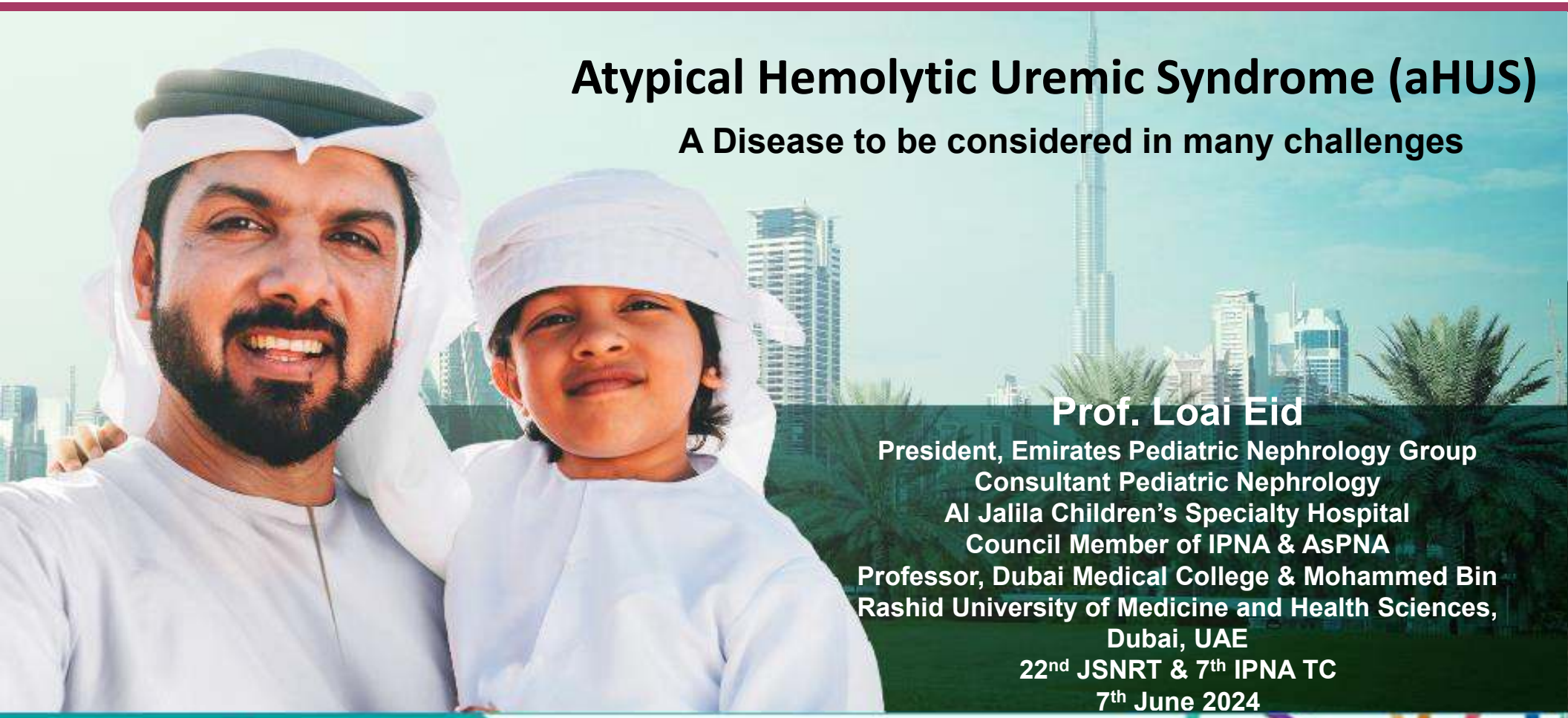
Developing Countries

- Late referral in developing countries
- Warady BA et al Pediatr Nephrol 2007

- Registries

Conclusions

- Thank you for your patience



Atypical Hemolytic Uremic Syndrome (aHUS)

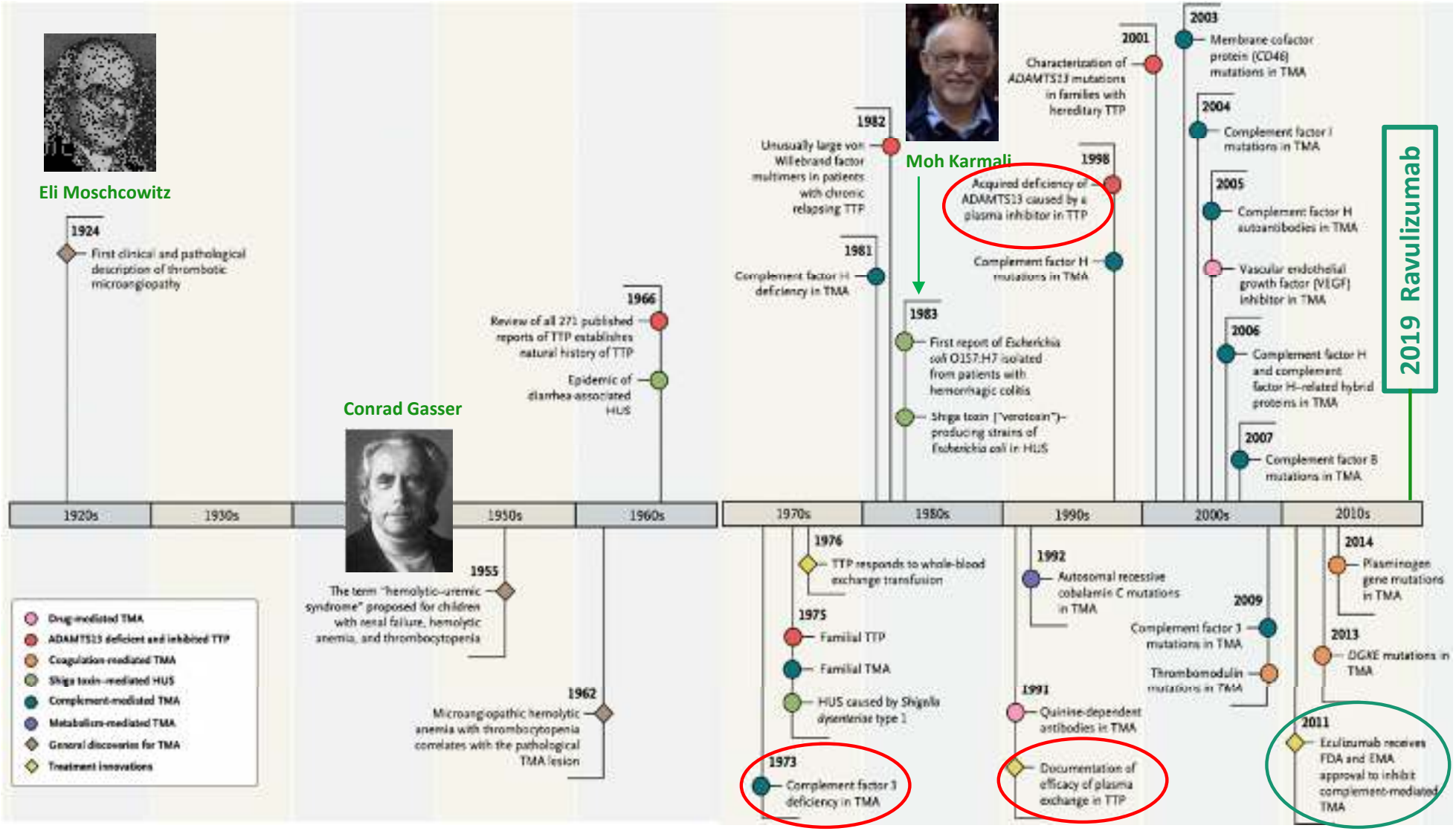
A Disease to be considered in many challenges

Prof. Loai Eid

President, Emirates Pediatric Nephrology Group
Consultant Pediatric Nephrology
Al Jalila Children's Specialty Hospital
Council Member of IPNA & AsPNA
Professor, Dubai Medical College & Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE

22nd JSNRT & 7th IPNA TC
7th June 2024

INDEX



George et al. NEJM 2014

A CHILD WITH BLOODY DIARRHEA

- 5 years old female
- Admitted with bloody diarrhea & abdominal pain
- GI PCR panel **positive:**

  Enteroaggregative E.Coli

  Shiga-like toxin producing E.Coli (STEC) (0157:H7)

  Rotavirus

- Weight 15.8kg
- WBC 24.3 KU/L, Hb 13.9 g/dl, Plt 363 KU/L, CRP 37 mg/L
- RFP (normal): Urea 2.5 mmol/L, Cr 50 umol/L, K 4.3 mmol/L, Bicarb 16 mmol/L
- Started on conservative management and stopped antibiotic.

DAY 3: BLOODY DIARRHEA

- **Progression marked by:**
- Continuing diarrhea
- Declining urine output
- kidney function started to deteriorate

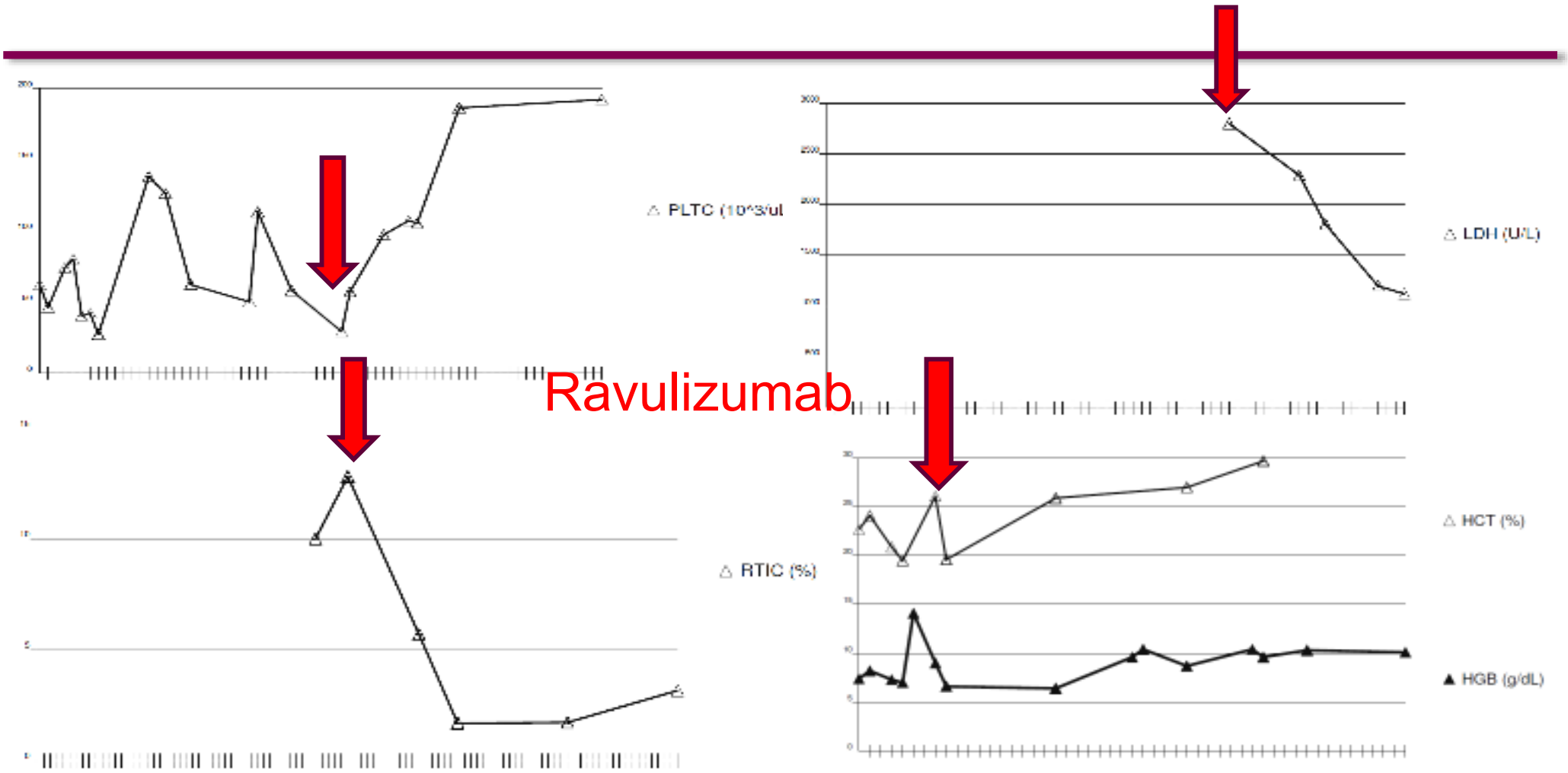
- Weight 17 kg, still on IV fluids
- WBC 27.5, HB 9.4, PLT 44, Ht 27.3
- Urea 15.8 mmol/l, Cr 274 umol/L, K 3.3
- High relic count & **Blood film** was consistent with Thrombotic Microangiopathy (**TMA**)
- LDH 2835, C4 NL, C3 0.73g/L & CH50 (low)

Labs	18/04	21/4	22/4	24/4	26/4	27/4	28/
CREAT umol/L	50	274	432	209	103	115	250
UREA mmol/L	2.5	15.8	24.1	17.1	8.2		22.5
K mmol/L	4.3	3.3	3.5	4.5			4.5
HB g/dL	13.9	9.4	7.5	9.8	9.6	9.3	8.4
HT %	39	27.3	22	28.4	27.9	26.8	24.1
PLT K/UL	363	44	35	54	22.7	75.5	138
LDH	NA	2835	2940		5042	3996	
Weight	15.8	17.0	18.1	16.5			

CLINICAL COURSE CONT....

- She became anuric and hypertensive
- Blood transfusion & Hemodialysis was done for 6 sessions over 10 days as she has remained anuric for 10 days
- Ravulizumab infusion (Loading and maintenance) given two doses
- Discharged home after three weeks off dialysis & on low dose of ACEi due to proteinuria
- Full **genetic testing** for aHUS; she carries a **homozygous CFHR1/CFHR3 deletions**

CLINICAL COURSE CONT....



What is atypical hemolytic uremic syndrome (aHUS)?

atypical

aHUS is not "typical" because it is not caused by Shiga toxin-producing *Escherichia coli* (STEC)[1]

Hemolytic

aHUS is characterized by nonimmune, intravascular, mechanical hemolysis (eg, the presence of schistocytes)[2]

Uremic

aHUS typically causes uremia, which is when waste products that are normally excreted in urine build up in the blood[3]

Syndrome

1. Loirat C, Fremeaux-Bacchi V. *Orphanet J Rare Dis* 2011;6:60. **2.** Dhaliwal G *et al. Am Fam Physician* 2004;69:2599–606. **3.** National Organization for Rare Disorders – atypical hemolytic uremic syndrome https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome Accessed January 2022.

What is Thrombotic Microangiopathy (TMA)?

Thrombotic

Thrombotic comes from the word thrombosis, meaning likely to develop a **clot** comprising various blood cells and proteins within the vasculature[1]

Micro

Clots form in the **small blood vessels**, such as the capillaries and arterioles[2]

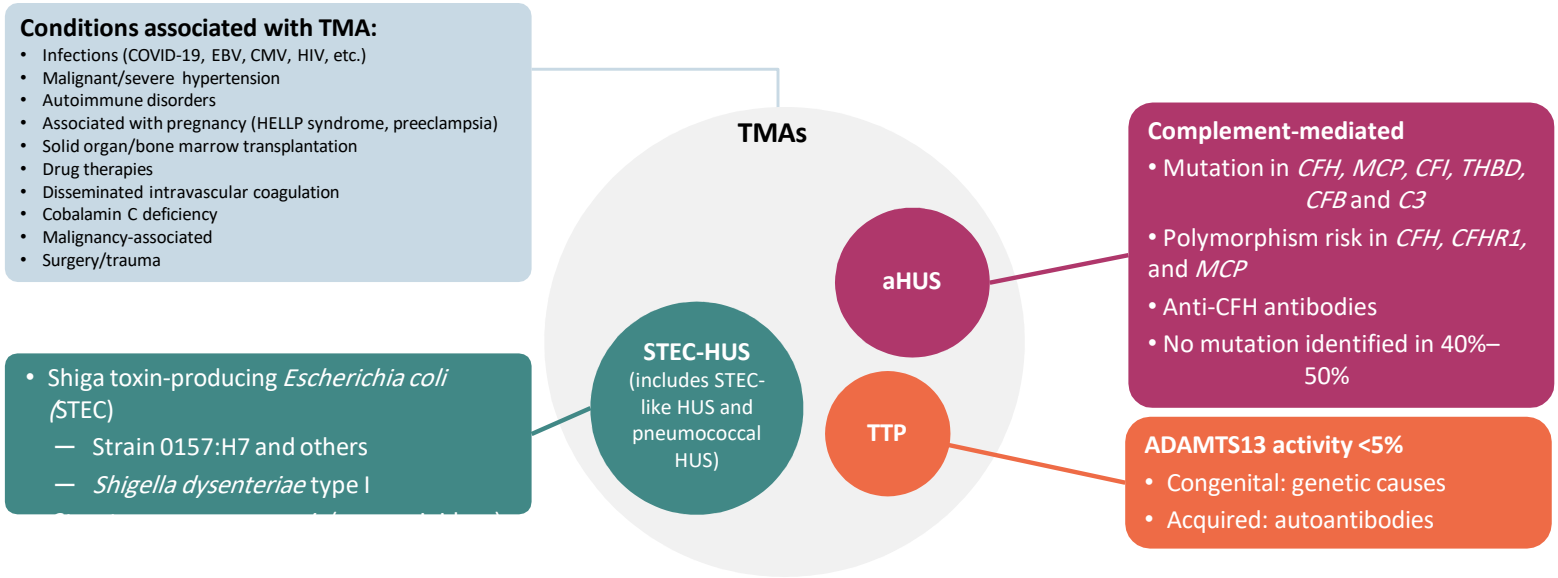
Angiopathy

Angiopathy is a disease of the **blood vessels**, evident if vessel lesions are in histologic sections[2]

The diffuse and systemic nature of TMA has the potential to affect the microvasculature of many organ systems, causing ischemia and eventual organ failure[2]

1. Pendleton RC, Rodgers GM. Thrombosis and antithrombotic therapy. In: Greer JP *et al.*, eds. *Wintrobe's Clinical Hematology*. 13th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014;pp 1218–57. **2.** Campistol JM *et al. Nefrologia* 2015;35:421–47.

The Spectrum of TMA[1-6]



ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; *C3*, complement component 3; *CFB*, complement factor B; *CFH*, complement factor H; *CFI*, complement factor I; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HELLP, hemolysis, elevated liver enzyme, low platelet count; HIV, human immunodeficiency virus; *MCP*, membrane cofactor protein; STEC-HUS, shiga toxin- producing *Escherichia coli* hemolytic uremic syndrome; *THBD*, thrombomodulin; TTP, thrombotic thrombocytopenic purpura; TMA, thrombotic microangiopathy

1. Azoulay E, et al. *Chest.* 2017;152(2):424-434. **2.** Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859. **3.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11 suppl 11):2-15. **4.** Gill J, et al. *J Nephrol.* 2021. https://link.springer.com/article/10.1007/s40620-021-01125-8 **5.** National Heart, Lung, and Blood Institute website. Updated March 24, 2022. Accessed February 28, 2022. https://www.nhlbi.nih.gov/ **6.** Beck BB, et al. *Pediatr Nephrol.* 2017;32(5):733-741.

aHUS is a complement-mediated TMA[1]

- Owing to a genetic deficiency of complement regulatory proteins, aHUS results from **chronic, uncontrolled complement activity** that leads to progressive and life-threatening complications[2–4]
- **Vicious cycle** of complement amplification and endothelial injury

- aHUS is defined by the clinical **triad** characteristics of TMA[5]
  - *Decreased platelet count (Thrombocytopenia)*
  - *Evidence of microangiopathic hemolysis*
  - *Evidence of organ impairment/damage (e.g., serum creatinine >ULN)*

- **Triggers** may unmask aHUS[5]

- First clinical manifestation can present at **any age**[6]

aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy; ULN, upper limit of normal.

1. Cofiell R *et al. Blood* 2015;125:3253–62. **2.** Jamme M *et al. PLoS One* 2017;12:e0177894. **3.** Noris M *et al. Nat Rev Nephrol* 2012;8:622–33. **4.** Willows J *et al. Clin Med (Lond)* 2020;20: 156-60. **5.** Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **6.** Afshar-Kharghan. *Hematology Am Soc Hematol Educ Program* 2016;1:217–25.

Epidemiology

aHUS is a rare disease, with <200,000 affected[1,2,5-8]

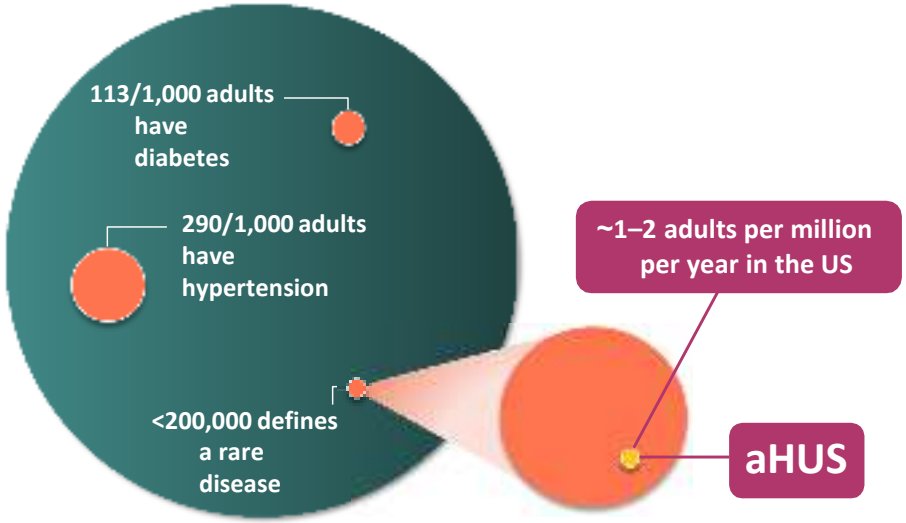
Annual Incidence per Million[2,6]

~1–2 cases in the US

0.23–1.9 per million in Europe

Prevalence of 11.88 per million per year among inhabitants below the age of 18 in Europe*[,7]

aHUS Annual Incidence in the Spectrum of Disease in the US[1-4]



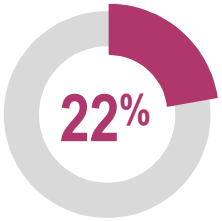
*The study considered HUS cases occurring in the region of Northern Italy which had an average general population of 9.6 million over a 10-year observation period (2003-2012) including 1.6 million people aged ≤18 years.[7]

1. National Institutes of Health website. Updated February 2023. Accessed February 28, 2023. https://rarediseases.info.nih.gov/diseases/8702/atypical-hemolytic-uremic-syndrome **2.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447. **3.** Centers for Disease Control and Prevention website. Updated September 30,2022. Accessed February 28, 2022. https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html. **4.** Fryar CD, et al. *NCHS Data Brief.* 2017;(289):1-8. **5.** Harari S. *Eur Respir Rev.* 2016;25:101-103. **6.** Yan K, et al. *Clin Epidemiol.* 2020;12:295-305. **7.** Ardissino G, et al. *Eur J Pediatr.* 2016;175(4):465-473. **8.** Wühl E, et al. *Nephrol Dial Transplant.* 2014(29):iv1-iv8.

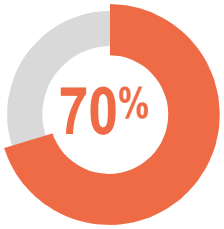
Demographics of aHUS

aHUS can occur at any age—from the neonatal period through late adulthood[1]

of patients diagnosed are pediatric patients*,[2]



have their first TMA manifestation before 6 months of age[3]



have their first TMA manifestation before 2 years of age†,[3]

TMA, thrombotic microangiopathy.

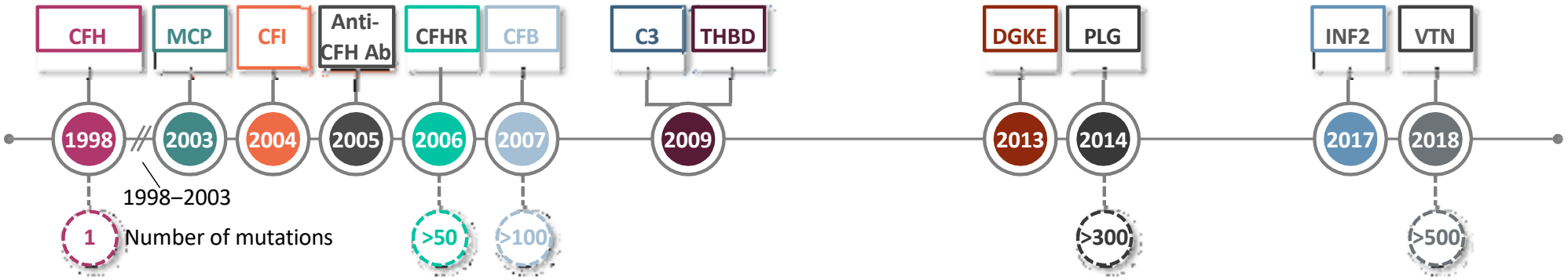
*A nationwide study was conducted with 214 French adult and pediatric patients with aHUS to assess the effect of complement gene mutations on age of onset, disease expression, and outcome.

†The study was carried out in 46 pediatric patients with aHUS to document the frequency of each of the genetic complement risk factors of aHUS and to define prognosis and therapeutic guidelines according to clinicobiological characteristics.

1. Loirat C, Fremeaux-Bacchi V. *Orphanet J Rare Dis.* 2011;6:60. **2.** Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562. **3.** Sellier-Leclerc AL, et al. *J Am Soc Nephrol.* 2007;18(8):2392-2400.

Genetic Abnormalities in aHUS

Mutations associated with aHUS continue to be discovered[6,7,9]

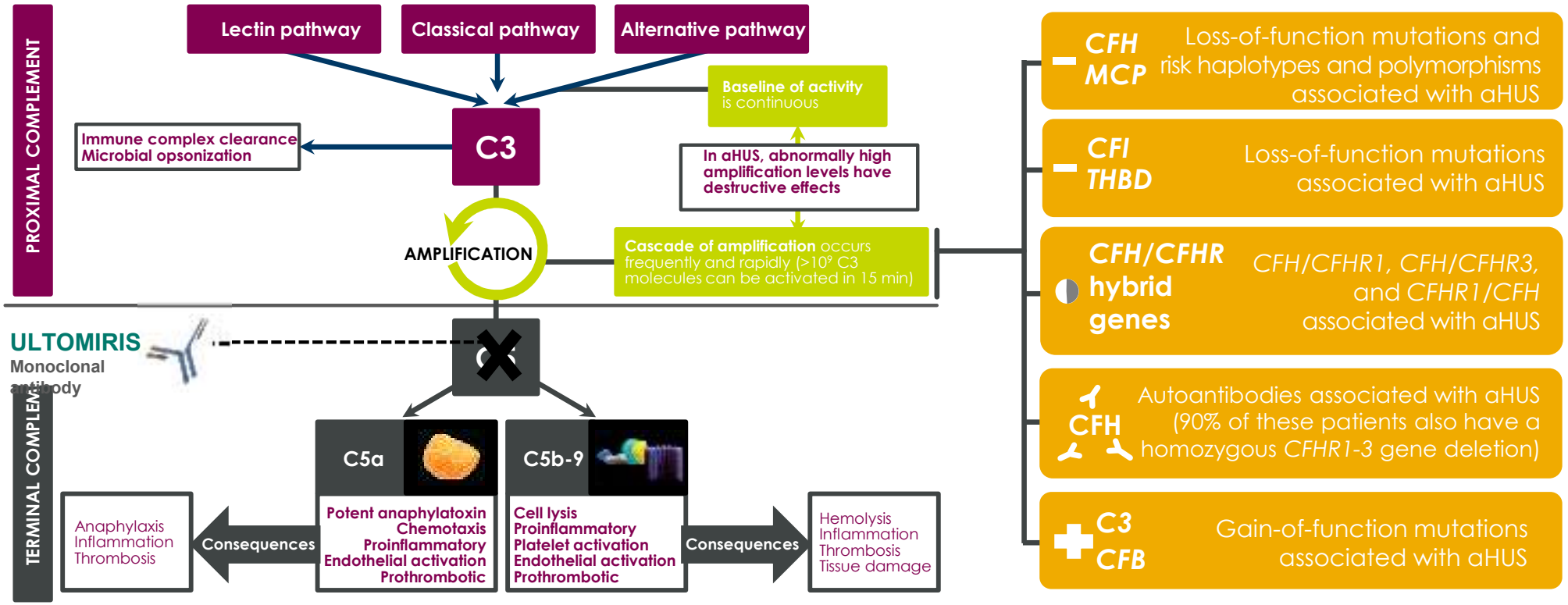


As more mutations are discovered, more potential patients with aHUS can be identified[11]

Anti-CFH Ab, Anti-complement factor H antibody; C3, complement component 3; CFB, complement factor B; CFH, complement factor H, CFHR, complement factor H-related protein; CFHR1, complement factor H-related protein-1; CFI, complement factor I; DGKE, diacylglycerol kinase epsilon; INF2, inverted formin-2; MCP; membrane cofactor protein; PLG, plasminogen; THBD, thrombomodulin; VTN, vitronectin

1. Fakhouri F, et al. *Clin J Am Soc Nephrol.* 2017;(12):50-59. **2.** George JN, Nester CM. *N Engl J Med.* 2014; 14;371(7):654-666. **3.** Feitz JCW, et al. *Med Genet.* 2018;30(4):400-409. **4.** Bu F, et al. *J Am Soc Nephrol.* 2018;29(12):2809-2819. **5.** Warwicker P, et al. *Kidney Int.* 1998;53(4):836-844. **6.** Saunders RE, et al. *Hum Mutat.* 2006;27(1):21-30. **7.** Saunders RE, et al. *Hum Mutat.* 2007;28(3):222-234. **8.** Rodríguez de Córdoba E, et al. *Semin Thromb Hemost.* 2014;40(4):422-430. **9.** Osborne AJ, et al. *J Immunol.* 2018;200(7):2464-2478. **10.** Challis RC, et al. *J Am Soc Nephrol.* 2017;28(4):1084-1091. **11.** Caprioli J, et al. *Blood.* 2006;108(4):1267-1279

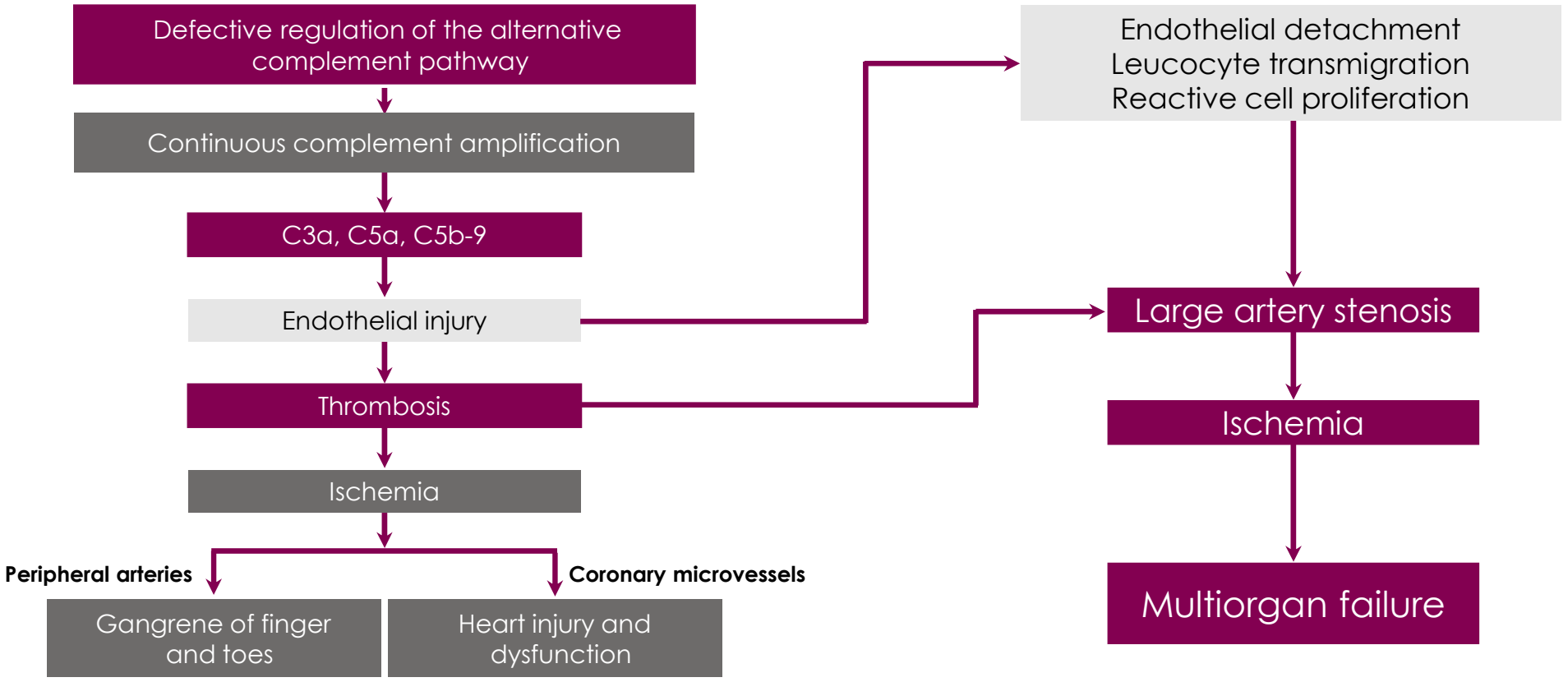
Genetic mutations, polymorphisms, autoantibodies and uncontrolled complement activity[1–6]



aHUS, atypical hemolytic uremic syndrome; *C3*, complement component 3 gene; *CFB*, complement factor B gene; *CFH*, complement factor H gene; *CFHR1*, complement factor H-related protein 1; *CFI*, complement factor I gene; *MCP*, membrane cofactor protein gene; *THBD*, thrombomodulin gene.

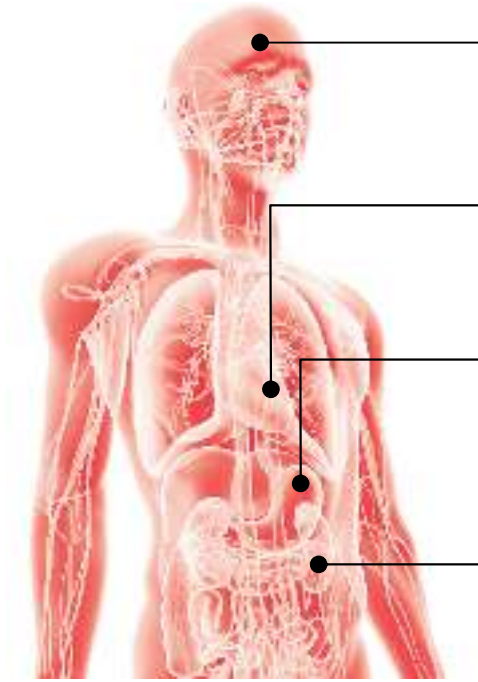
1. Noris M *et al. Nat Rev Nephrol* 2012;8:622–33. **2.** Campistol JM *et al. Nefrologia* 2015;35:421–47. **3.** Jokiranta TS. *Blood* 2017;129:2847–56. **4.** Maga TK *et al. Hum Mutat* 2010;31:E1445–60. **5.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59. **6.** Noris M, Remuzzi G. *N Engl J Med* 2009;361:1676–87.

Uncontrolled complement activation and organ involvement



Adapted from: Noris M, Remuzzi G. *Nat Rev Nephrol* 2014;10:174–80.
aHUS, atypical hemolytic uremic syndrome

Patients with aHUS and risk of complications[a]



Up to 25% experience neurological symptoms, including[5]:

- Confusion[3]
- Encephalopathy[4,5]
- Stroke[5]
- Seizure[3]

Up to 33% experience CV symptoms, including[8]:

- Arterial thrombosis[5]
- Vascular stenosis[4]
- Cardiomyopathy[3]
- Hypertension[3]
- Myocardial infarction[4,5]

Up to 47% experience GI symptoms, including[5]:

- Colitis[5]
- Abdominal pain[3]
- Pancreatitis[5]
- Nausea/vomiting[5]
- Gastroenteritis[2,7]
- Diarrhea[3]

More than 49% progress to ESRD[4,5]:

- Elevated creatinine[3]
- Decreased eGFR[1]
- Proteinuria[6]

Other macrovascular complications[8]:

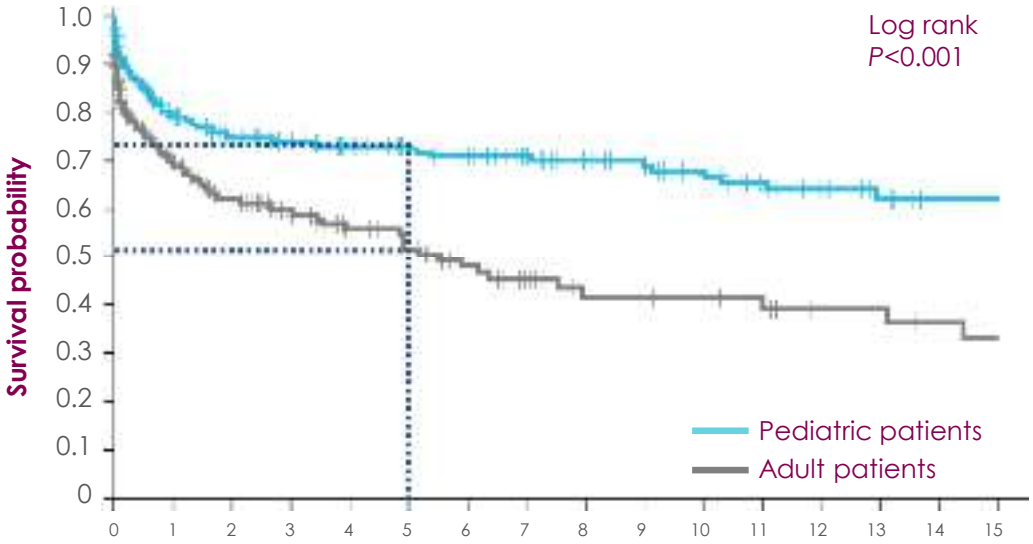
Peripheral arterial disease
Phalangeal gangrene

aHUS, atypical hemolytic uremic syndrome; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal.
[a]The organ-specific symptoms associated with aHUS are reported from the published literature and are not limited to only those listed in this slide.

1. Legendre CM *et al. N Engl J Med* 2013;368:2169–81. **2.** Goodship THJ *et al. Kidney Int* 2017;91:539–51. **3.** Jamme M *et al. PLoS One* 2017;12:e0177894. **4.** Hofer J *et al. Front Pediatr* 2014;2:97. **5.** Campistol JM *et al. Nefrologia* 2015;35:421–47. **6.** Krishnappa V *et al. Ther Apher Dial* 2018;22:178–88. **7.** Schonermarck U, Ries W *et al. Clin Kidney J* 2020;13:208-16. **8.** Noris M, Remuzzi G. *Nat Rev Nephrol* 2014;10:174–80.

Consequences of unpredictable complement-mediated TMA[1,2]

ESRD survival probability in patients with aHUS[3]



Time from initial aHUS presentation (years)

Pediatric	Events	56	9	2	1	1	2	0	1	1	1	2	1	1	0	0
	At risk	376	169	146	124	110	95	89	76	68	64	56	45	38	31	26
Adult	Events	96	11	3	4	4	3	2	2	0	0	0	1	0	1	1
	At risk	432	119	85	68	55	44	35	27	20	20	19	18	14	14	11

- In an observational study of 851 patients from the Global aHUS Registry, ESRD-free survival was 79% in pediatric patients and 69% in adult patients at 1 year[3]
- At 5 years, ESRD-free survival was 73% in pediatric patients and 51% in adult patients[3]

Patients with aHUS are at continuous risk of TMA[3]

Reprinted from *Kidney Int* 94(2): 408–418, Schaefer F *et al*. Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome, © 2018, with permission from Elsevier.
aHUS, atypical hemolytic uremic syndrome; ESRD, end-stage renal disease.
1. Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **2.** Legendre CM *et al. N Engl J Med* 2013;368:2169–81. **3.** Schaefer F *et al. Kidney Int* 2018;94:408–18.

aHUS can be challenging to diagnose[1,6]

aHUS is rare[2]

- About 2 cases per million people per year in the United States[2,3]
- 0.11 to 0.23 cases per million people in Europe[1,4]

aHUS has clinical features in common with other conditions[5]

- TMAs all present with thrombocytopenia and hemolytic anemia

aHUS requires a clinical diagnosis[1,5,6]

- No diagnostic test for aHUS is available
- Diagnostic tests available for other TMAs are used to rule out aHUS

aHUS may present with other conditions[5]

- Triggers may complicate diagnosis

aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Campistol JM *et al. Nefrologia* 2015;35:421–47. **2.** Yoshida Y *et al. Ren Replace Ther* 2017;3:5. **3.** Constantinescu AR *et al. Am J Kidney Dis* 2004;43:976–82. **4.** Fremeaux-Bacchi V *et al. Clin J Am Soc Nephrol* 2013;8:554–62. **5.** Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **6.** Lee H *et al. Korean J Intern Med* 2020;35:25–40.

TMA diagnosis (1/2)[1,2]

Thrombocytopenia

Platelet count <150,000/mm^3 or
>25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or
Elevated LDH level and/or
Decreased haptoglobin level and/or
Decreased hemoglobin level

Plus one or more of

Neurological symptoms
Confusion and/or
Seizures and/or
Stroke and/or
Other cerebral abnormalities

Renal impairment
Elevated creatinine and/or
Decreased eGFR and/or
Elevated blood pressure and/or
Abnormal urinalysis

GI symptoms
Diarrhea ± blood and/or
Nausea/vomiting and/or
Abdominal pain and/or
Gastroenteritis/pancreatitis

CV symptoms
MI and/or
Hypertension and/or
Arterial stenosis and/or
Peripheral gangrene

Pulmonary symptoms
Dyspnea and/or
Pulmonary hemorrhage and/or
Pulmonary edema

Visual symptoms
Pain and blurred vision and/or
Retinal vessel occlusion and/or
Ocular hemorrhage

Figure used with permission from Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LDH, lactate dehydrogenase; MI, myocardial infarction; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TMA, thrombotic microangiopathy.
1. Azoulay E *et al. Chest* 2017;152:424–34. **2.** Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15.

TMA diagnosis (2/2)[1–3]

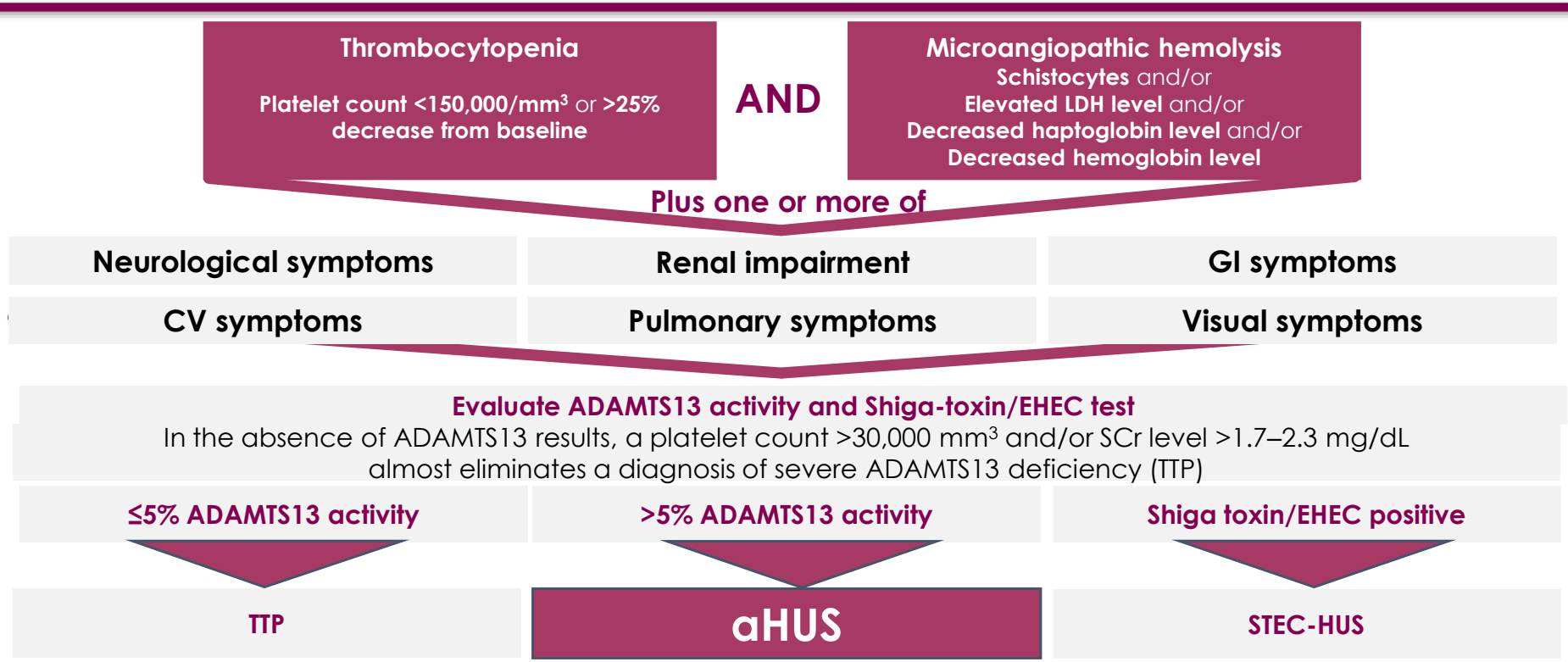
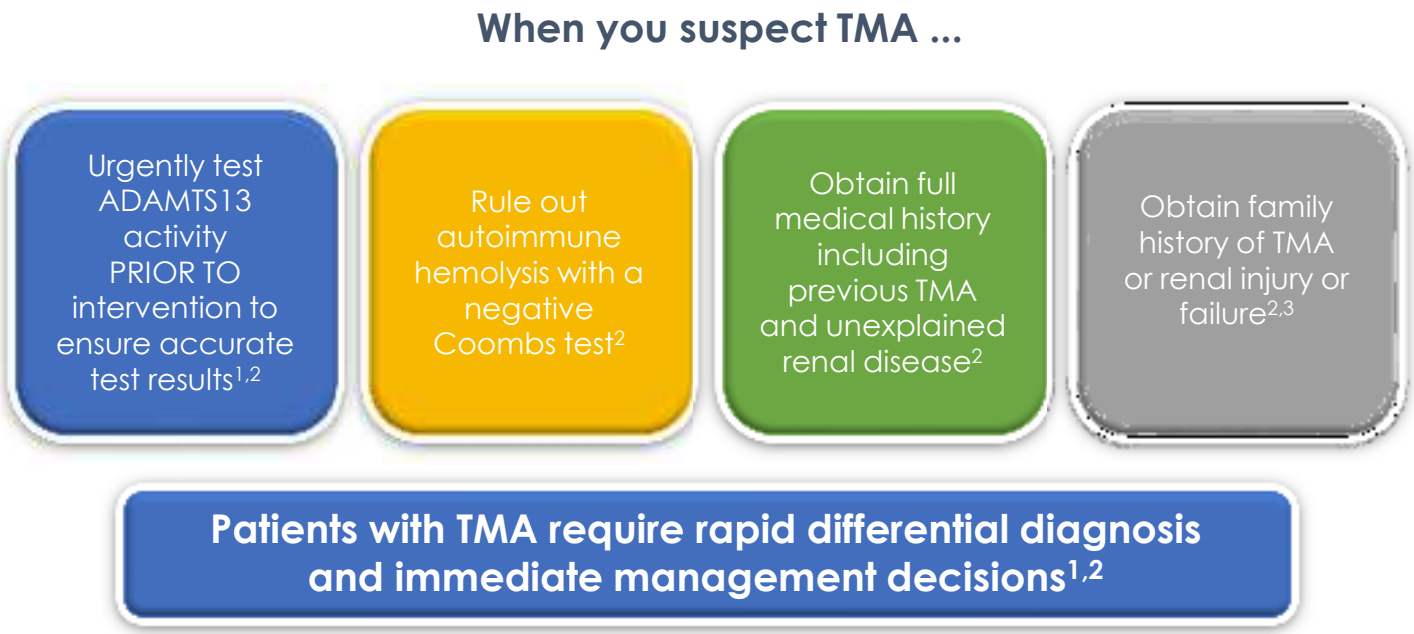


Figure used with permission from Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; aHUS, atypical hemolytic uremic syndrome; CV, cardiovascular; EHEC, enterohemorrhagic *Escherichia coli*; GI, gastrointestinal; LDH, lactate dehydrogenase; SCr, serum creatinine; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

1. Azoulay E *et al. Chest* 2017;152:424–34. **2.** Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **3.** Lee H *et al. Korean J Intern Med* 2020;35: 25–40.

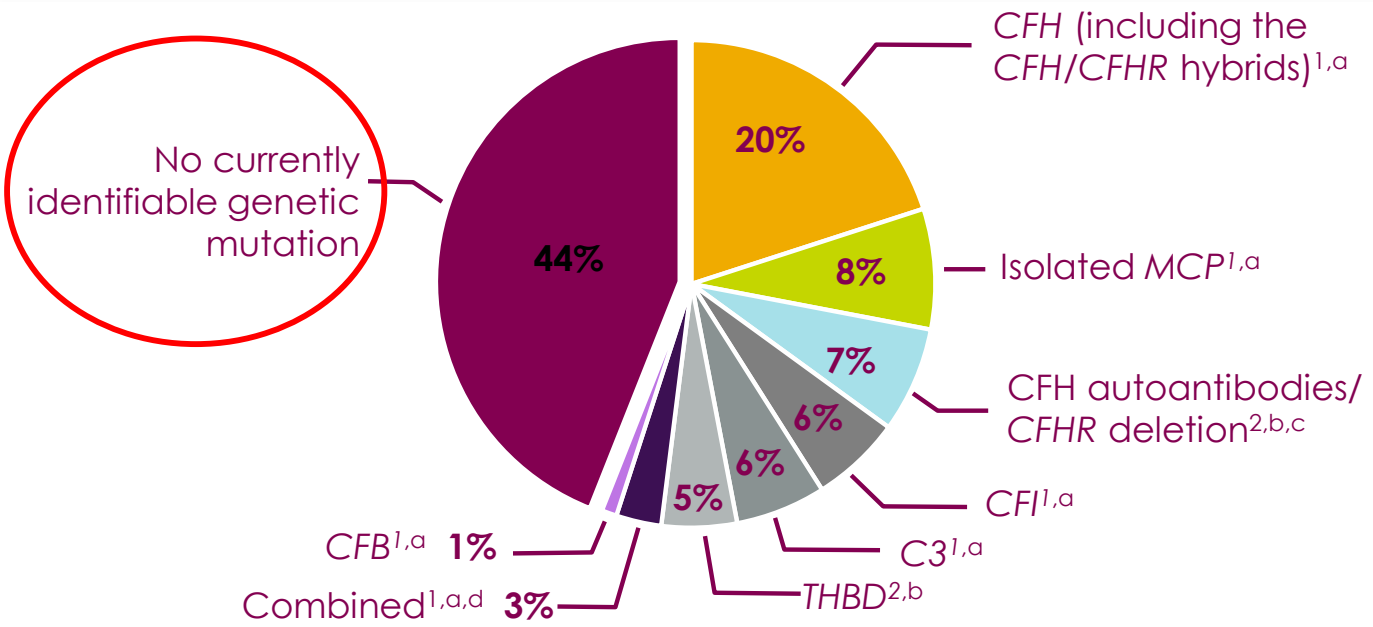
Importance of early diagnosis of aHUS



ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; aHUS, atypical hemolytic uremic syndrome;
TMA, thrombotic microangiopathy.

1. Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **2.** Azoulay E *et al. Chest* 2017;152:424–34. **3.** Kato H *et al. Pediatr Int* 2016;58:549–55

Genetic mutations in aHUS



A diagnosis of aHUS does not require identification of a mutation[5,6]

- *DGKE* mutations have been identified in 5–27% of patients ≤ 13 months of age[3,4]

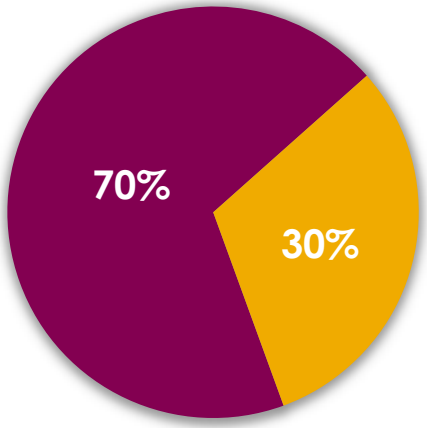
aHUS, atypical hemolytic uremic syndrome; *CFB*, complement factor B gene; *CFH,* complement factor H gene ; *CFHR*, complement factor H-related protein gene; *CFI,* complement factor I gene; C3, complement component 3 gene; *DKGE*, diacylglycerol kinase epsilon gene; *MCP*, membrane cofactor protein gene; *THBD*, thrombomodulin gene.
[a]Study population: N = 795.[2] [b]Study population: N = 273.[3] [c]Ninety percent of patients with CFH autoantibodies had complete deficiency of FH-related proteins secondary to a *CFHR1-3* deletion, suggesting a genetic basis for complement dysregulation in patients with CFH autoantibodies.[3] [d]Patients with ≥ 2 genetic abnormalities.[2]

1. Bresin E *et al. J Am Soc Nephrol* 2013;24:475–86. **2.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59.
3. Lemaire M *et al. Nat Genet* 2013;45:531–6. **4.** Sánchez Chinchilla D *et al. Clin J Am Soc Nephrol* 2014;9:1611–19. **5.** Azoulay E *et al. Chest* 2017;152:424–34.
6. Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15.

Non-genetic causes of aHUS

- In some cases, genetic mutations alone are not enough to cause aHUS[1]
- aHUS is often unmasked by a new or preexisting condition that promotes complement activation and endothelial damage (trigger)[1,2]

aHUS unmasked by a trigger[2,a]

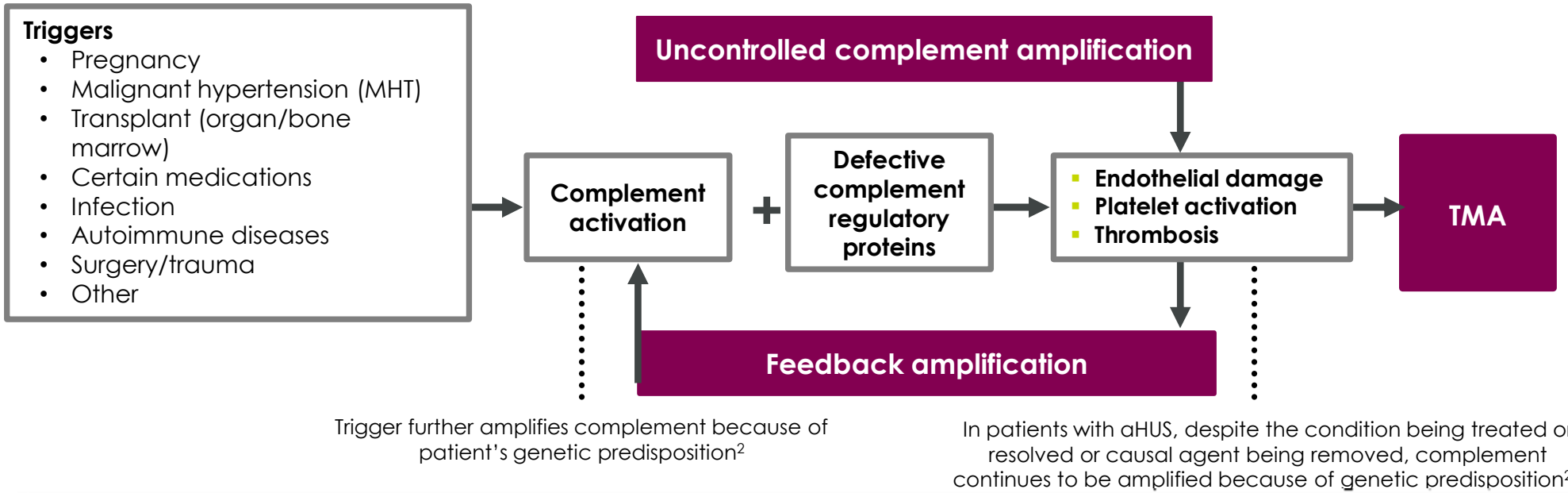


aHUS with no identifiable trigger [2,a]

70% (191/273) of patients with aHUS presented their first clinical manifestations while experiencing a trigger[2,a]

aHUS, atypical hemolytic uremic syndrome.
[a]From a study of 273 patients with aHUS enrolled in the International Registry of Recurrent and Familial HUS/TTP between 1996 and 2007.[2]
1. Riedl M *et al. Semin Thromb Hemost* 2014;40:444–64. **2.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59.

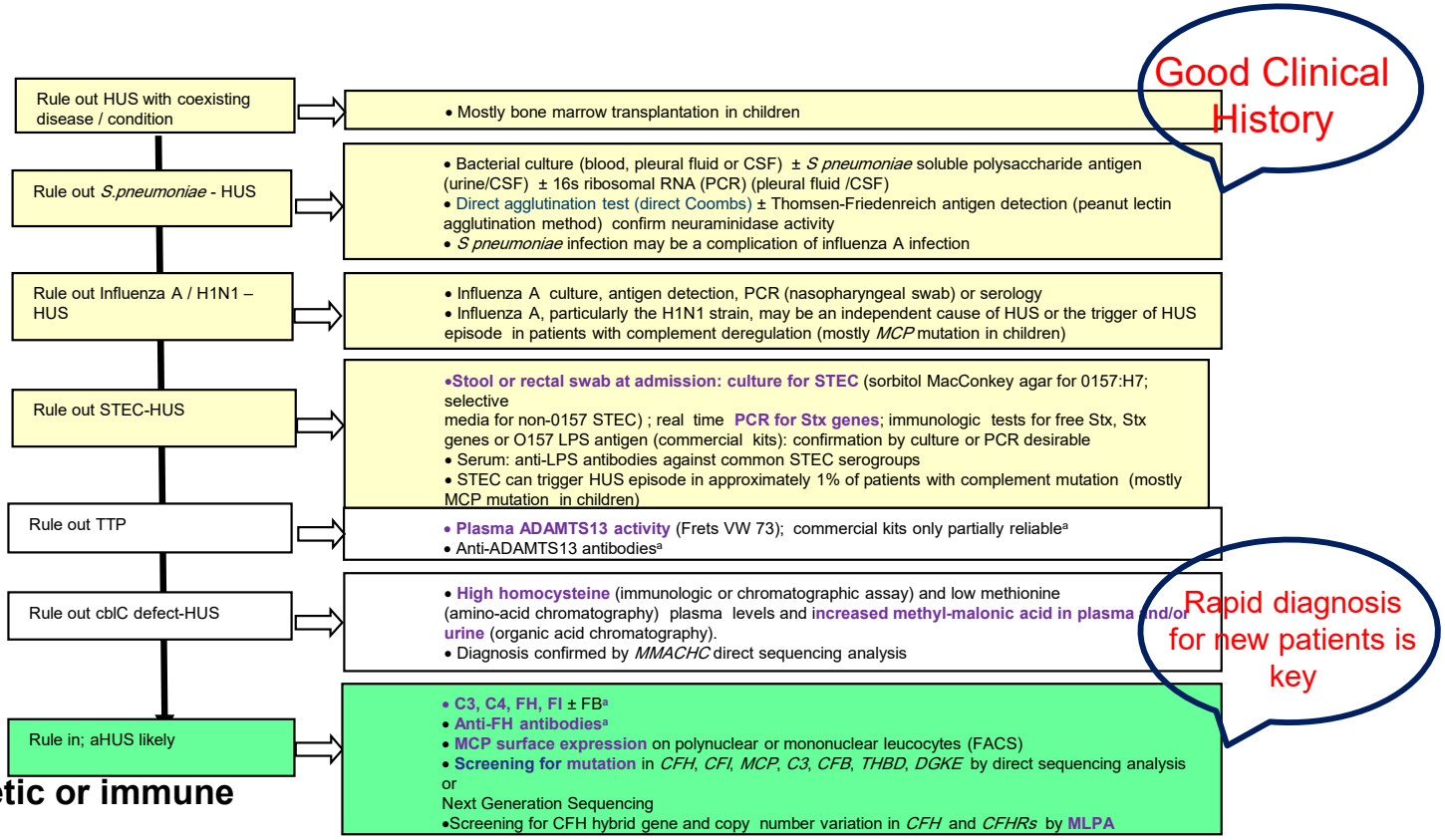
Triggers in aHUS and TMA manifestations [1–3]



If the signs and symptoms of TMA do not rapidly resolve in response to trigger management, continue to evaluate following the differential diagnostic pathway of TMAs[2]

Used with permission from Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15.
aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.
1. Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **2.** Riedl M *et al. Semin Thromb Hemost* 2014;40:444–64. **3.** Asif A *et al. J Nephrol* 2017;30:347–62.

Diagnosis Algorithm for aHUS in Children



- **When to suspect genetic or immune background?**
- Early onset under two years old
- Consanguine marriage or family history
- Multiple episodes
- Abnormal complements; low C3

Loirat *et al* for HUS International, Pediatr Nephrol 2015

ULTOMIRIS®
(ravulizumab)
injection for intravenous use

INTRODUCTION to ULTOMIRIS

Eculizumab and aHUS: first successful treatment

The NEW ENGLAND JOURNAL of MEDICINE

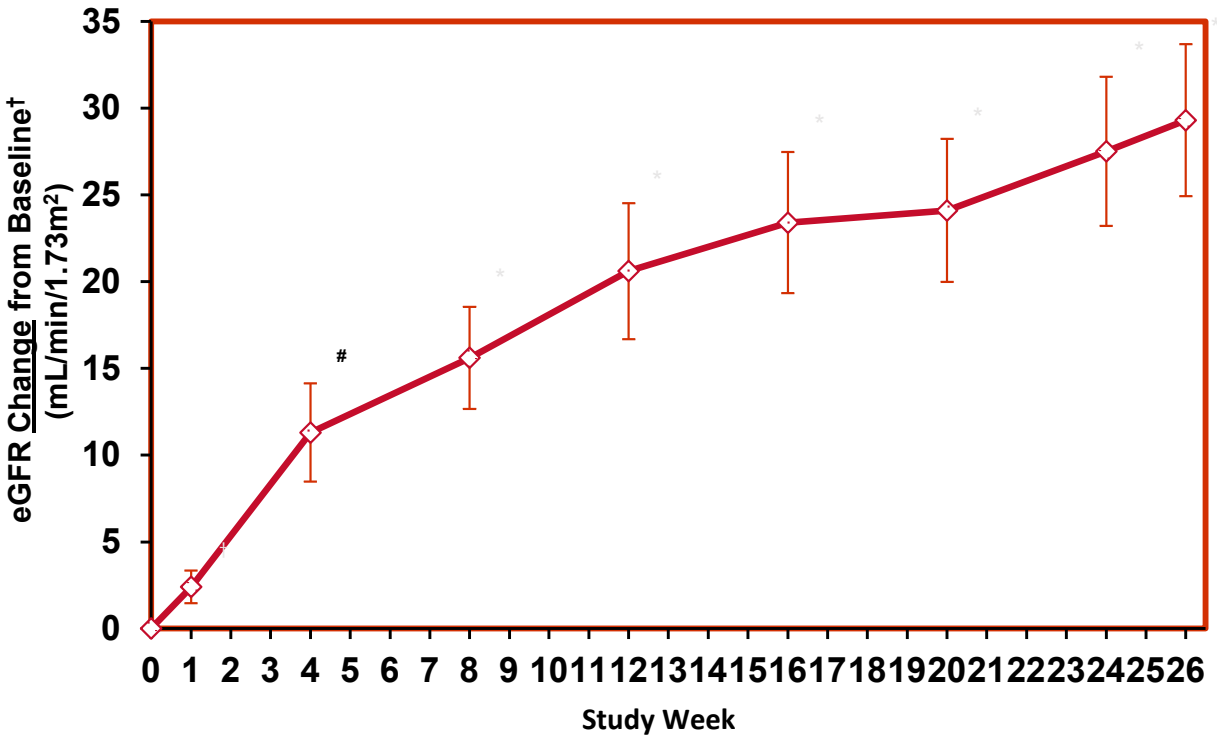
ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

Legendre CM et al. N Engl J Med 2013;368:2169-81

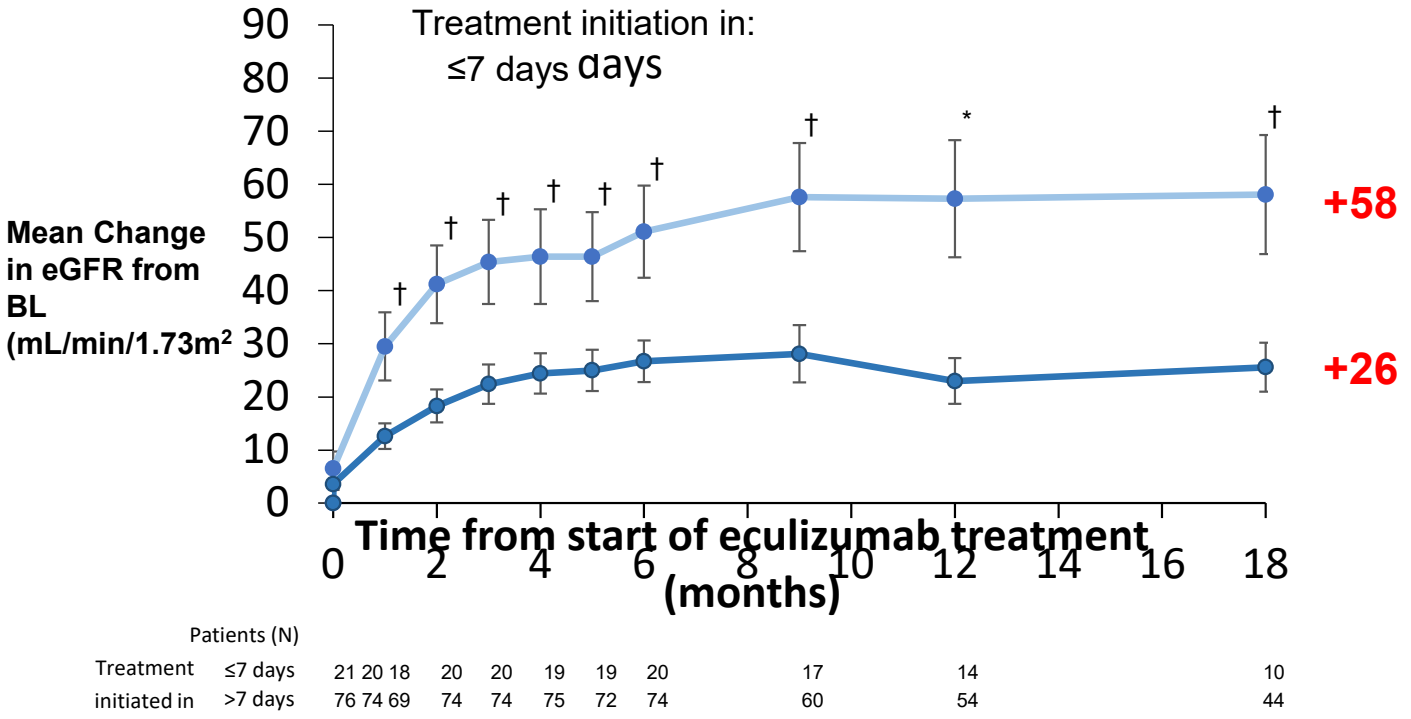
Rapid and Continued Improvement in eGFR in aHUS Patients with Ongoing Eculizumab Treatment



†Mean (SD) eGFR at baseline: 17.3 (12.05); Mean (SD) eGFR at Week 25: 47.0 (24.35).

Before Soliris, 100% of patients had eGFR <60 mL/min/1.73m^2

Significantly better recovery in eGFR in early treated patients

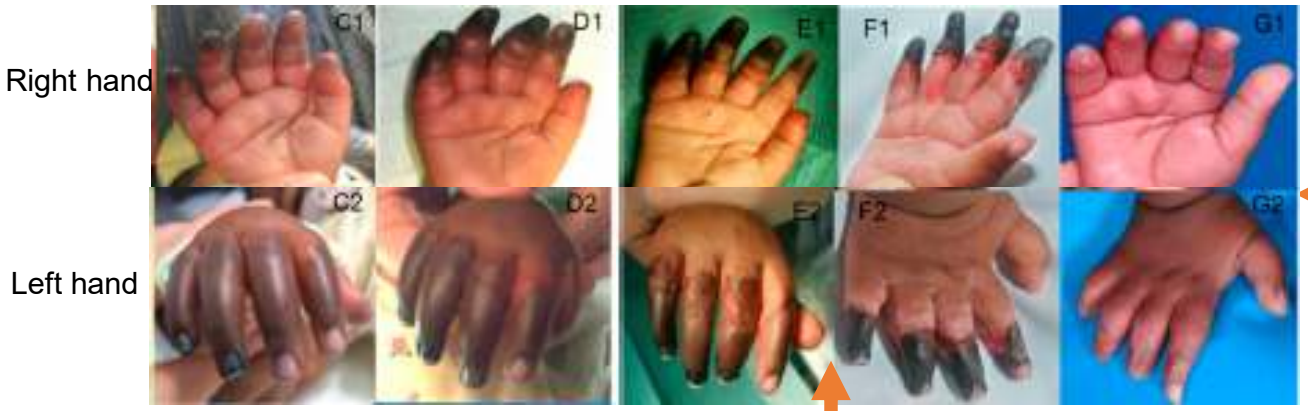


Data shown are mean change from baseline ± standard error
* p<0.05 and † p<0.01 ≤7 days vs >7 day group; BL, baseline

Eculizumab rescues distal ischaemic manifestations of aHUS

Ariceta *et al.* AJKD 2012
28-day-old child, 3.6 kg
- No mutation
- Leg skin necrosis, intestinal perforation
- **Eculizumab → remission within 3 days**
- Recovery of skin lesions and renal function
- **Follow-up 18 months, Screatinine 23 µmol/L, remission**

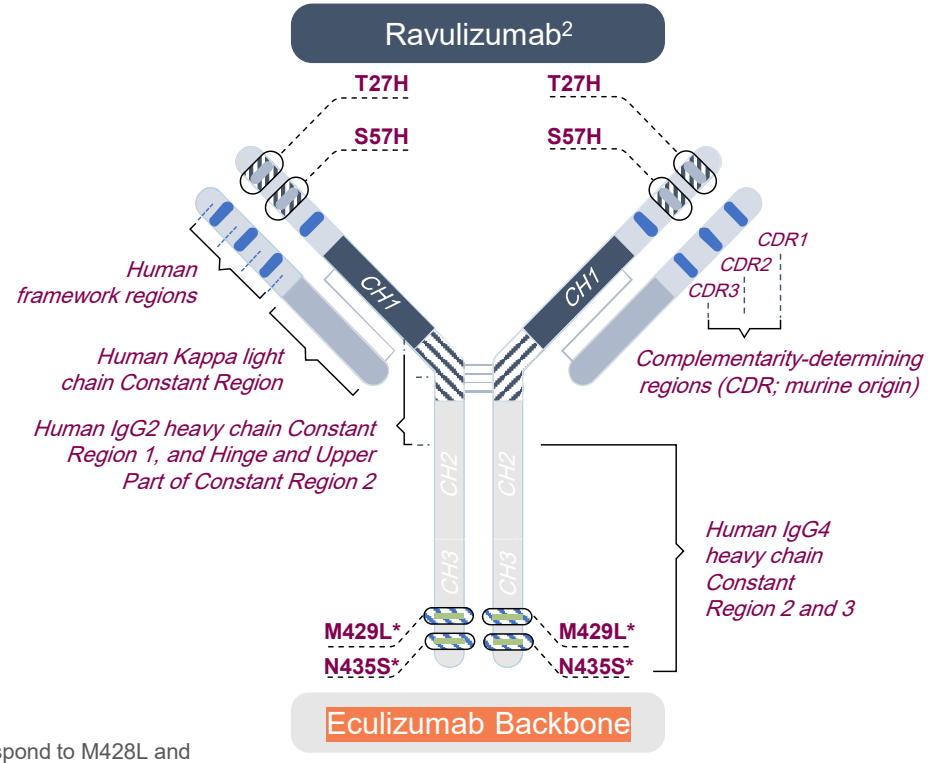
Malina *et al.* Pediatrics 2013
2-month-old child
- ESRD, multiple relapses despite plasma infusions
- C3 gain of function mutation
- At 9 months, acute ischaemia of feet and hands, resistant to PE
- **Eculizumab → immediate reversal of distal ischaemia**
- **Follow-up 22 months, remission**



ULTOMIRIS® (Ravulizumab) Indications

- **atypical hemolytic uremic syndrome (aHUS)** adults and pediatric patients one month of age and older
- **Paroxysmal Nocturnal Hemoglobinuria (PNH)** adult and pediatric patients one month of age and older
- **generalized Myasthenia Gravis (gMG)** adult patients anti-acetylcholine receptor (AChR) antibody-positive

Ravulizumab: Built on the backbone of Eculizumab, providing pH-dependent elimination of C5[1]



Modifications to Promote Release of C5 in the Endosome[2,3]

- Replacement of Tyr-27 and Ser-57 in variable heavy chain CDR-1 and -2 with His residues designed to accelerate pH-dependent dissociation from C5 in acidified endosomes
- Affinity for C5 at endosomal pH 6.0 is reduced by a factor of 36 but minimally impacted at pH 7.4

Modifications to Enhance FcRn Binding[2,3]

- Met-429 replaced with Leu and Asn-435 replaced with Ser in the heavy chain CH3 domain to enhance pH-dependent binding to FcRn
- Affinity for FcRn at endosomal pH is increased by a factor of 10

*M429L and N435S correspond to M428L and N434S under the EU numbering system, respectively

FcRn, neonatal Fc receptor; **IgG,** Immunoglobulin G; **MOA,** mechanism of action.

1. Roth A, et al. *Blood Adv.* 2018;2(17):2176-2185 **2.** Andrien BA Jr, Sheridan DL, Tamburini PP, inventors; Alexion Pharmaceutical, Inc, assignee. Anti-C5 antibodies having improved pharmacokinetics. US patent 9,079,949 B1. July 14 2015; **3.** Sheridan D et al. *PLoS One* 2018;13:e0195909.

ULTOMIRIS® is the first-and-only[a] long-acting C5 inhibitor for aHUS, which has been shown to resolve complement-mediated TMA in the majority of patients[b1,7]

IMMEDIATE AND COMPLETE

Complete **C5 inhibition** after the **first infusion of ULTOMIRIS®** in adult and paediatric patients[1,7]

SUSTAINED

Up to 8 weeks[c] of **sustained C5** inhibition and the possibility to live dialysis-free in adult and paediatric patients[1,7]

8 WEEKS[c]

With infusions every 8 weeks[c], and the possibility to have no more than seven treatment visits per year,[1] your aHUS patients can spend **less time undergoing treatment and more time on what matter most**

[a]As of today 12.02.2024 UAE SmPC Dec 2021. [b]In two phase 3 clinical trials: adult patients: 53.6% (n=56) and paediatric patients: 78% (n=18).[1,7]
[c]Starting 2 weeks after the loading dose, maintenance doses are administered once every 4 or 8 weeks (depending on body weight).[1]
aHUS, atypical haemolytic uraemic syndrome; TMA, thrombotic microangiopathy.

ULTOMIRIS (ravulizumab)

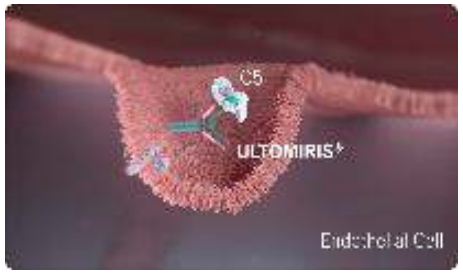
ULTOMIRIS®
(ravulizumab)
injection for intravenous use

MECHANISM OF ACTION

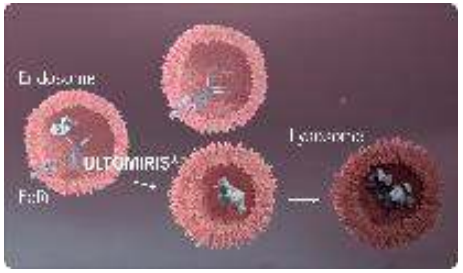
MECHANISM OF ACTION

With its extended half-life,[7-9] ULTOMIRIS® minimises the number of infusions your patients need

01 Both **ULTOMIRIS®** and eculizumab **bind to C5 in the bloodstream to prevent its activation**.[8]



02 **ULTOMIRIS®** is specifically engineered to **release C5 into the acidified endosome**, leaving C5 to be degraded by the lysosome.[7,8]



03 **ULTOMIRIS®** has also been engineered to bind to FcRn with greater affinity, with a half-life up to **4 times longer** than Soliris® **to provide immediate, complete and sustained inhibition of C5 for up to 8 weeks**.[1,8,9]

FcRn, Neonatal Fc receptor.

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PAEDIATRIC PATIENTS

With ULTOMIRIS®, immediate and complete C5 inhibition was observed from day 1 in paediatric patients[1,10]

Day 1

100% of paediatric patients demonstrated complete C5 inhibition with ULTOMIRIS® on Day 1*[1,10]

Day 8

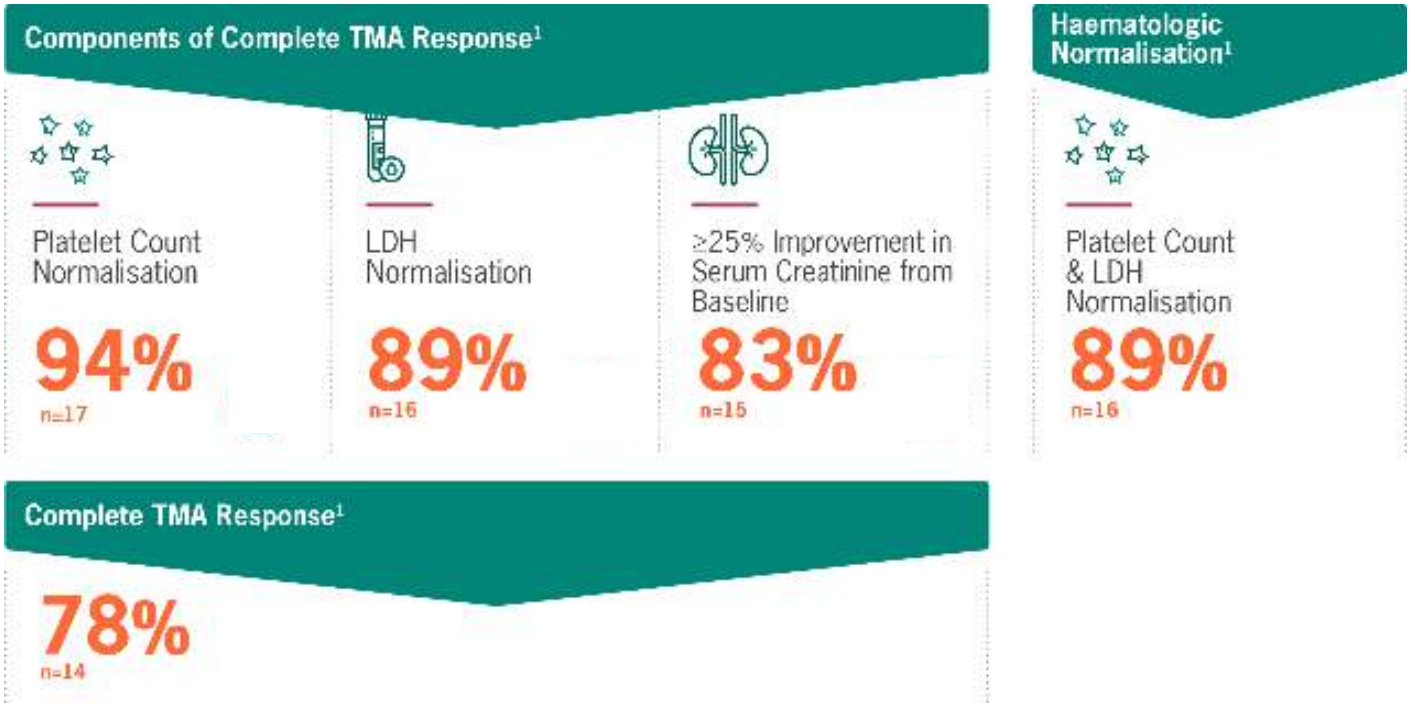
Mean platelet count increased~ 5-fold vs baseline[b1]

[a]As defined by free C5 in serum concentrations less than 0.5 µg/mL. [b]Mean platelet on day 8 was 296.67 x 10^9/L vs 60.5 x 10^9/L at baseline.[1]

ULTOMIRIS (ravulizumab)

With ULTOMIRIS®, over 70% of paediatric patients achieved a complete and sustained TMA response[1]

Paedriatic patients[a] who responded at week 26



[a]Total number of patients, n=18.[1]
LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

ULTOMIRIS (ravulizumab)

PAEDIATRIC PATIENTS. EFFICACY: Sustained

ULTOMIRIS® can help provide your patients with the opportunity to live dialysis-free while offering the potential for recovery of kidney function[1]

100% (6/6)

of paediatric patients who required dialysis at study entry were able to discontinue dialysis[a1]

88% (15/17)

patients improved by 1 or more CKD stages by Day 183, 14/17 improved by 2 or more stages[1]

eGFR improved by nearly 5x from baseline with ULTOMIRIS® in paediatric patients[b1]

Number of patients defined by the available data for each specific assessment at Day 183.[1]
[a]5/6 of which had discontinued dialysis by Day 43. No patient started dialysis during the study.[1]
[b]Median eGFR at Week 26 was 108 mL/min/1.73 m^2 vs 22.0 mL/min/1.73 m^2 at baseline.[1]
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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ULTOMIRIS®
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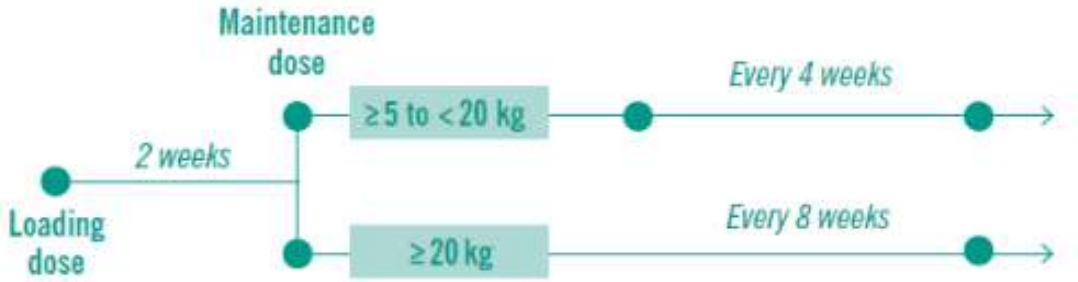
injection for intravenous use

DOSING

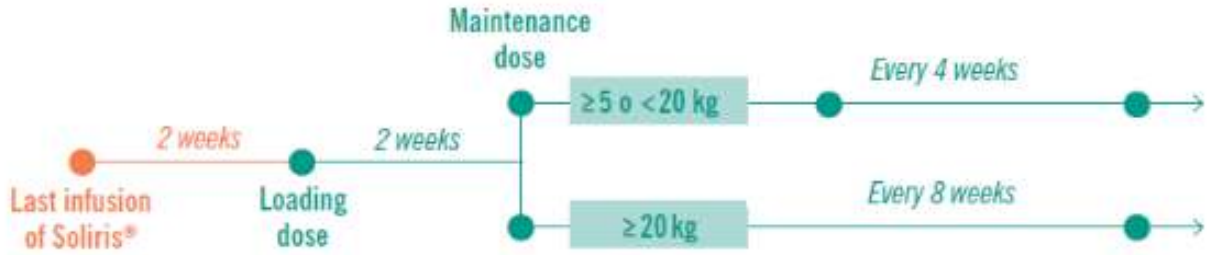
DOSING

With infusions every 8 weeks, and no more than 7 treatment visits per year*[1], your patients can spend less time undergoing treatment and more time on what matters most

Patients with no prior Soliris® treatment[1]



Patients switching from Soliris® to ULTOMIRIS®[1,3]



*Starting 2 weeks after the loading dose, maintenance doses are administered once every 4 or 8 weeks (depending on body weight).[1]
Dosing schedule is allowed to occasionally vary +/- by 7 days from the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS®), but the subsequent dose should be administered according to the original schedule.[1]
ULTOMIRIS® must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological or renal disorders.[1]
aHUS, atypical haemolytic uraemic syndrome.

ULTOMIRIS
(ravulizumab)

DOSING

ULTOMIRIS® is indicated in the treatment of patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naïve or have received Soliris® for at least 3 months and have evidence of a response to Soliris®[1]

aHUS, atypical haemolytic uraemic syndrome.

ULTOMIRIS®
(ravulizumab)
injection for intravenous use

SAFETY
no unexpected safety concerns identified,
The most common adverse reaction reported in paediatric patients was pyrexia.

Summary

- aHUS is a chronic, unpredictable, life threatening, genetic disease.
- Patients with TMA require rapid differential diagnosis to make immediate management decisions
- Persistent TMA in patients with triggering conditions after addressing the underlying condition may suggest aHUS.
- Don’t delay monoclonal antibody to block complement factor C5; especially if aHUS is highly suspected

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Monogenic forms of hypertention in childreh

Dr Mahdi Frehat

Consultant of pediatric Nephrology

Arab board of pediatric nephrology

European board of pediatric nephrology ESPN

RMS,QRCH

Definition of HTN in children

	ESH 2016		AAP 2017	
	0–15 years SBP and/or DBP percentile	16 years and older SBP and/or DBP values (mm Hg)	1–13 years SBP and/or DBP percentile	13 years and older SBP and/or DBP values (mm Hg)
Normal	<90th	<130/85	<90th	<120/80
High-normal Elevated HT	90th to <95th percentile	130-139/85-89	90th to <95th percentile	120/80 to 129/80
Hypertension	≥95th percentile	**≥ 140/90**	≥95th percentile	**≥ 130/80**
Stage I hypertension	95th percentile to the 99th percentile and 5 mm Hg	**140-159/90-99**	≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	**130/80 to 139/89 mm Hg**
Stage II hypertension	>99th percentile and 5 mm Hg	**160-179/100-109**	≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)	**≥140/90 mm Hg**
H				

boys

		SBP (mmHg) for percentile of height							DBP (mmHg) for percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	90th	125	126	128	130	131	133	134	79	79	79	80	81	82	82
→	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
→	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

girls

15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
→	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
→	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Modified from Task Force on High Blood Pressure in Children and Adolescents [7]. Boxed area corresponds to reference values of boys 16 years or older in which the reference values for adults are recommended. BP, blood pressure.

2016 ESH Guideline. J Hypertens 2016; 34: 1887-1920

Etiology of HTN IN children

- **Renal**
  - Renal parenchymal
    - Glomerulonephritides
    - Polycystic kidney disease (PKD)
    - Pyelonephritis
  - Obstructive uropathy
- **Vascular**
  - Renovascular
    - Main renal arterie
  - Coarctation of aorta

- **Endocrine**
  - Adrenal
    - Adrenal adenoma
  - Thyroid
    - Hyperthyroidism
    - Hypothyroidism
  - Parathyroid
    - Associated with hyperparathyroidism
  - Pituitary
    - Cushing syndrome
    - Pituitary tumors
- **Central**
  - Sympathetic nervous system abnormalities

- Monogenic disorders of hypertension

I. Gordon syndrome
II. Liddle syndrome
III. Glucocorticoid responsive aldosteronism (GRA)
IV. Apparent mineralocorticoid excess (AME)
V. Congenital adrenal hyperplasia (CAH)

Monogenic disorders of hypertension

are a group of diseases causing dysregulation of the renin–angiotensin–aldosterone system and are characterized by low plasma renin activity

Classification of monogenic HTN

(i) Excessive aldosterone synthesis

- familial hyperaldosteronism)

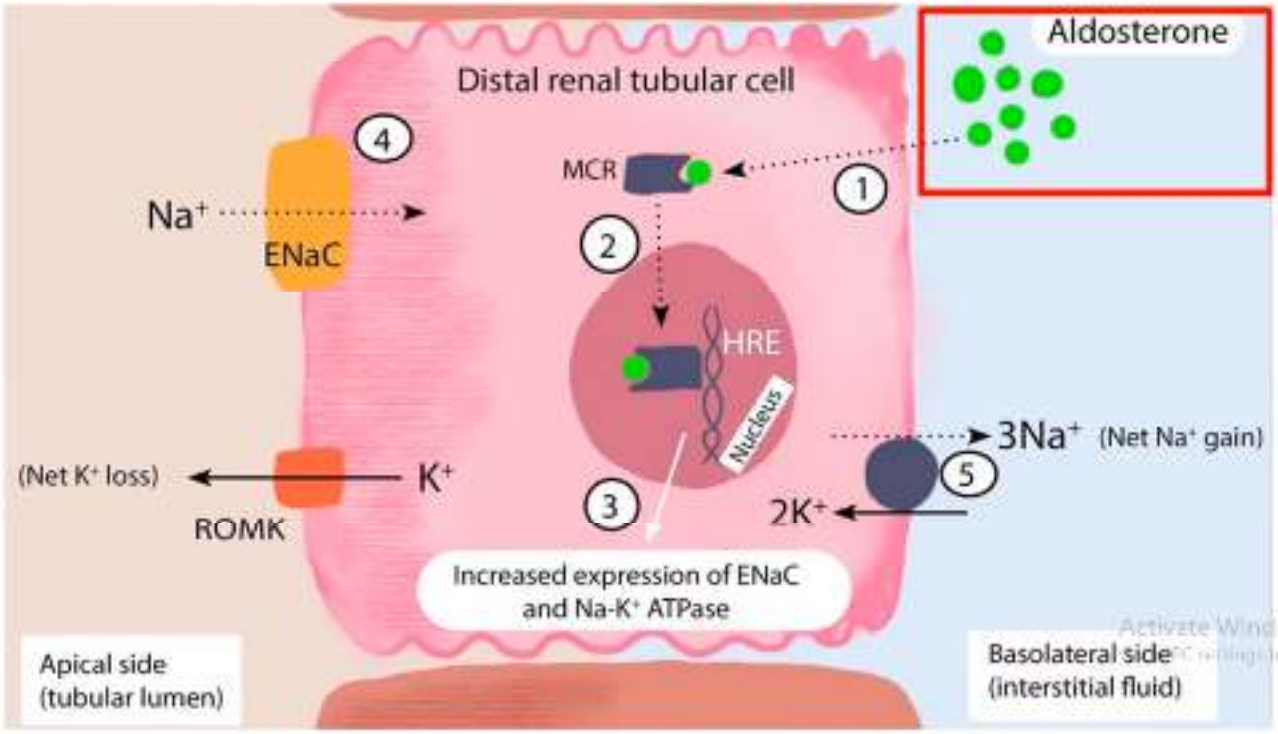
(ii) Dysregulated adrenal steroid metabolism and action

- apparent mineralocorticoid excess,
- congenital adrenal hyperplasia,

(iii) Hyperactivity of sodium and chloride transporters in the distal tubule

- Liddle syndrome
- pseudohypoaldosteronism type 2

Etiology and Pathogenesis:



familial hyperaldosteronism

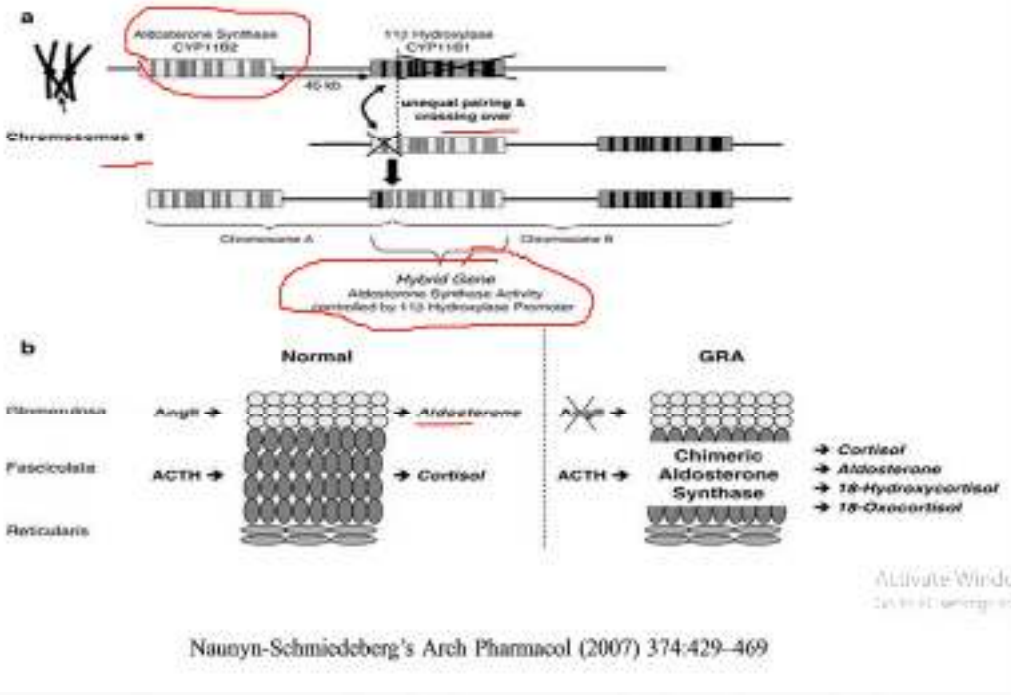
Table 1 Clinical features, genetic defects, and management of familial hyperaldosteronism (FHA) types I to IV

FHA type	Gene	OMIM genotype, locus	Protein	Inheritance	Age of onset	Hypertension; potassium	Clinical and biochemical features	Diagnosis	Therapy
Type I	*CYP11B1/ CYP11B2*	*610613, 8q24.3	Aldosterone synthase ①	AD	Variable, infancy to young adulthood	Moderate–severe; usually normal	Intracranial aneurysms, early-onset stroke; occasional bilateral adrenal hyperplasia	High ARR, long-PCR sequencing; aldosterone < 4 ng/dL following DST, high 18OHF	Low-dose steroids ± MRA or ENaC blocker
Type II	*CLCN2*	*600570, 3q27.1	Voltage-gated chloride channel-2 ②	AD	Variable, average age of 15 years[a]	Severe (incomplete penetrance reported); low in 9 patients[a]	Normal adrenals; rarely unilateral nodule or mild hyperplasia in two patients	High ARR (may be normal), genetic testing; family history ≥ 2 affected members differentiated from PA	MRA, other antihypertensive agents
Type III	*KCNJ5*	*600734, 11q24.3	G protein–activated inward rectifier potassium channel ③	AD	Infancy, early childhood[b]	Severe; usually very low[b]	Bilateral adrenal hyperplasia in severe forms; polyuria, metabolic alkalosis[b]	High ARR, genetic testing; high 18OHF; DST does not suppress aldosterone	MRA; bilateral adrenalectomy (severe forms)
Type IV	*CACNA1H*	*607904, 16p13.3	T-type voltage-gated calcium channel (Cav3.2) ④	AD	Variable, infancy to adulthood[c]	Severe, two normotensive; very low[c]	Unilateral nodule or adrenal hyperplasia in three patients; developmental delay or attention deficit in two patients[c]	High ARR, genetic testing; normal 18OHF; DST suppressed aldosterone in one patient	MRA

Glucocorticoid-remediable hyperaldosteronism (GRA). familial hyperaldosteronism type 1

- It is caused by an autosomal dominant inheritance
- The 11β-hydroxylase enzyme mediates synthesis of cortisol in the zona fasciculata in response to adrenocorticotropic hormone (ACTH)
- angiotensin II regulates synthesis of aldosterone synthase in the zona glomerulosa
- Mutation of a chimeric gene causing unequal crossing-over of the genes *CYP11B1* (11β-hydroxylase) and *CYP11B2* (aldosterone synthase) during meiosis
- In case of mutation the aldosterone synthase in inappropriately regulated by ACTH

Pathogenesis: GRA



Nanoyn-Schmiedeberg's Arch Pharmacol (2007) 374:429–469

GRH

- HTN, high risk of hemorrhagic stroke at an early age
- Hypokalemia
- metabolic alkalosis
- High aldosterone–renin ratio (ARR)
- Plasma renin is suppressed
- aldosterone levels are increased.
- Demonstration of the chimeric gene by long polymerase chain reaction is the gold standard for diagnosis

Management

- Dexamethasone (8–10 mg/m2/day is the first line of management.
- Mineralocorticoid receptor antagonists (eplerenone or spironolactone),
- ENaC antagonists (amiloride or triamterene)
- Dihydropyridine calcium channel blockers
- Therapy with angiotensin-converting enzyme inhibitors and beta-blockers are not advised due to suppressed renin.

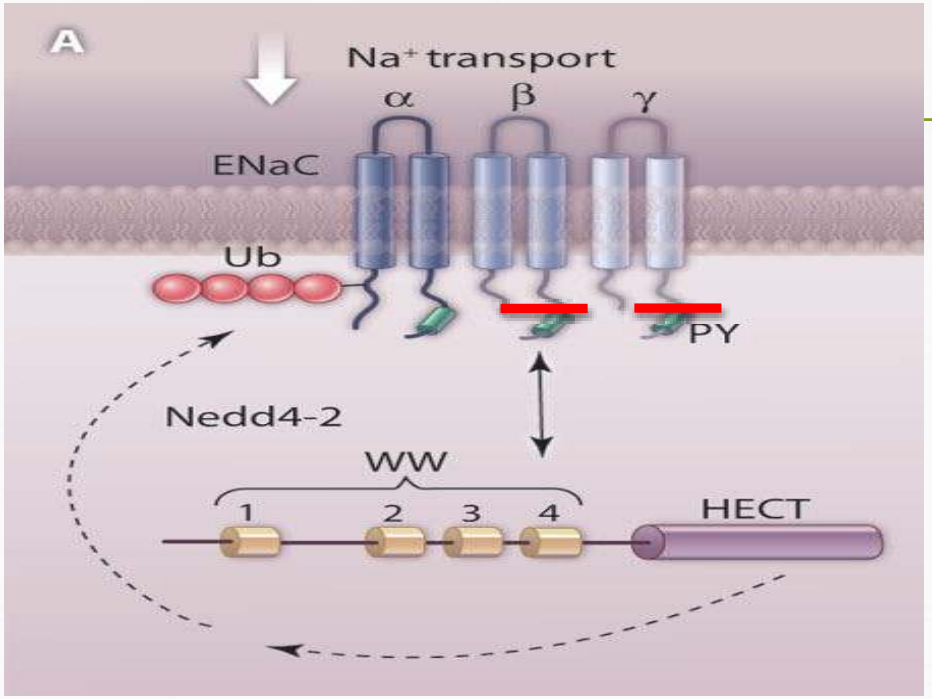
Primary aldosteronism

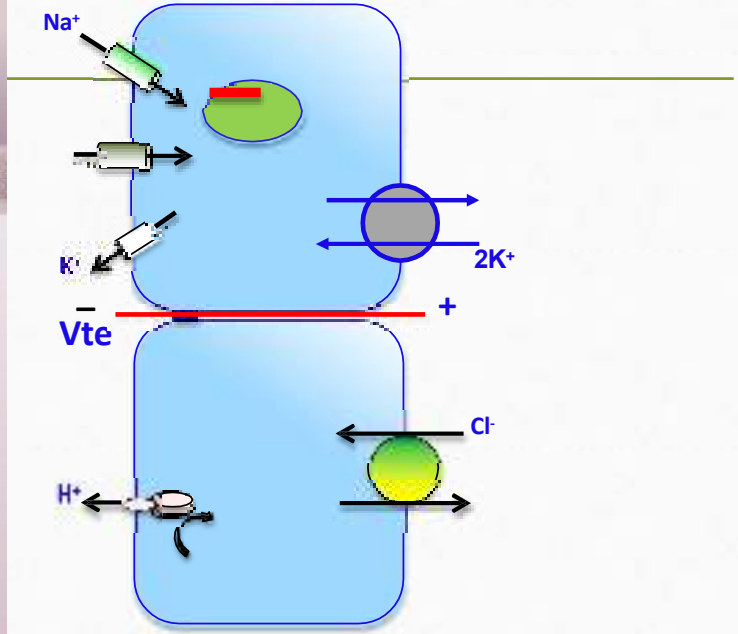
- is the most common hypertensive disorder that is associated with low renin and high aldosterone levels.
- High levels of aldosterone are due to increased secretion of this hormone by either adrenal cortical adenoma or bilateral hyperplasia of the gland.
- Aldosterone promotes Na+ reabsorption and K+ secretion in the distal nephron. As a result, plasma volume is increased with an increase in serum [Na+] and volumedependent

- refractory hypertension (HTN), hypokalemia, hypernatremia, metabolic alkalosis
- Plasma renin level is low because of volume expansion
- aldosterone levels are high due to autonomous secretion of this hormone by the adenoma or bilateral hyperplasia of the adrenal gland.

- Treatment Spironolactone or amiloride is the drug of choice for HTN
- Surgery
-

Liddle Syndrome





Liddle Syndrome

- Autosomal Dominant Inheritance
- Hypertension
- Hypokalaemia
- Metabolic alkalosis
- Low renin and aldosterone levels

Diagnosis

- low levels of urinary aldosterone or its metabolites (< 5 μg/day)
- genetic sequencing is confirmatory *SCNN1B - SCNN1C - SCNN1A*

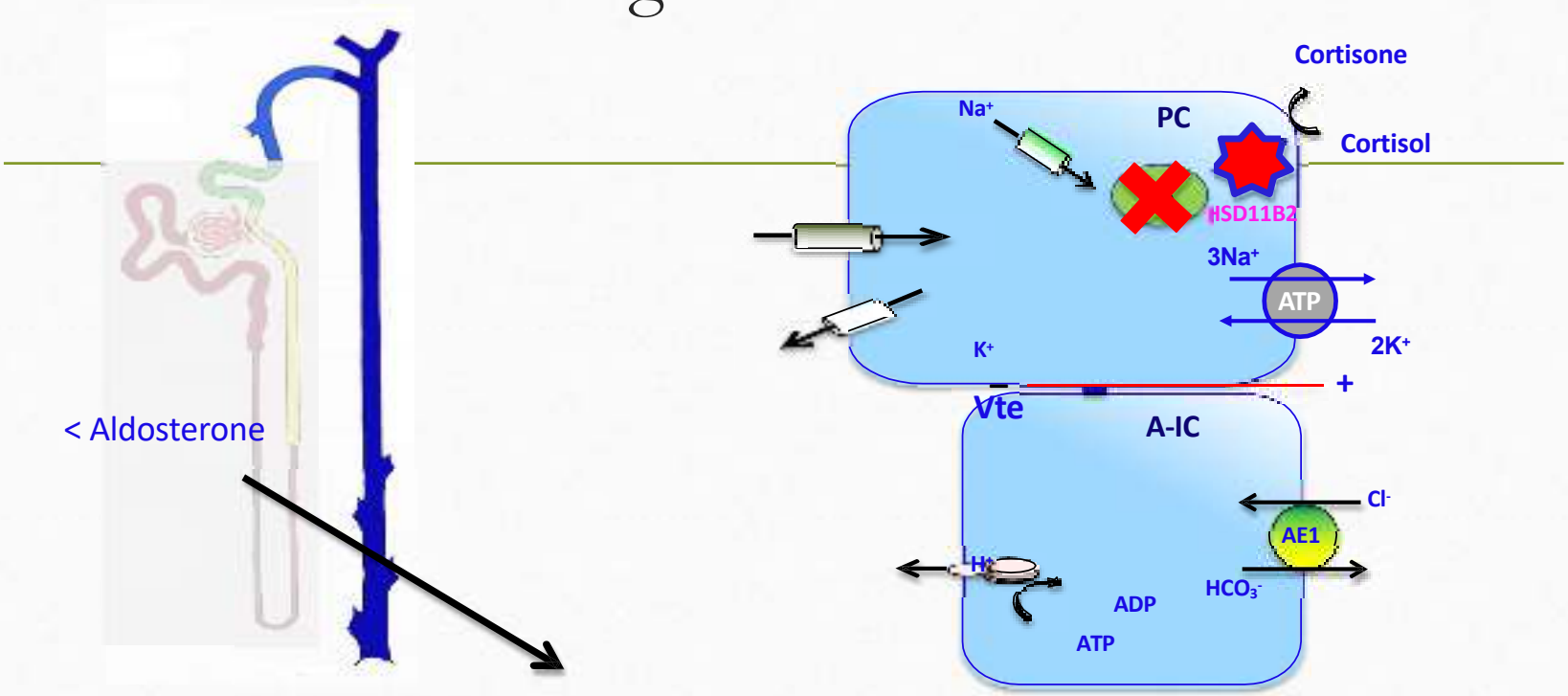
Management

- Dietary salt restriction
- Therapy with ENaC blockers (amiloride and triamterene)

Apparent mineralocorticoid excess

- (AME) is an autosomal recessive disorder
- deficiency of the 11β-hydroxysteroid dehydrogenase type 2

Pathogenesis of AME



Apparent Mineralcorticoid Excess Syndrome

- Failure to thrive and low stature
- Hypertension
- Hypokalaemia with metabolic alkalosis
- Low renin and aldosterone levels
- Polyuria and polydipsia
- Nephrocalcinosis
- Increased cardiovascular risk

The diagnostic hallmark

- elevated 24-h urinary free cortisol-to cortisone ratio (1.3–10; normal 0.5)
- or their metabolites ratio of tetrahydrocortisol (THF) + 5αTHF to tetrahydrocortisone (THE) (2.4–55; normal 1–1.3)
- Sequencing of the *HSD11B2* gene confirms the diagnosis.

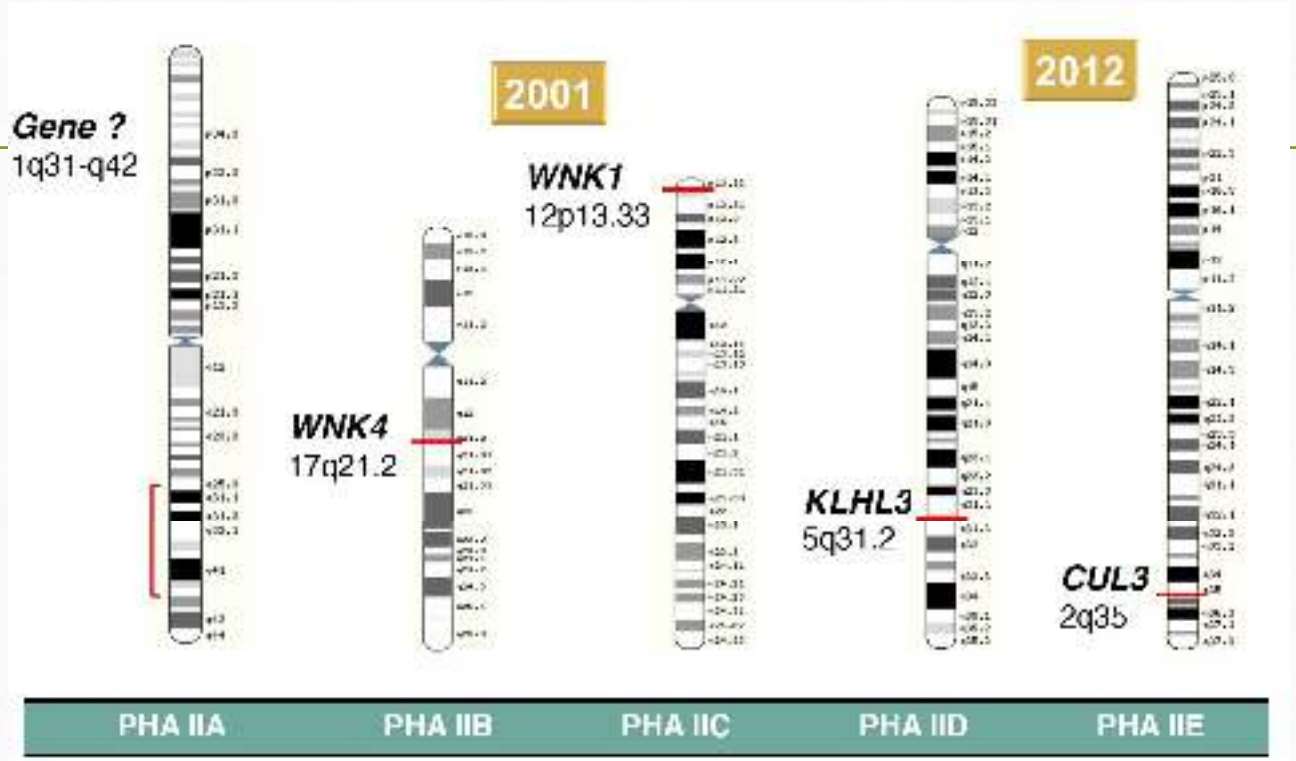
Management

- dietary salt restriction
- potassium supplementation
- Mineralocorticoid receptor antagonists (spironolactone or eplerenone),
- Spironolactone has been used at a dose of 2–12.5 mg/kg/day in AME. Eplerenone at 25–100 mg/day, approved for patients > 4 years,
- dexamethasone may be used in the lowest effective dose of
- Thiazides is controversial due to propensity to aggravate hypokalemia

Gordon Syndrome
Familial Hyperkaliemic Hypertension
PseudoHypoAldosteronism type II

- When mutations in WNK1 occur it will remove the inhibitory effect of WNK4 on Na/Cl cotransporter activity
- Overexpression and activity of Na/Cl cotransporter in the distal tubule results in PHA 2

Gene involvement



Additional clinical features

	WNK1	*WNK4*	*KLHL3*	*CUL3*
Hypertension	Least severe phenotype and metabolic disorder often precedes hypertension	Metabolic disorder often precedes hypertension	Recessive mutations are more severe and diagnosed at an earlier age than dominant mutations	Most severe phenotype. Presents at youngest age (>90% had hypertension <age 18.
Hyperkalaemia	Least severe	Yes	Dominant mutations had significantly higher serum K^+ than recessive mutations	Most severe Presents at youngest age
Metabolic Acidosis	Least severe	Yes	Yes	Most severe
Other features		Hypercalciuria Hypocalcaemia Decreased bone mineral density Renal calcium stones		Fertility likely affected in de novo mutations. Growth impairment most likely

Gordon Syndrome

Familial Hyperkaliemic Hypertension

PseudoHypoAldosteronism type II

Gordon is a mirror image of Gitelmam syndrome

autosomal dominant disease.

Hyperkalaemia

- Met. Acidosis
- Hypercalciuria
- Low Renin
- Hypertension

Treatment

.

- PHA II responds to thiazide diuretics such as HCTZ
- HCTZ decrease the overactivity of Na/Cl cotransporter

Table 2 Clinical, biochemical, and genetic characteristics of hypertension associated with low plasma renin activity (PRA) and low plasma aldosterone[a]

Disease	Gene	OMIM genotype, locus	Protein	Inheritance	Age of onset	Hypertension; potassium	Clinical and biochemical features	Diagnostic markers	Therapy
Apparent mineralocorticoid excess	*HSD11B2*	*614232,16q22.1	11β-Hydroxysteroid dehydrogenase-2 ⑨	AR	Infancy, early childhood (later in type 2)	Severe; markedly low (mild in type 2)	LBW, growth failure, polyuria, metabolic alkalosis, nephrocalcinosis, hypercalciuria	Urinary THF + 5αTHF:THE > 1 or free cortisol:cortisone > 0.5	MRA, ENaC blocker; dexamethasone
Congenital adrenal hyperplasia	*CYP17A1* *CYP11B1*	*609300,10q24.32 *610613,8q24.3	17α-Hydroxylase ⑩ 11β-Hydroxylase ⑪	AR AR	*CYP17A1*: adolescence, *CYP11B1*: childhood	Variable; hypokalemia in *CYP17A1* defect	*CYP17A1*: delayed puberty, sexual infantilism *CYP11B1*: ambiguous genitalia, short stature, advanced bone age, precocious puberty	Screen: low morning cortisol *CYP17A1*: high progesterone relative to 17α-progesterone *CYP11B1*: high 11-deoxycortisol and deoxycorticosterone	Hydrocortisone replacement, MRA if required
Glucocorticoid resistance	*NR3C1*	*138040,5q31.3	Glucocorticoid receptor ⑧	AD, AR	Usually adults; 9 children aged 2–12 years reported	Severe in children, low or normal	Adrenal hyperplasia, virilization, poor growth, precocious puberty, hypoglycemia, metabolic alkalosis	High urinary free cortisol; cortisol > 50 nmol/L after overnight DST	Dexamethasone, MRA if required
Activating MR mutation	*NR3C2*	*600983,4q31.23	Mineralocorticoid receptor ⑧	AD	Adolescence, adults	Severe, low	Hypertension exacerbated in pregnancy	Exacerbation of hypertension by spironolactone	Finerenone, ENaC blocker
Liddle syndrome									
Type 1	*SCNN1B*	*600760	ENaC ⑬ β subunit	AD	Late childhood, adolescence; can occur at any age	Usually severe but might be normal; low to normal	Metabolic alkalosis, family history in 90%	Low urinary aldosterone (< 5 μg/day) or its metabolites	ENaC blocker
Type 2	*SCNN1G*	*600761,16p12.2	γ Subunit	AD					
Type 3	*SCNN1A*	*600228, 12p13.31	α Subunit	AD					
PHA type II									
PHA 2A	–	1q31–q42	–	AD	Adolescence, adulthood (infancy, childhood in types 2D and 2E)	Variable; hyperkalemia with rare instances of normokalemia	Variable metabolic acidosis, short stature, hypercalciuria in *WNK* mutations	Thiazide trial: normalizes blood pressure, electrolytes	Thiazide
PHA 2B	*WNK4*	*601844,17q21.2	With no lysine kinase 4 ⑭	AD					
PHA 2C	*WNK1*	*605232,12p13.33	With no lysine kinase 1 ⑮	AD					
PHA 2D	*KLHL3*	*605775,5q31.2	Kelch-like 3 ⑫	AD, AR					
PHA 2E	*CUL3*	*603136,2q36.2	Cullin 3 ⑫	AD					

Thank you for your attention

CLINICAL AND GENOMIC PROFILING OF ALPORT SYNDROME

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Kasr Al Ainy Faculty of Medicine
Cairo University

ASNRT, JSNRT Congress – IPNA TC
Amman, 05 June 2024
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Nephrology

Clinical Genomics

مركز البحوث الطبية والطب التجديدي

E.C.R.R.M

Egypt Center for Research and Regenerative Medicine

OUTLINE

- Historical background and Classification
- Histopathology
- Hidden genetics behind AS
- Clinical phenotype
- Diagnostic approach and therapeutic options
- Real world cases
- Key message

ALPORT SYNDROME

- Genetically and phenotypically heterogeneous disorder of glomerular, cochlear, and ocular basement membranes

- Caused by variants in the α-chain (3, 4 or 5) of the collagen IV genes

ALPORT SYNDROME

- Alport syndrome can be transmitted as an X-linked, autosomal recessive, or autosomal dominant disorder

- Individuals with Alport syndrome have a significant lifetime risk for kidney failure, as well as sensorineural deafness and ocular abnormalities

ALPORT SYNDROME

- The availability of effective intervention for Alport syndrome–related kidney disease makes early diagnosis crucial

- Yet, this can be impeded by the genotypic and phenotypic complexity of the disorder

1927

Dr. Cecil Alport

published a series on “hereditary familial congenital haemorrhagic nephritis” where he described its association with deafness and the gender differences in disease severity

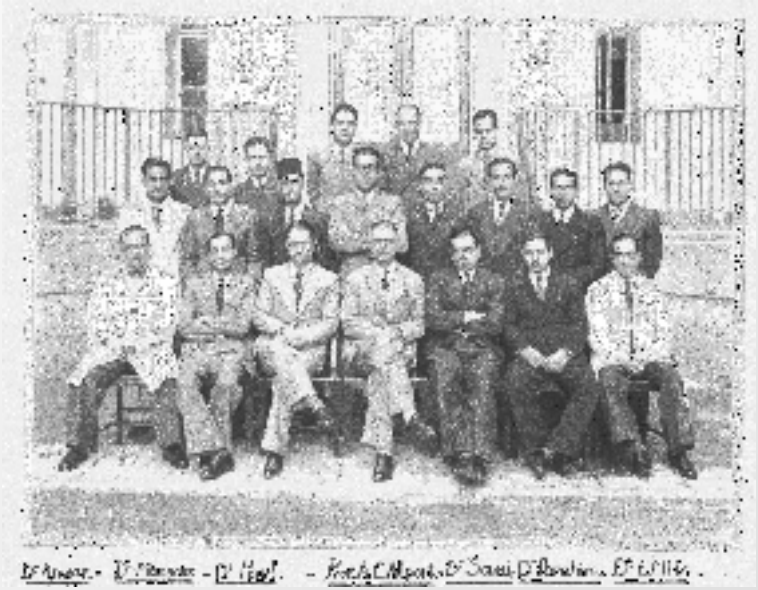
https://www.ncbi.nlm.nih.gov/pubmed/20773074


HEREDITARY FAMILIAL CONGENITAL HAEMORRHAGIC NEPHRITIS.

1927

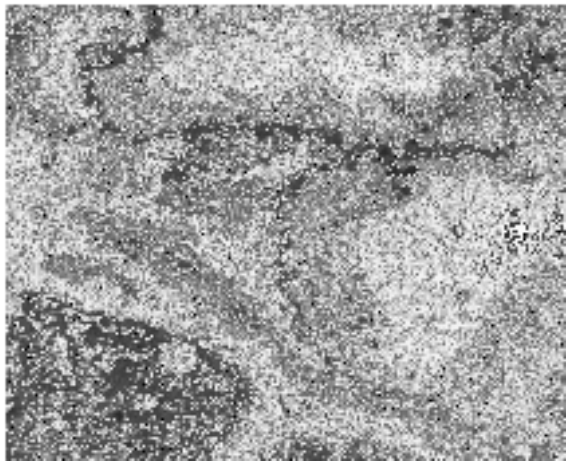
Dr. Cecil Alport

He initially believed the etiology of the disorder was an individual susceptibility to a toxin of an unknown organism, probably belonging to the streptococcal group



1970

The pathogenesis of the disorder known as Alport syndrome remained unknown until early 1970's, when advances in electron microscopy allowed the identification of characteristic abnormalities in GBMs



1988

Dr Curtis L. Atkin

mapped for the first time the affected gene to the long arm of the X chromosome (Xq22)

Am. J. Hum. Genet. 42:249–255, 1988

Mapping of Alport Syndrome to the Long Arm of the X Chromosome

Curtis L. Atkin,* Sandra J. Hasstedt,† Lynelle Menlove,‡ Lisa Cannon,‡ Nancy Kirschner,‡[1] Charles Schwartz,‡[2] Kim Nguyen,‡ and Mark Skolnick‡

Departments of *Medicine and Biochemistry, †Human Genetics, and ‡Medical Informatics, University of Utah Medical Center, Salt Lake City

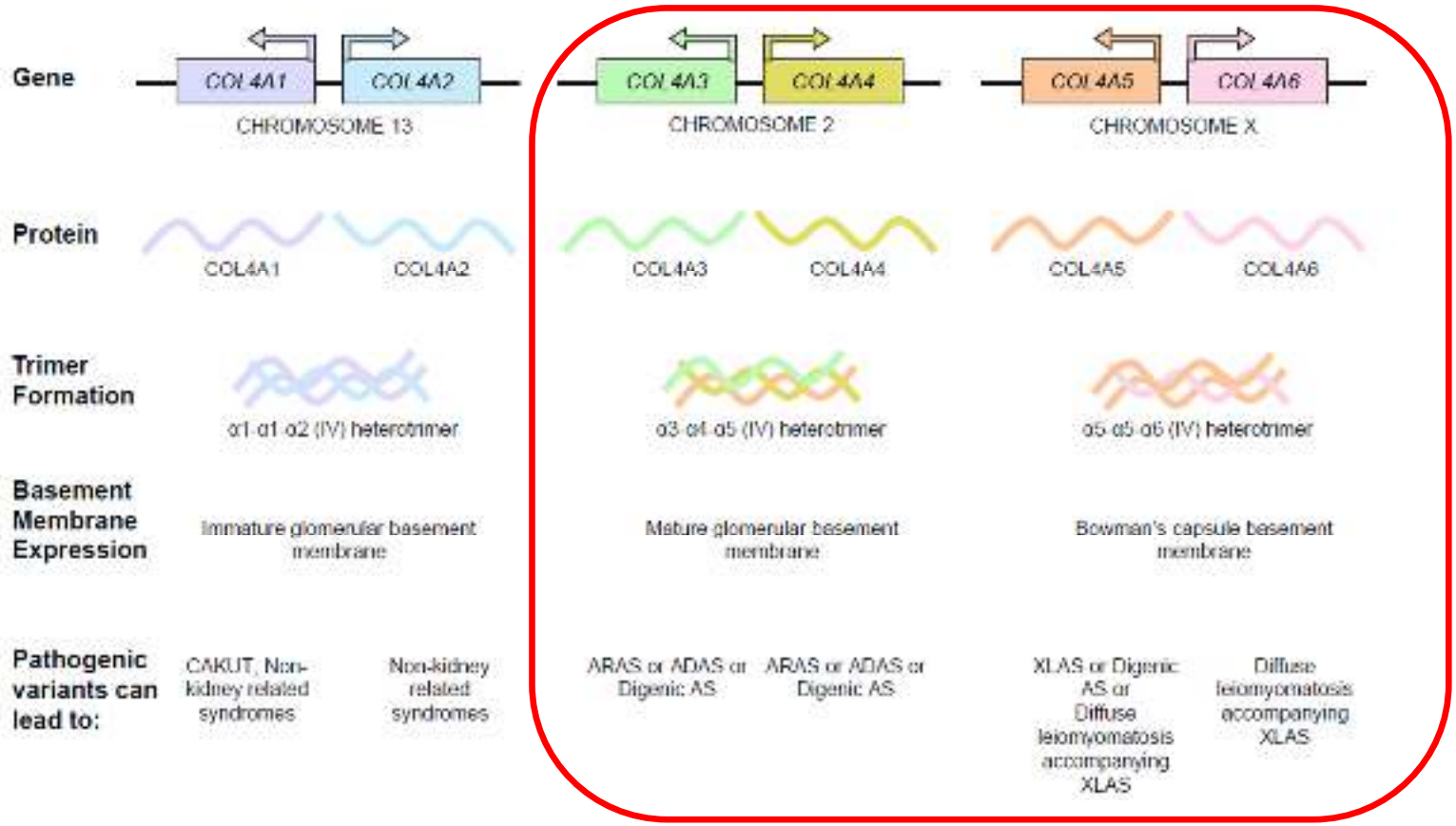
Summary

Alport Syndrome Classification

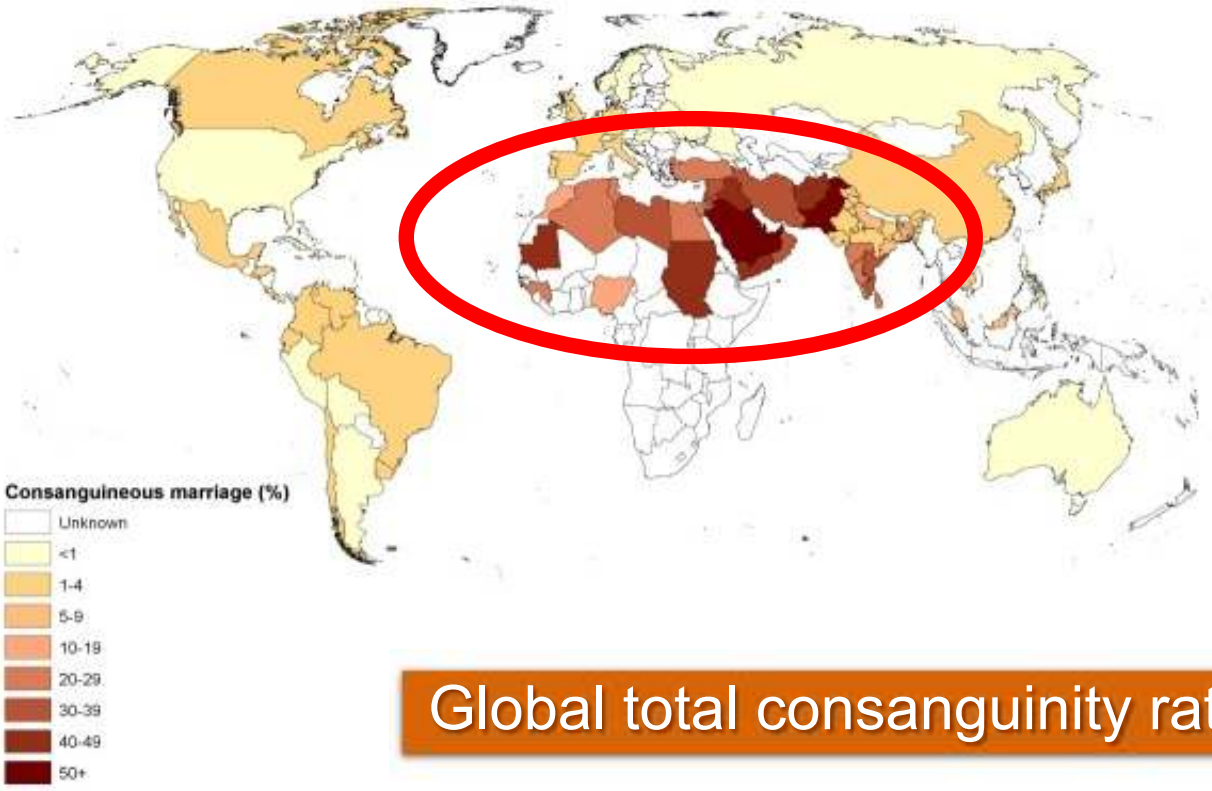
Inheritance	Affected Gene(s)	Genetic State
X-Linked	*COL4A5*	Hemizygous (males) Heterozygous (females)
Autosomal	*COL4A3* or *COL4A4*	Recessive (homozygous or compound heterozygous) Dominant (heterozygous)
Digenic	*COL4A3*, *COL4A4*, and *COL4A5*	*COL4A3* & *COL4A4* variants in *trans* (recessive) *COL4A3* & *COL4A4* variants in *cis* (dominant) Variants in *COL4A5* and in *COL4A3* or *COL4A4* (non-Mendelian)
Suspected	—	Clinical, pedigree, tissue data are highly suggestive of Alport syndrome but genetic data are not confirmatory

Kashtan. AJKD 2021

Type IV collagen from gene to protein trimerization to disease



Gregorio et al., Kidney Medicine 2023



Global total consanguinity rates

Romeo & Bittles. Human Heredity 2014

Genetic Testing: Why, How, Whom, and When?

Indications for Genetic Testing for Alport Syndrome

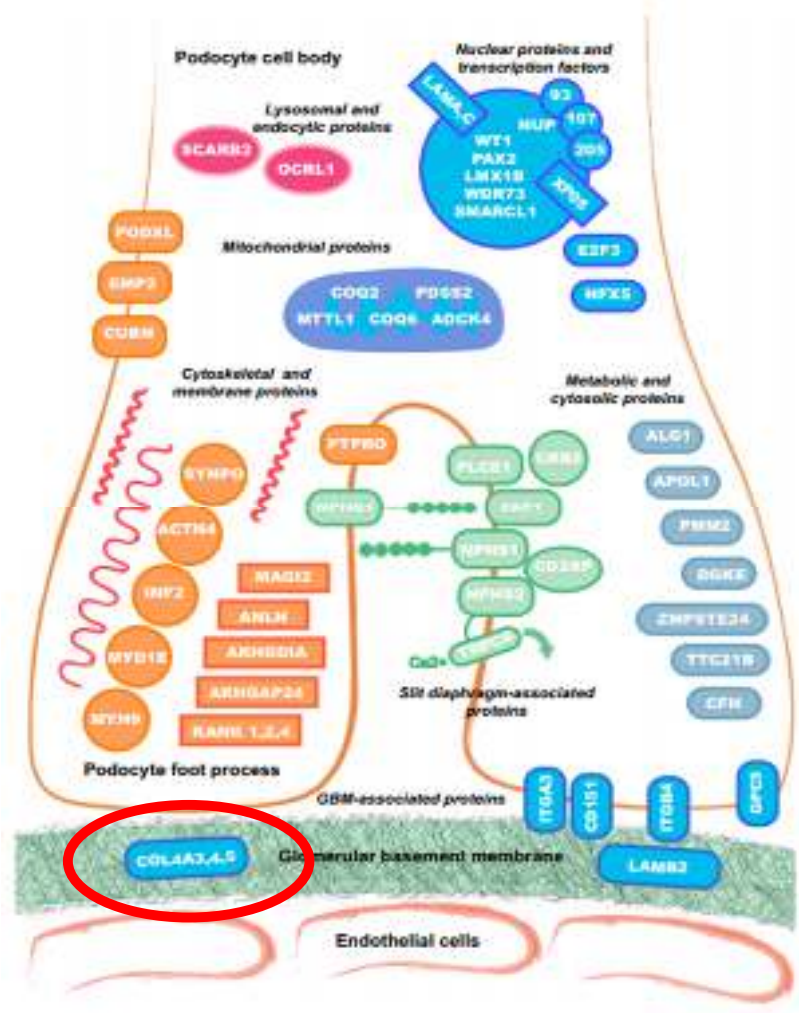
(COL4A3, COL4A4, and COL4A5 Genes)

Persistent glomerular hematuria, plus ≥1 of the following:

- Clinical findings
  - Sensorineural deafness
  - Anterior lenticonus and/or characteristic retinopathy
- Family history findings
  - Hematuria
  - CKD/kidney failure
  - Deafness associated with CKD
- Pathologic findings on kidney biopsy
  - Negative or nonspecific routine immunofluorescence
  - Thin glomerular basement membranes
  - Characteristic glomerular basement membrane thickening, lamellation, and scalloping
- Other
  - Steroid-resistant FSGS (as part of NGS panel for FSGS, or WES)

Kashtan. AJKD 2021

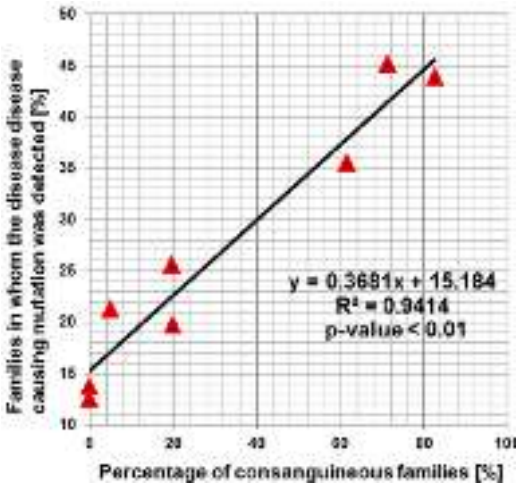
Genetic variants associated with SRNS grouped according to location and function within the glomerular filtration barrier



BASIC RESEARCH www.jasn.org

A Single-Gene Cause in 29.5% of Cases of Steroid-Resistant Nephrotic Syndrome

Carolin E. Sadowski,* Svjetlana Lovric,* Shazia Ashraf,* Werner L. Pabst,* Hasan Yasin Gee,* Stefan Kohl,* Susanne Engelmann,* Virginia Vega-Warner,† Humphrey Fang,* Jan Halbritter,* Michael J. Somers,* Weizhen Tan,* Shirlee Shril,* Inga Fessi,* Richard P. Lifton,‡ Bertil Bockenhauer,§ Sherif M. Emma,‖ Jameela A. Kari,¶ Rasha Zenker,** Markus J. Kemper,** Dominik Müller,†† Heon M. Fathy,‡‡ Hasnaa A. Soliman,§§ the SRNS Study Group, and Friedhelm Hildebrandt*‖



WGS in SRNS

Soliman et al., under review

جينوم مصر
EGYPT GENOME

Genetic Testing for Alport Syndrome

Advantages and Limitations

Advantages

- Confirmation of diagnosis
- Genotype has implications for:
  - Prognosis and monitoring
  - Identification of at-risk relatives
  - Predicting risk for recurrence in future pregnancies
  - Personalized treatment (future)

Limitations

- ~10% of patients with clinically and pathologically confirmed Alport syndrome have mutations that are not identified by NGS or WES
- Significance of some variants will be uncertain
- Insurance coverage is variable
- Access to genetic counseling is variable

Kashtan. AJKD 2021

Genomic Testing

Identifying
genetic basis in testing naive patients

Re-evaluation
of previously tested patients to unravel the underlying genetic defect that was overlooked by gene panel/ES testing

Enabling genomic-driven healthcare
In nephrology

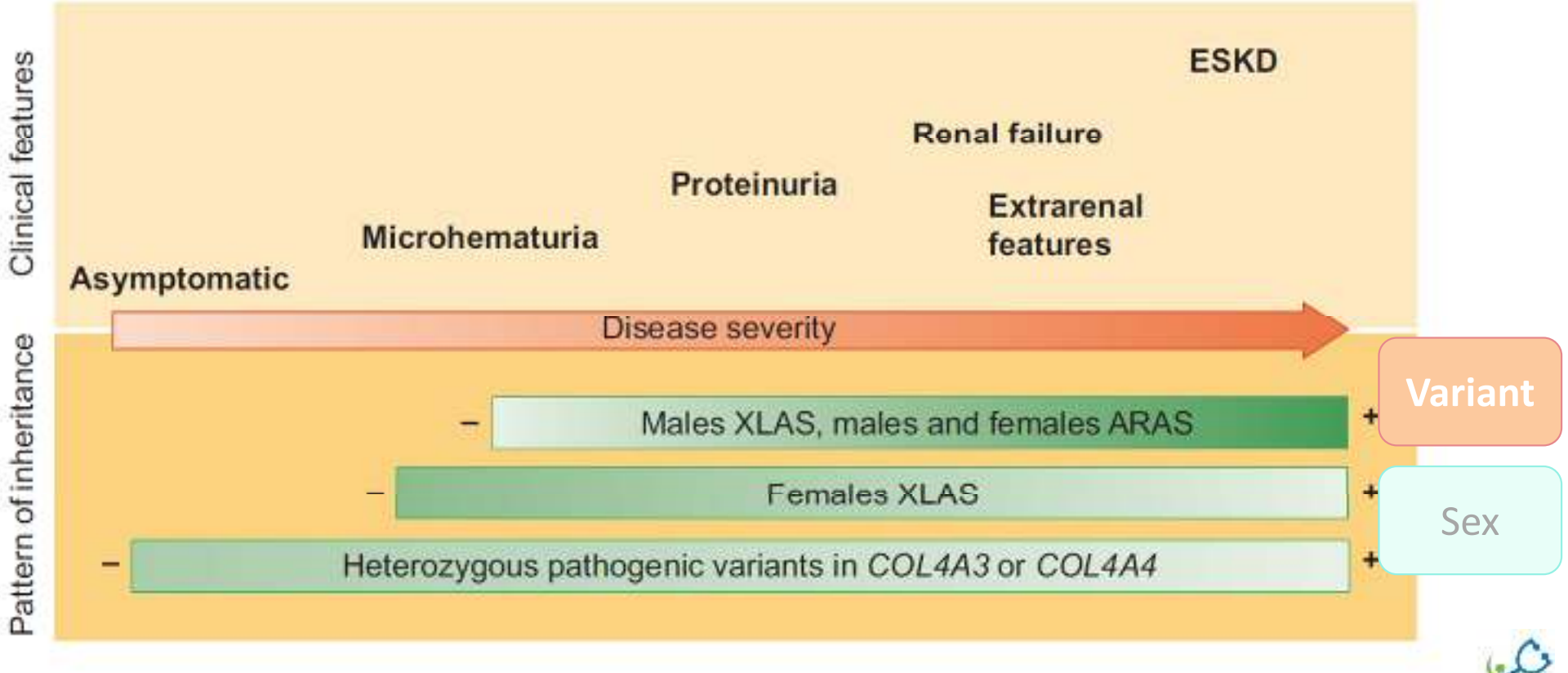
Precision Medicine

New trends and dimensions in kidney diseases prevention and treatment

Are clinicians Keeping Pace with Genetic and Genomic Discoveries?

Increasing move towards genetic and genomic understanding of Alport syndrome

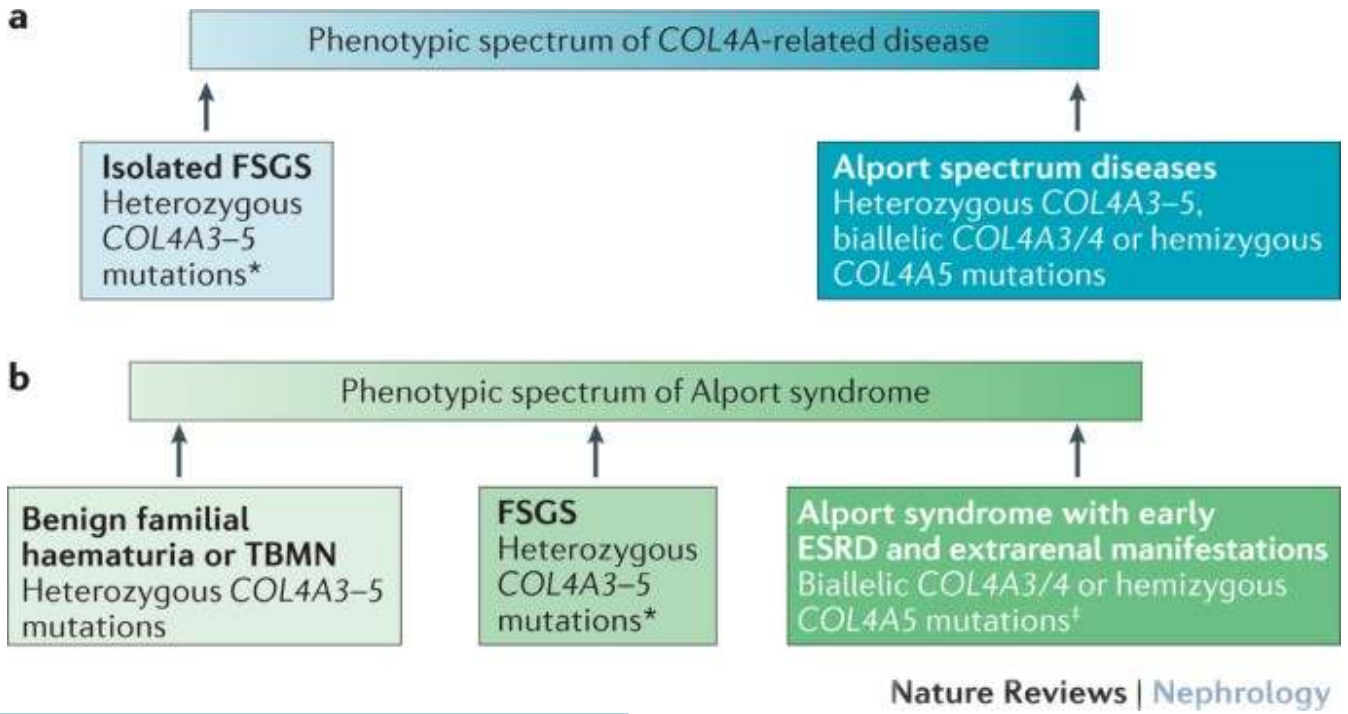
Clinical spectrum of Alport syndrome according to the pattern of inheritance



Torra et al., Clin. Kidney J. 2020

Factors that affect disease severity

Gregorio et al., Kidney Medicine 2023



Individuals with any genetic variant that interferes with the normal synthesis, deposition, and function of the collagen IV α345 network of basement membranes

Stockman et al., Nat. Rev. Nephrol 2016

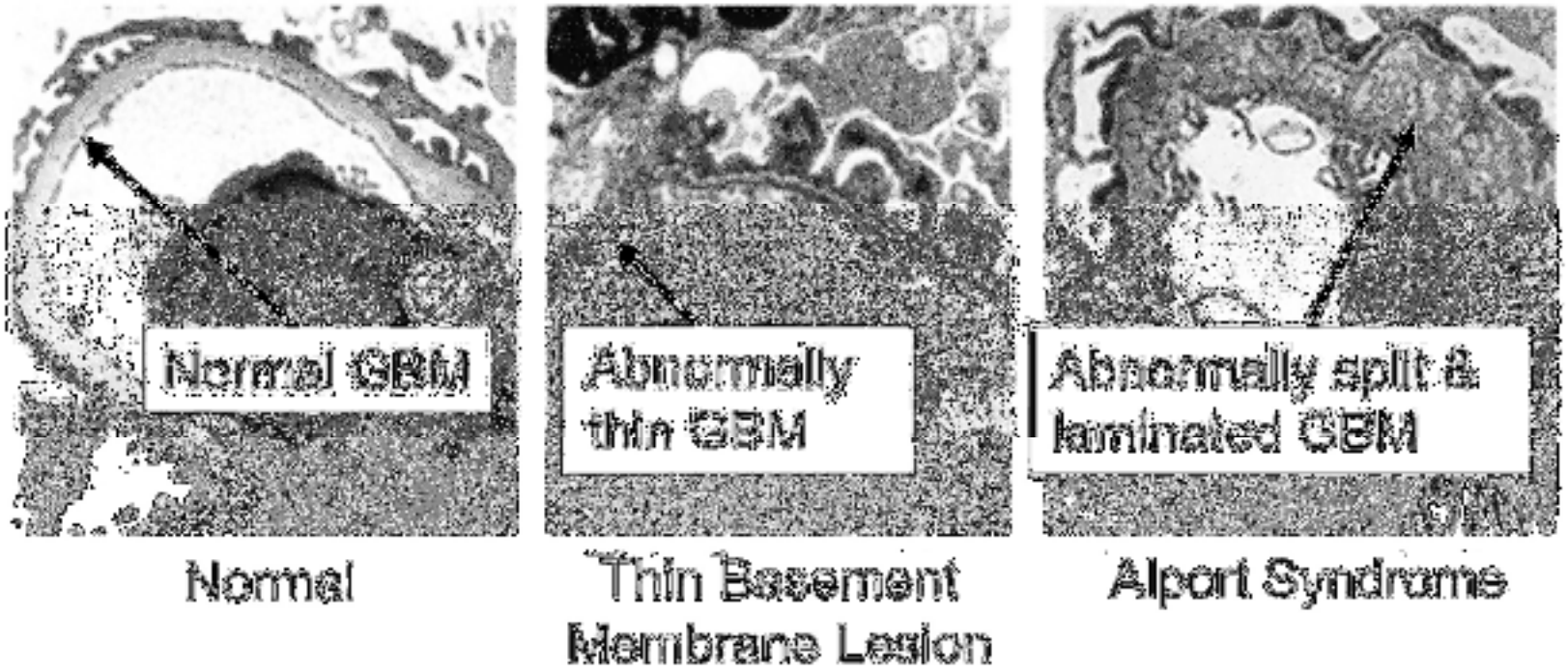
Clinical characteristics and GBM features observed in Alport syndrome

Clinical Manifestations	Microscopic hematuria	Albuminuria with some macroscopic hematuria attacks possible; eye deformities and hearing loss may begin	Albuminuria and hematuria worsen; eGFR declines; eye deformities and hearing loss worsens	**Kidney failure**
Electron Microscopy Pathology	Some GBM thinning and splitting may be observed	GBM begins to thicken; splitting may worsen	GBM has a basketweave appearance; Some glomerulosclerosis and foot process effacement may be visible	**Severe GBM abnormalities; extreme glomerulosclerosis and foot process effacement**

Mild ⟷ **Severe**

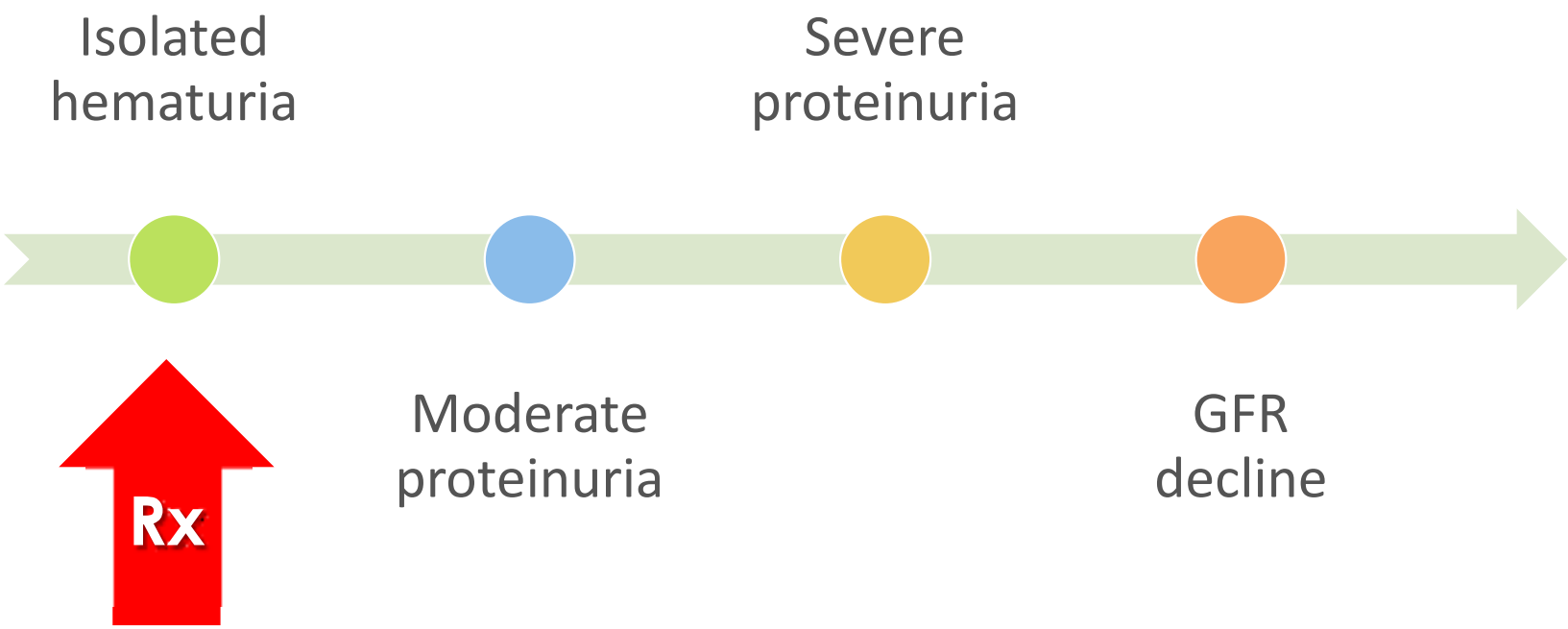
Gregorio et al., Kidney Medicine 2023

COL4A3, COL4A4, and COL4A5 variantss cause dysfunctional glomerular basement membrane (GBM) in Alport syndrome



Warady et al., Kidney Medicine 2020

Alport Nephropathy Milestones

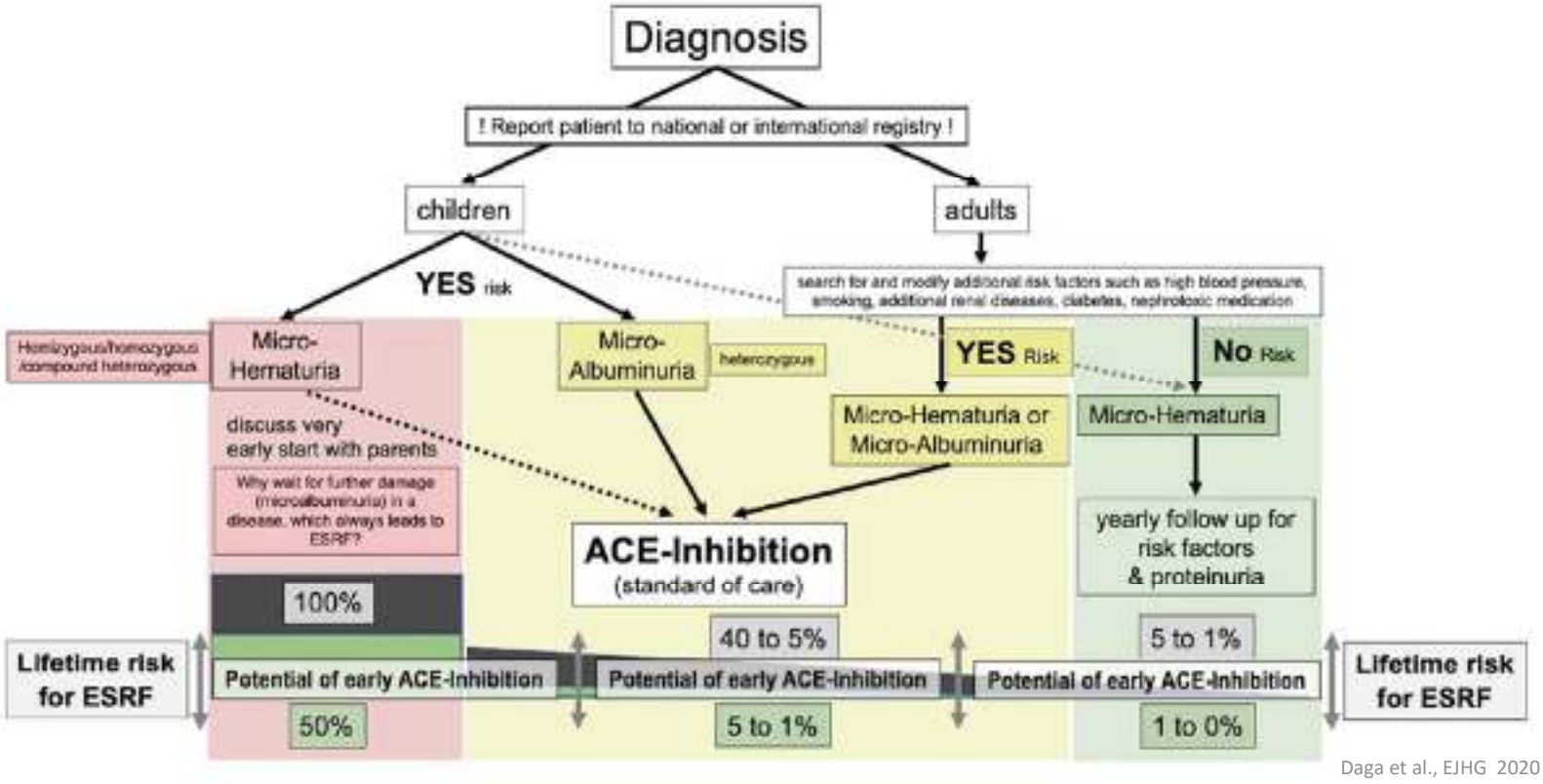


Dramatically delay progression to kidney failure if initiated before declining GFR

Imperative

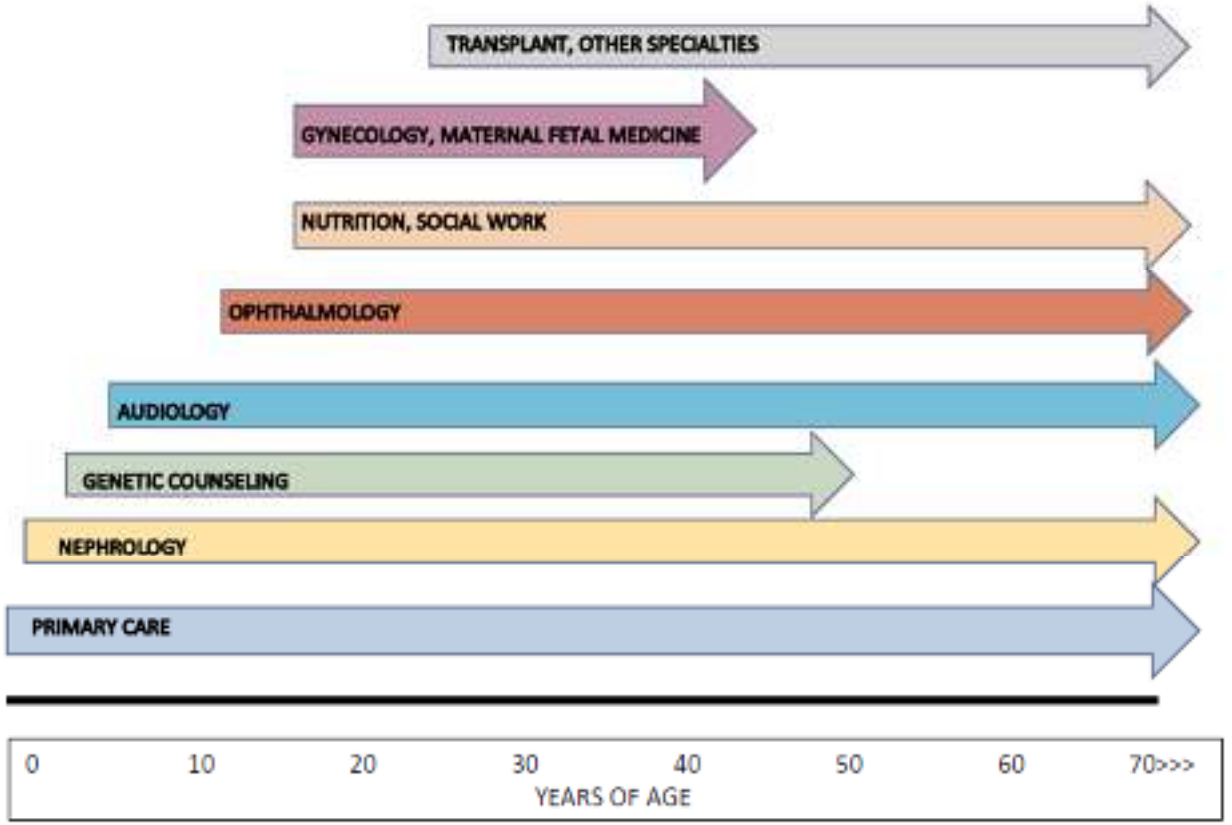
Ameliorate the natural history of AS–related kidney disease

Current standard of care treatment recommendations and individual lifetime risk for ESKD according to the gene variant and additional risk factors



Daga et al., EJHG 2020

Timeline for Multidisciplinary Care for Alport Syndrome



Kashtan, Journal of multidisciplinary Healthcare 2021

ALPORT SYNDROME TREATMENT

- ✓ ACEi and ARBs are currently the mainstay of therapy, reducing albuminuria and slowing progression, which is the most marked with **early intervention**.
- ✓ **SGLT2is** have promise and are already being used as adjunctive therapy to ACEi and ARBs, while awaiting larger clinical trials in Alport syndrome and other proteinuric conditions.

Table 1. Current Phase 2 Clinical Trials Testing Safety and Efficacy of Different Agents in Alport Syndrome.

Agent	Class	Sponsor	Study Population	Clinical Trials Link
ELX-02	Aminoglycoside analog	Eloxx Pharmaceuticals	Alport syndrome (nonsense mutations)	https://clinicaltrials.gov/ct2/show/NCT05448755
Atrasentan	Endothelin A receptor antagonist	Chinook Therapeutics U.S., Inc	IgA nephropathy FSGS Alport syndrome Diabetic kidney disease	https://clinicaltrials.gov/ct2/show/NCT04573920
Sparsentan	Dual endothelin Angiotensin Receptor Antagonist	Travere Therapeutics	FSGS Minimal change IgA nephropathy IgA vasculitis Alport syndrome	https://clinicaltrials.gov/ct2/show/NCT05003986
R3R01	Lipid-modifying	River 3 Renal Corp	Alport syndrome FSGS	https://clinicaltrials.gov/ct2/show/NCT05267262
Hydroxychloroquine sulfate (HCQ) Benazepril hydrochloride	HCQ ACEi	Shanghai Children's Hospital	X-linked Alport syndrome	https://clinicaltrials.gov/ct2/show/NCT04937907

ACEi, angiotensin-converting enzyme inhibitor; FSGS, focal and segmental glomerulosclerosis; HCQ, hydroxychloroquine.

- In recent years, there has been renewed interest in **elaborating the therapeutic spectrum further**, and several agents have been or are currently in clinical trials

- These novel therapeutics highlight **the growing knowledge in Alport syndrome** and provide optimism for improved clinical outcomes in the future.

Gregorio et al., Kidney Medicine 2023

CASE 1

- A 4-year-old boy is evaluated for fever.
- Urinalysis shows 50 to 75 RBCs/HPF
- Urine culture is negative.
- Repeat urinalysis several weeks later again shows hematuria and he is referred to a pediatric nephrologist
- FHx: his mother states that she has hematuria since childhood but has been told that she likely has a benign disorder.

What next?

CASE 1

- A 4-year-old boy is evaluated for fever.
- Urinalysis shows 50 to 75 RBCs/HPF
- Urine culture is negative.
- Repeat urinalysis several weeks later again shows hematuria and he is referred to a pediatric nephrologist
- FHx: his mother states that she has hematuria since childhood but has been told that she likely has a benign disorder.

Hemizygous pathogenic variant in *COL4A5*

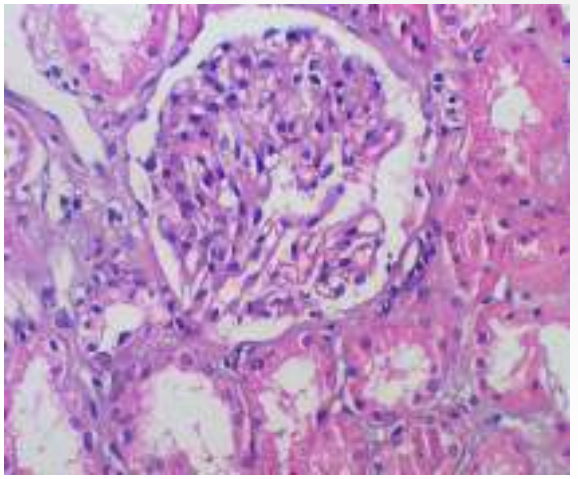
CASE 2

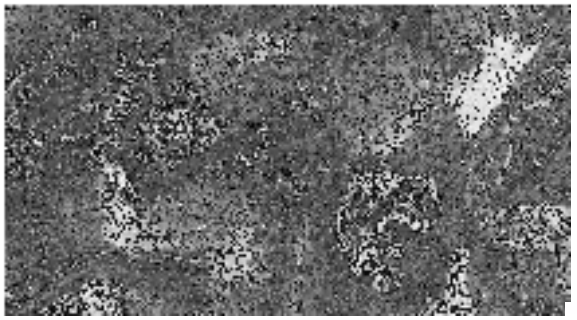
- Mother: transformative management
  - Proteinuria U P/Cr ratio 1.5 mg/mg, CKD 2, Cr: 1.6 mg/dl
- Transplantation strategy: donor selection
  - Avoid mother as potential donors
- Prediction of extra-renal involvement:
  - Auditory
  - Ocular
- Cascade screening
  - Presymptomatic genetic testing counseling

CASE 2

- A 15-years-old female adolescent
- Consanguineous parents
- Nephrotic syndrome at the age of 12 years
- No apparent extra-renal manifestations
- K Bx at age 14 years: FSGS (LM) FPE (EM)

- **What next?**





CASE 2

- A 15-years-old female adolescent
- Consanguineous parents
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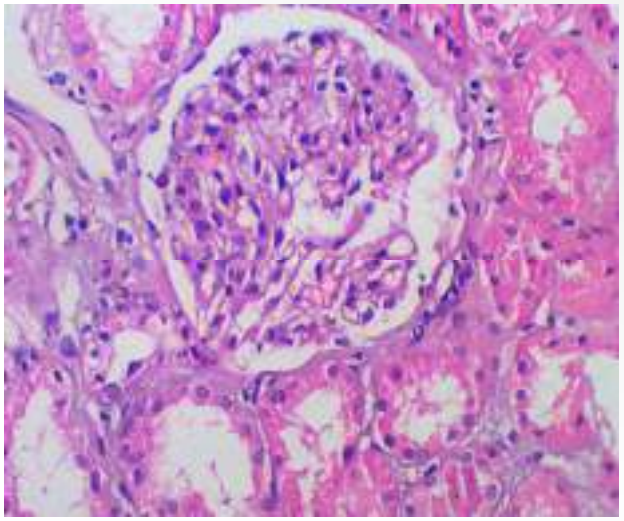
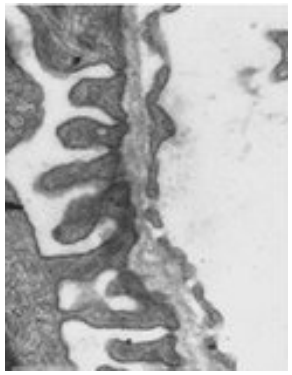
- No apparent extra-renal manifestations
- K Bx at age 14 years: FSGS (LM) FPE (EM)

- K Bx at the age of 18 years: GBM splitting and lamellation (EM)





CASE 2

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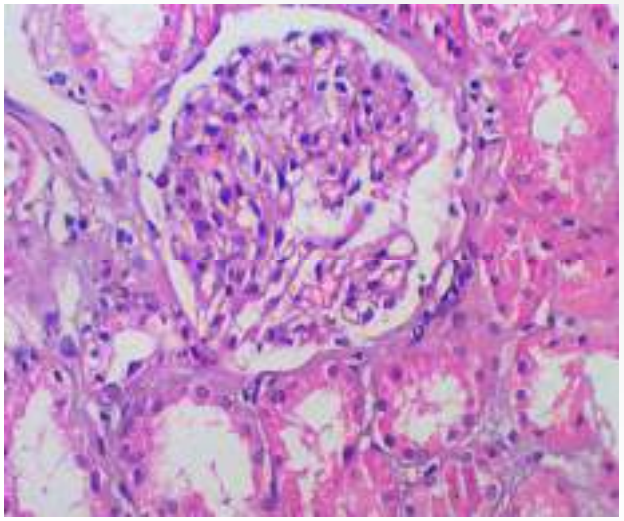
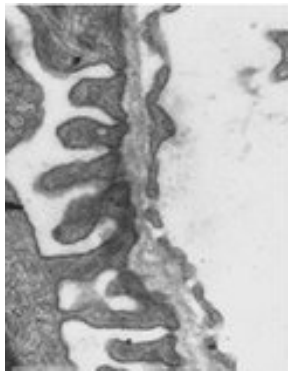




✓ ES: homozygous pathogenic variant in the *COL4A3* gene

CASE 2

- Transplantation strategy: donor selection
  - Avoid parents as potential donors
- Prediction of extra-renal involvement:
  - Auditory
  - Ocular
- Cascade screening
  - Presymptomatic genetic testing counseling
- Reproductive counseling
  - Preimplantation genetic diagnostics

Key Message

AS is an **inherited disorder caused by pathogenic variants** in COL4A3, COL4A4, or COL4A5, encoding the α3-α4-α5(IV) chains expressed in the **mature GBM** of the kidney

It is **phenotypically heterogeneous** presenting as a broad spectrum of disease influenced by genetic factors in affected individuals

ACEi and ARBs are currently the **mainstay therapeutics** while awaiting **larger clinical trials** reflecting renewed interest in elaborating the therapeutic spectrum further

Edwin Smith Medical papyrus

1600 BC

Oldest Medical Textbook

Nephrotic syndrome diverse presentation case study

DR. REEM HANI ALHADIDI MD

CONSULTANT PEDIATRIC NEPHROLOGY

HEAD OF PEDIATRIC DEPARTMENT-

NEW SALT HOSPITAL –MOH 2024

1st case

A 3 year-old girl presented to the pediatric nephrology clinic with generalized edema that had originated periorbital and then progressed to cover here entire body. There was no family history of edema. her weight was 15 kg height was 97 cm (25th percentile), and body mass index (BMI) 0.63

Positive family history of diabetes.

Product of a non-consanguineous marriage.

Negative family history of renal disease.

Laboratory investigations

1. Normal kidney function
2. hypoalbuminemia, proteinuria (4+)
3. hyperlipidemia
4. protein-to-creatinine ratio of 3.5
5. normal thyroid function
6. C3&C4 normal
7. Vitamin D 14.65 (Deficiency < 20)

Diagnosis and Treatment

Diagnosis: Idiopathic nephrotic syndrome

Treatment: Prednisolone 60 mg/m^2 for one month to be tapered over 6 months

Response to Treatment:

Symptoms: Improved

Proteinuria: Disappeared within 12 days after initiating steroid treatment

Complications:

Glucose in Urine: +3 several times

Blood Sugar Levels: 300-400 mg/dl

HbA1c: 7.9

Endocrinology Consultation and Diabetes Management

Pediatric Endocrinologist consulted

Treatment:

Insulin Therapy: Total: 1U/kg/day

Short-acting insulin: Administered before each meal, three times per day

Long-acting insulin glargine: Administered once per day

Lifestyle:
Healthy diet
Regular exercise

Lab Results:
Celiac Screening Test: Negative
C-peptide: 3.4 (normal range: 0.81-3.85)
Anti-GAD Antibodies: Negative
Anti-Islet Cell Antibodies: Negative

I started to follow up urine for glucose instead of protein

Test Name	Result	Ref. Range	Unit
HUH URINE PH	5.0 Acid		
HUH URINE GLUCOSE	NEGATIVE		
HUH URINE PROTEIN	+3		
HUH URINE WBC	2-4		/HPF
HUH URINE RBC	20-22		/HPF

KEY: "L"=Abnormal low, "H"=Abnormal high, "*"=Critical value

Test Name	Result	Ref. Range	Unit
HUH URINE PH	5.0 Acid		
HUH URINE GLUCOSE	+3		
HUH URINE PROTEIN	NEGATIVE		
HUH URINE WBC	0-1		/HPF
HUH URINE RBC	0-1		/HPF
HUH URINE KETONES	NEGATIVE		

KEY: "L"=Abnormal low, "H"=Abnormal high, "*"=Critical value

Treatment Adjustment and Outcome

Decision:

Tapered steroids rapidly

Initiated mycophenolate mofetil

Outcome:

HbA1c decreased from 7.9 to 6.3

No diabetic complications (retinopathy, neuropathy)

Follow-Up and Relapse Management

Two Months Later:

Developed cough and runny nose

Experienced edema and proteinuria (first relapse)

Treatment:

Restarted on prednisolone

Administered human albumin

Complications:

Blood glucose levels increased

Management:

Initiated insulin sliding scale

Steroid-Induced Diabetes Mellitus (SIDM)

Recognized complication of glucocorticoid therapy for over six decades.

Rare among children in developing countries.

Clinical Challenges:

- *Difficult to detect clinically.*
- *Rarity of case reports and studies.*

Screening for SIDM:

- Recommended for all patients on medium to high doses of steroids.
- Vital for early detection and management.

Ensures Comprehensive Care:

- Facilitates timely intervention to reduce risks.
- Enhances patient safety and treatment outcomes.

Glucocorticoid induced diabetes mellitus

Definition:

An abnormal increase in blood glucose levels associated with glucocorticoid use, regardless of prior diabetes history.

Prevalence:

The exact prevalence is unknown.

Incidence:

Over 50% of hospitalized patients without known diabetes develop hyperglycemia (blood glucose >200 mg/dl) when treated with corticosteroids.

Risk Factors and Protective Measures

Risk Factors:

Depend on dosage, duration of administration, and individual factors.

Protective Measures:

Early withdrawal from steroid therapy offers protection.

Gender Influence:

Gender was not identified as a predictive factor.

Mechanisms of Glucocorticoid-induced Diabetes

Various mechanisms contribute to this, including increased insulin resistance, glucose intolerance, β-cell dysfunction, and impaired hepatic glucose production. Steroids also reduce peripheral glucose uptake and alter body composition, culminating in hyperglycemia and dyslipidemia.

Treatment of Glucocorticoid-Induced Diabetes

Insulin therapy is the preferred treatment for glucocorticoid-induced diabetes mellitus due to its efficacy and safety compared to oral hypoglycemic agents.

Insulin offers immediate onset of action, easy titration, and unlimited hypoglycemic power.

Different types of insulin allow clinicians to tailor administration schedules to patients on various corticosteroid regimens

Continuous monitoring and adjustment are essential for successful long-term management of glucocorticoid-induced diabetes mellitus.

Nephrotic Syndrome in Children: Incidence and Progression in Type 1 Diabetes Mellitus

Incidence:

- United States and Europe: 1–7 per 100,000 children.

Diabetic Nephropathy:

- In Type 1 Diabetes Mellitus (T1DM):
  - Proteinuria typically presents late stage, approximately 12 years after diabetes onset.
  - Non-diabetic nephropathy indicated by short T1DM duration and absence of target organ damage.
  - Renal biopsy is crucial for accurate diagnosis.

Progression in T1DM:

- Early diabetic nephropathy detected by increased glomerular filtration rate induced by hyperglycemia.
- Microalbuminuria manifests about 5 years after T1DM onset.
- Nephropathy with proteinuria (>300 mg/day) develops 10–15 years after T1DM onset.
- End-stage renal failure seen in 50% of patients within 10 years of T1DM onset.

Case Studies: Concurrent T1DM and Nephrotic Syndrome

Case Descriptions:

- A 3-year-old boy diagnosed with both T1DM and nephrotic syndrome simultaneously.

- A 4-year-old boy with T1DM developed nephrotic syndrome.

HLA Antigens:

Both cases tested positive for:

- HLA A24
- DR4
- DR53 antigens

Shared HLA Loci:

T1DM and steroid-sensitive nephrotic syndrome may share HLA loci, indicating a genetic predisposition to both diseases

Table 2. Summary of prior reports of nephrotic syndrome associated with early-onset type 1 diabetes mellitus in pediatric patients.

References	Age at onset of diabetes (years)	Age at onset of nephrotic syndrome (years)	Proteinuria level (g/24 h)	Treatment	Outcome
Urizar et al.[17]	4	4 (1 week after DM1)	3.4	Insulin	Resolved completely
Urizar et al.[17]	8	8	7.2	Steroid	Resolved completely
Urizar et al.[17]	3	4	14	Steroid	Resolved completely
Urizar et al.[17]	5	5	17	Steroid	Recurrence
Urizar et al.[17]	2 months	10	7.3	Steroid	Recurrence
Robinson et al.[18]	3	3 (2 months after DM1)	–	Steroid	Resolved completely
Agras et al.[13]	3	3 (10 months after DM1)	–	Steroid	Relapsed
Otukesh and Torabi[6]	Infancy	5	–	Steroid	Recurrence
Rego Filho et al.[14]	3	3	0.529	Steroid–cyclophosphamide	Relapsed
Dizdar et al.[15]	17	35	3.7 g/day	Cyclophosphamide	Resolved completely
Moyses Neto et al.[10]	15	19	5.3 g/24 h	Steroid	Resolved completely

HLA and Autoimmune Diseases

HLA-Related Association Among Autoimmune Diseases

- Celiac Disease
- Autoimmune Thyroiditis
- Autoimmune Hepatitis

T1DM with Nephrotic Syndrome

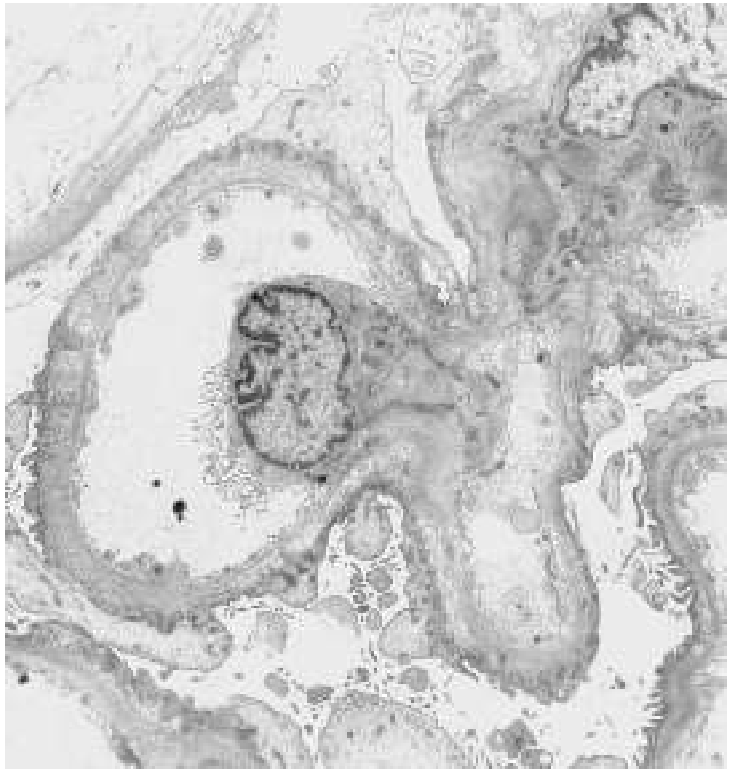
Implications: HLA may play a crucial role in the development of autoimmune diseases, including the association between T1DM and nephrotic syndrome

Conclusion

Steroid-induced diabetes mellitus poses a significant risk in children undergoing glucocorticoid therapy, underscoring the importance of careful monitoring for hyperglycemia. Early intervention by endocrinologists is essential to reduce the potential life-threatening consequences associated with this complication.

Furthermore, the co-existence of nephrotic syndrome and Type 1 Diabetes Mellitus (T1DM) in pediatric patients raises stimulating questions about a potential immunological link between these conditions. This warrants further investigation to demonstrate the underlying mechanisms and guide more effective therapeutic approaches in the future.

Case 2 : Pierson syndrome



Case study 2

Female infant(leen) , 2700g, delivered via emergency C-section at 35 weeks due to oligohydramnios.

Mother: 21-year-old gravida 2 para 1.

Prenatal ultrasound showed hyperechoic kidneys.

Born to second-degree cousins; they have a healthy 3-year-old boy.

Neonatal Clinical Profile and Laboratory Results

Apgar scores: 8 at 1 minute, 9 at 5 minutes.

Developed respiratory issues and oliguria.

Transferred to peripheral hospital's neonatal intensive care unit for 10 days.

Laboratory Findings:

Elevated:

- Blood urea nitrogen: 35 mg/dL
- Creatinine: 1.8 mg/dL

Hyponatremia: 133 mEq/L.

Clinical Presentation and Laboratory Finding

Referred to our hospital due to edema, abdominal distension, and impaired kidney function tests.

Urine Analysis: Protein: +3 to +4 , RBC: 18-20

Serum Albumin: 6.9 g/L (Normal: 38-54 g/L)

Calcium: 1.57 mmol/L (Normal: 2-2.6 mmol/L)

Magnesium: 0.49 mmol/L (Normal: 0.62-0.91 mmol/L)

Culture Results:

Urine: No growth

Blood: No growth

Imaging findings

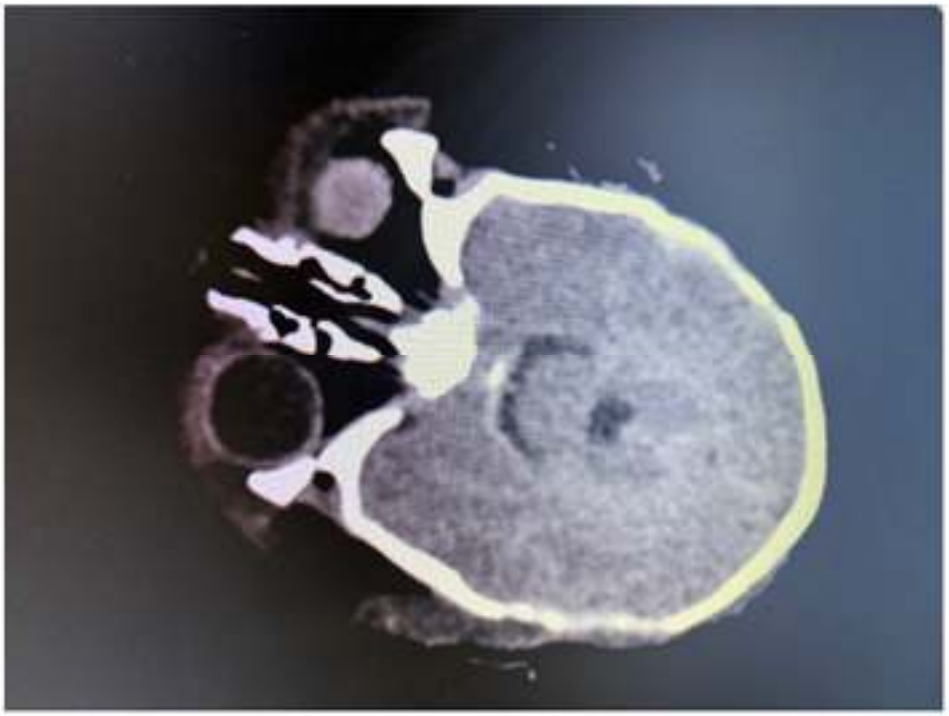
2D-Echo:

- Normal heart structure and function.

Abdominal Ultrasound:

- Liver and spleen: Normal size, shape, and echogenicity.
- Both kidneys: Hyperechoic with moderate hydronephrosis.
- Moderate ascites fluid present in the abdomen and pelvis during examination.

Brain CT scan
Hypo plastic left eye globe with hyper density
No focal brain lesion



Ophthalmology consultation

Left eye

- Microphthalmic
- Congenital chemosis microcornea
- Reflex could not be assessed

right eye

- Clear cornea
- Small non –dilating irregular pupil

  Bilateral Persistent fetal vasculature

Treatment and Clinical Challenges

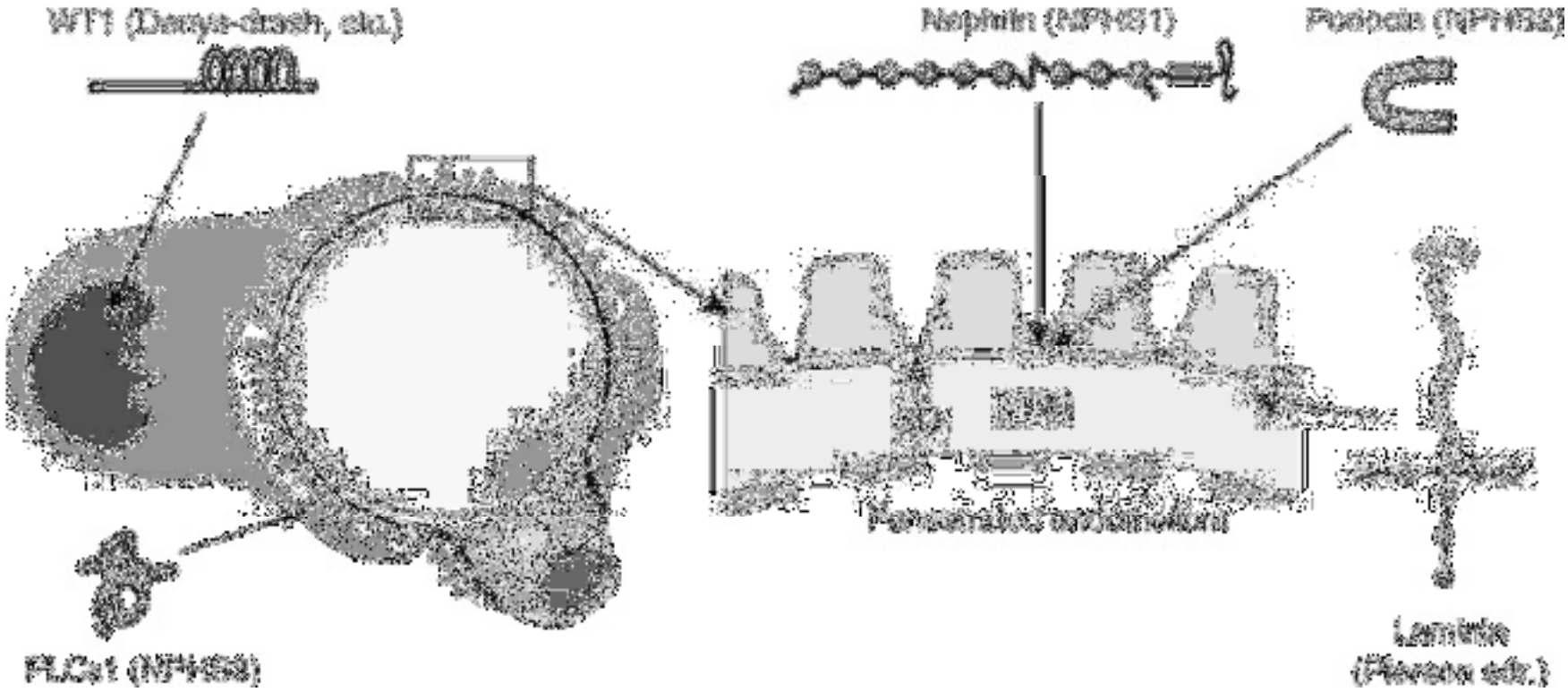
- Leen initiated on daily human albumin infusion and IV furosemide.

- Challenges encountered with sample withdrawal and central line or cannula insertion.

- Unfortunately, Leen passed away before genetic study could be conducted.

Congenital Nephrotic Syndromes and Associated Gene Mutations

Gene / Mutation	Associated Syndrome
Nephrin (NPHS1)	CNF (Congenital Nephrotic Syndrome of the Finnish Type), isolated NS
Podocin (NPHS2)	Isolated NS
Phospholipase C epsilon 1 (PLCE1)	NPHS3, isolated NS
Wilms tumor suppressor 1 (WT1)	Denys–Drash syndrome, isolated NS
Laminin β2 (LAMB2)	Pierson syndrome, isolated NS
Laminin β3 (LAMB3)	Herlitz junctional epidermolysis bullosa
Lim homeobox transcription factor 1b (LMXB1)	Nail–patella syndrome
OCRL gene defect	Lowe syndrome
ARHGDIA gene mutations	RhoGDIα defect
Mutations in genes encoding mitochondrial coenzyme Q10 synthesis (COQ2, COQ6, ADCK4)	-
Galloway–Mowat syndrome	Gene defect not yet known


WT1 (Denys-drash, etc.)
Nephrin (NPHS1)
Podocin (NPHS2)
PLCε1 (NPHS3)
Laminin
(Fibrosis etc.)

Secondary Causes of Congenital Nephrotic Syndrome

1. Congenital Syphilis
2. Toxoplasmosis
3. Malaria
4. Cytomegalovirus
5. Rubella
6. Hepatitis B
7. HIV
8. Maternal Systemic Lupus Erythematosus (SLE)
9. Neonatal Antibodies against Neutral Endopeptidase
10. Maternal Steroid-Chlorpheniramine Treatment

Pierson syndrome

Pierson syndrome is an autosomal recessive condition associated with *LAMB2* mutations and loss of laminin β2 expression

Patients classically present with congenital nephrotic syndrome and characteristic ocular abnormalities including microcoria

Renal biopsy most commonly demonstrates diffuse mesangial sclerosis with Alport-like alterations of glomerular basement membranes by electron microscopy.

Pierson syndrome

Additional extrarenal manifestations involving the central nervous and skeletal systems may also be found in patients with *LAMB2* mutations

The role of laminin β2 in the central nervous system is not completely understood, and the full spectrum of changes seen with *LAMB2* mutations remains to be completely explored.

The prognosis for Pierson syndrome is poor; however, patients with partial expression of laminin β2 may have a less severe clinical course.

Thank you so much

International Society of Nephrology

International Pediatric Nephrology Association

Jordan Society of Nephrology and Renal Transplantation

The Royal College of Physicians / Edinburgh

Arab Society of Nephrology and Renal Transplantation

Iraqi Society of Nephrology and Renal Transplantation

Kidney and Bone Beyond Vitamin D

Reham Almardini

Pediatric Nephrology consultant

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JORDAN SOCIETY OF NEPHROLOGY AND TRANSPLANTATION

Case 1

- 27 year lady non-proportional short stature with sever bone pain, multiple (>7) surgeries during childhood, hearing loss On NSAID, colchicine, Alendronate
- Lab; normal KFT, VBG, urine analysis, S & U calcium, LFT
- Low serum phosphorous 1.9-2.2 mg/dl
- 25Vit D 25, PTH 40
- Parents non consanguineous
- No similar cases

Case 1	Case 2
• 27 year lady non-proportional short stature with sever bone pain, multiple (>7) surgeries during childhood, hearing loss On NSAID, colchicine, Alendronate • Lab; normal KFT, VBG, urine analysis, S & U calcium, LFT • Low serum phosphorous 1.9-2.2 mg/dl • 25Vit D 25, PTH 40 • Parents non consanguineous • No similar cases	• 9 y F. short stature bow legs, relatively large head 56cm, bad multiple dental caries, repeated visits to endocrine orthopedic and general pediatric and lastly immunology clinic seeking for GH for seeking for surgeries • Parents R cousins, father had same condition short stature with deformed bone

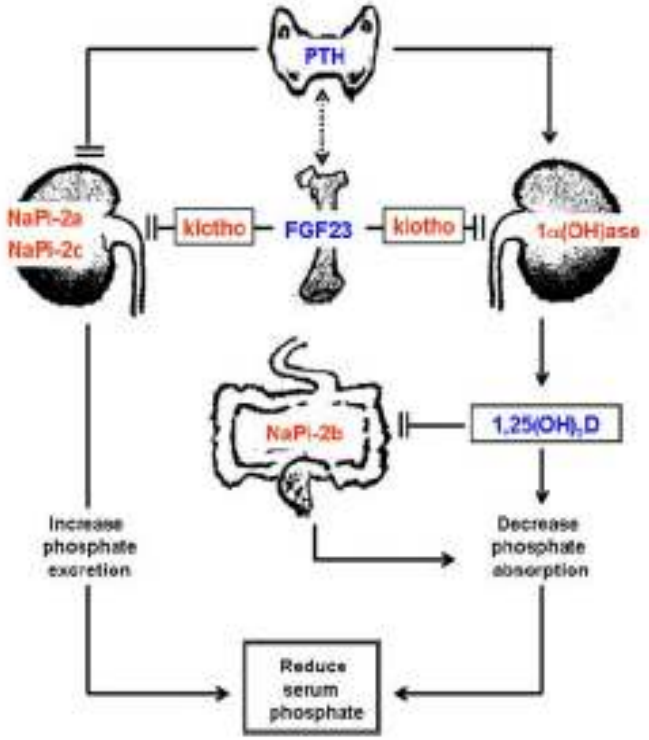
Case 1	Case 2	Case 3
• 27 year lady non-proportional short stature with sever bone pain, multiple (>7) surgeries during childhood, hearing loss On NSAID, colchicine, Alendronate • Lab; normal KFT, VBG, urine analysis, S & U calcium, LFT • Low serum phosphorous 1.9-2.2 mg/dl • 25Vit D 25, PTH 40 • Parents non consanguineous • No similar cases	• 9 y F. short stature bow legs, relatively large head 56cm, bad multiple dental caries, repeated visits to endocrine orthopedic and general pediatric and lastly immunology clinic seeking for GH for seeking for surgeries • Parents R cousins, father had same condition short stature with deformed bone	• 3 y F. repeated visits to G. pediatric clinic bow legs, delayed walking & teething dental enamel hypoplasia short stature bow legs, delayed closure of ant fontanel • received many courses of vitamin D many readings some low few normal and one in the toxic level(125) ALP 1500, phosphorous 2.4

Target of the talk

- The evaluation of Hypophosphatemic Rickets
- Identify opportunities for improvement & treatment
- Understand the natural history over the patient's lifetime and the impact of drug treatments and other interventions

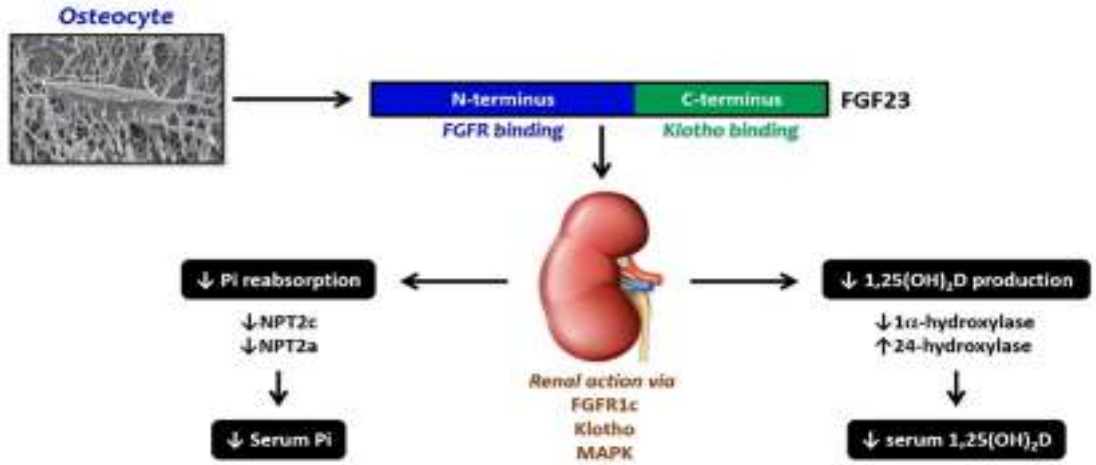
Low Serum Phosphate reduces Hydroxyapetite causing Hypophosphatemic Rickets

- 90% is stored in bone as hydroxyapatite
- Deficiency impairs mineralization, rickets in children & osteomalacia in adults

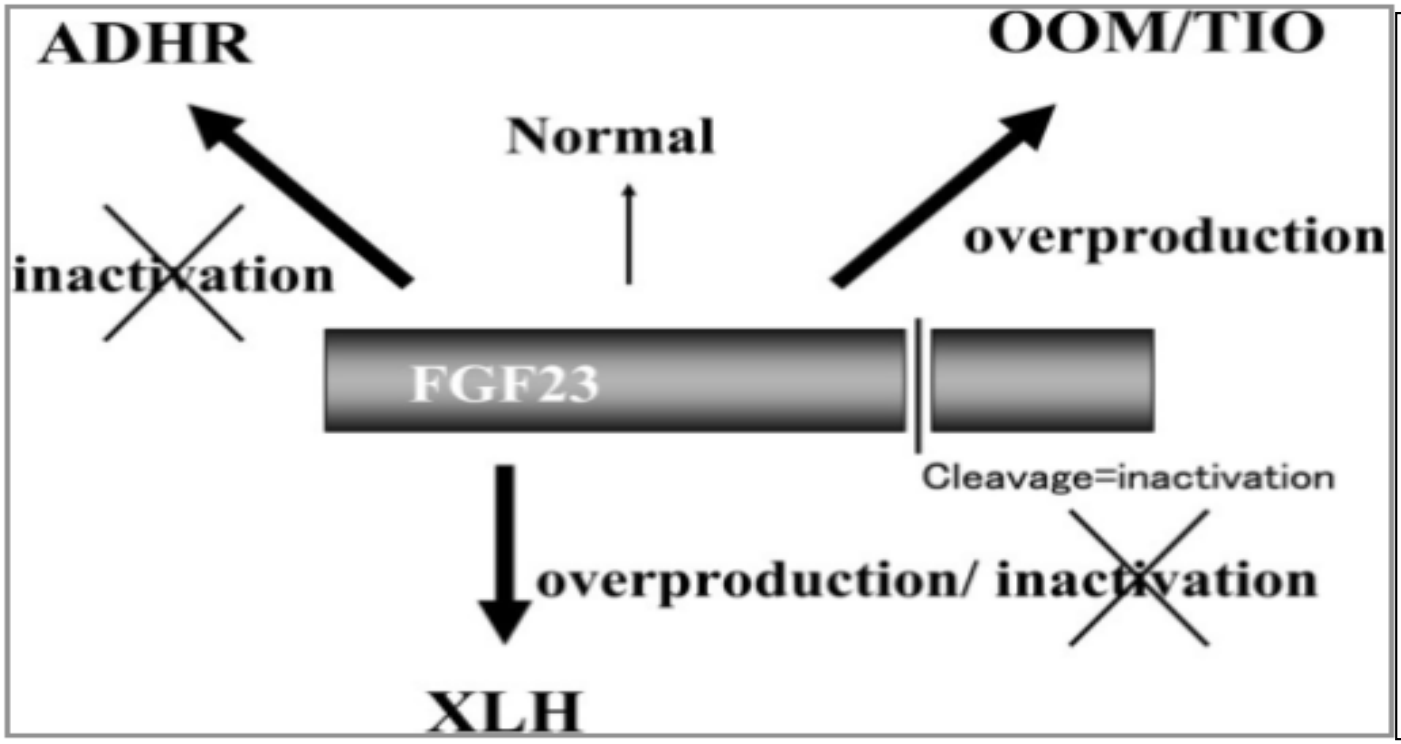


Satoko Osuka et al. Journal of Bone and Mineral Metabolism

Fibroblast Growth Factor 23 (FGF23)



Hypophosphatemic Rickets



ARHR: ENPP1 deficiency

ENPP1 potentially inhibits FGF23 production

Diagnosis: Hypophosphatemic rickets

Children

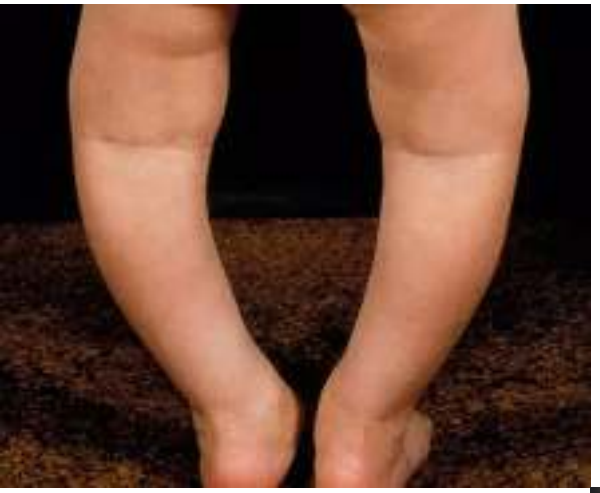
- Clinical and radiological abnormalities, impaired growth velocity, low phosphate level and renal wasting
- Absence of vitamin D or calcium deficiency

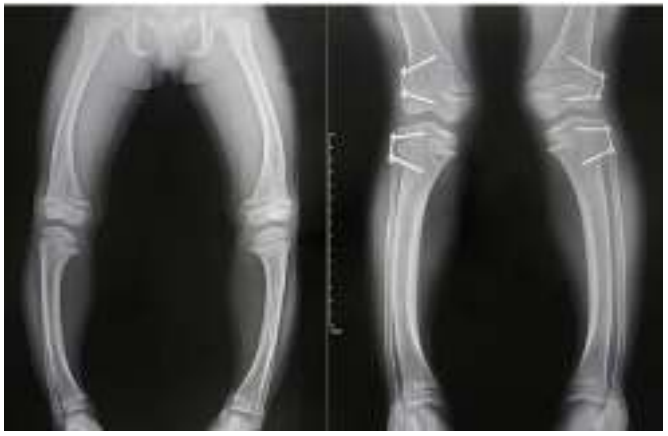
Adult

- Lower limb deformity, impaired growth velocity, low phosphate level and renal wasting, clinical or radiological evidence of osteomalacia, including pseudo-fracture, early osteoarthritis and ensethopathy
- Absence of vitamin D and calcium deficiency

During evaluation pay attention to

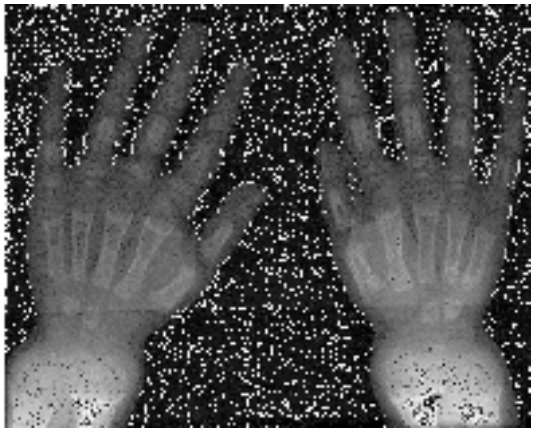
1. Dental anomalies
2. Craniosynostosis and/or intracranial hypertension





Rickets X ray finding in children

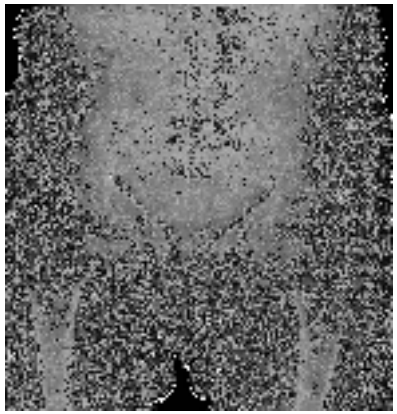
Low bone density



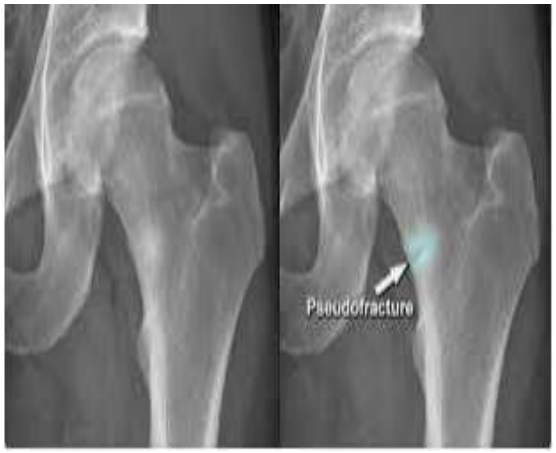
Cupping and wide wrist

Coxa Vara

Adult patients with Hypophosphatemic Rickets

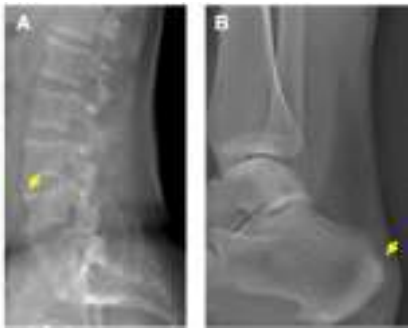


Osteomalacia



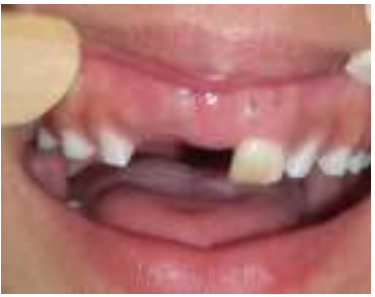
Pseudofracture

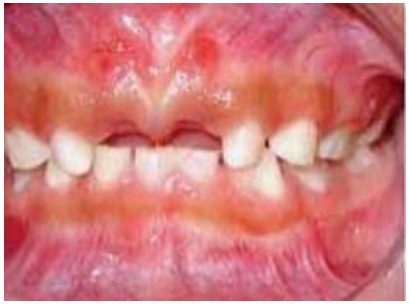
Degenerative osteoarthropathy

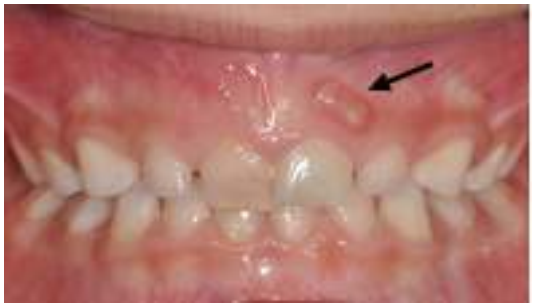


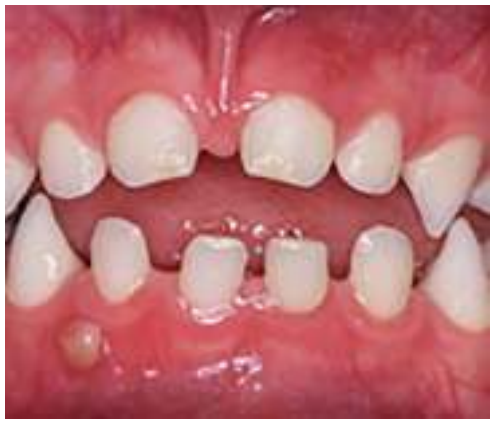
Enthesopathy: Calcification of Tendons & Ligaments

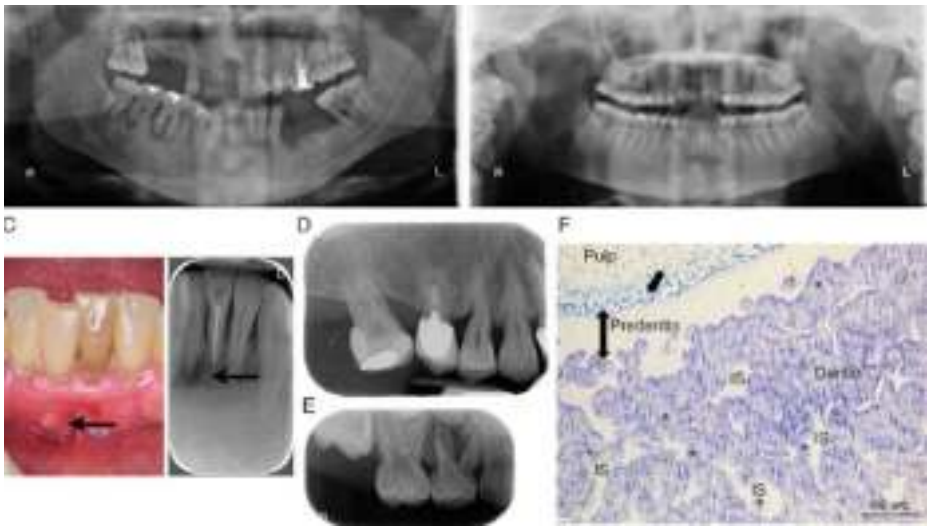
Dental Abnormalities In Hypophosphatemic Rickets





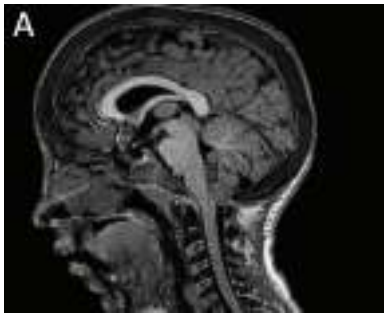


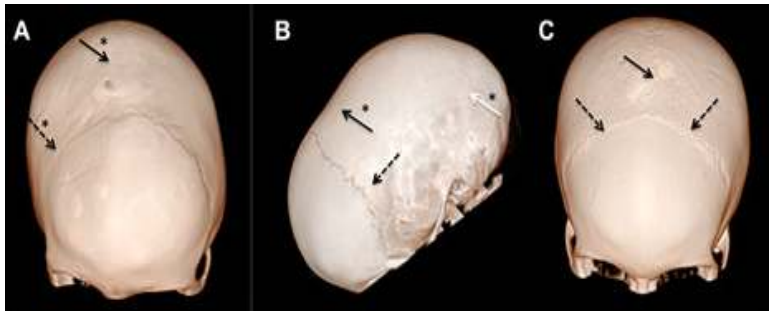


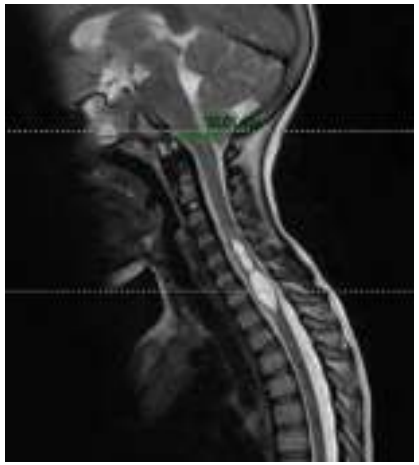


1. Enamel Hypoplasia
2. Occlusion defect
3. Dental abscess
4. Enlarged pulp chambers
5. Hypomeneralization

CNS Complication of Hypophosphatemic Rickets





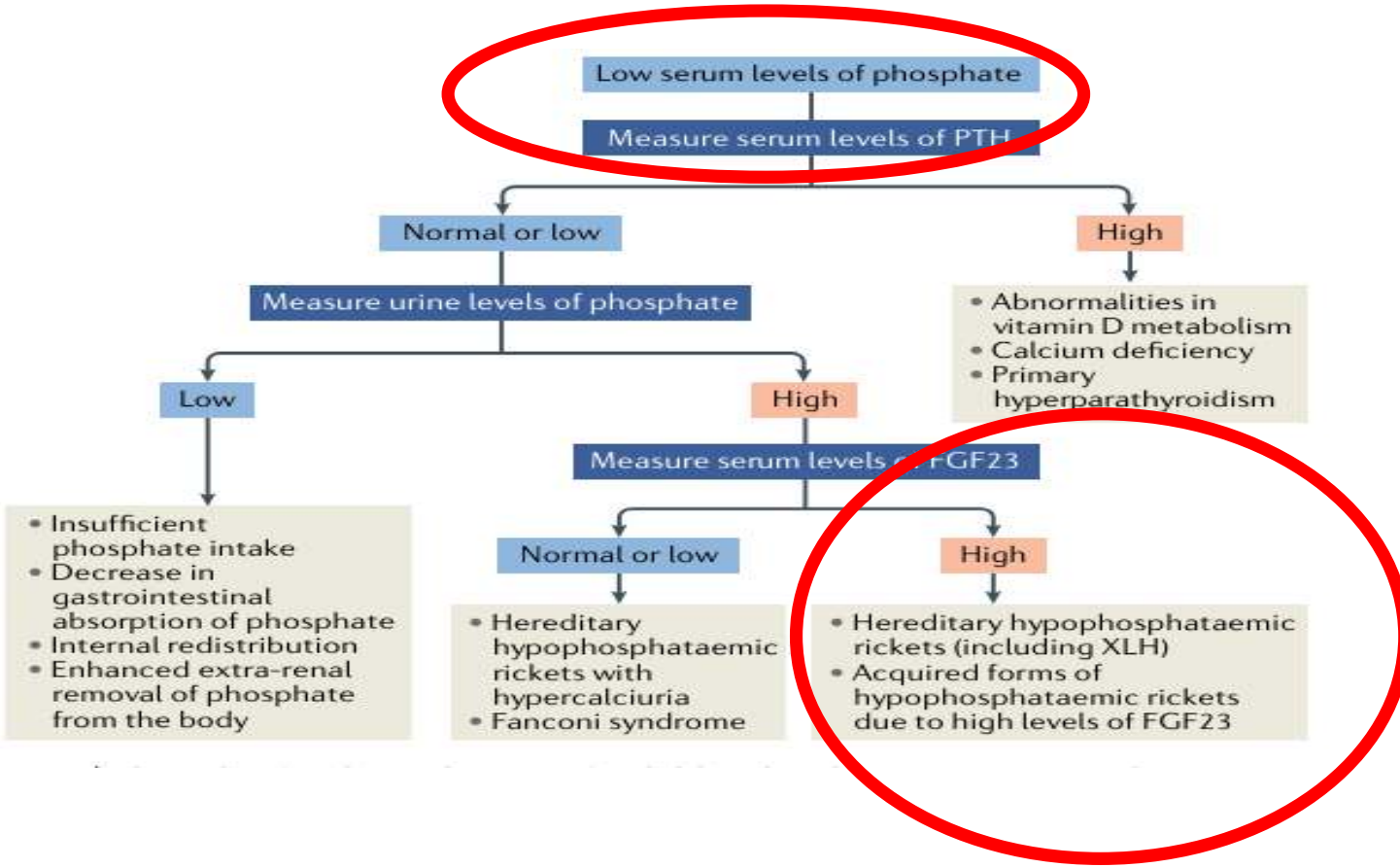


1. **Spinal stenosis**
2. **Chiari malformation**
3. **Cranial Synostosis**
4. **Hearing Loos**
5. **Tinnitus**
6. **Vertigo**

Biochemical evaluation of Hypophosphatemic Rickets

Serum Phosphorous	Low
ALP	High
Serum calcium	Normal
Urinary calcium	In the normal range
TPR/GFR	Low
PTH	Upper Normal
25 Vit D	Normal
1,25 Vit D	Low or inappropriately normal in sitting of hypophosphatemia
FGF23 level	High

Algorithm for the diagnosis of Hypophosphatemia

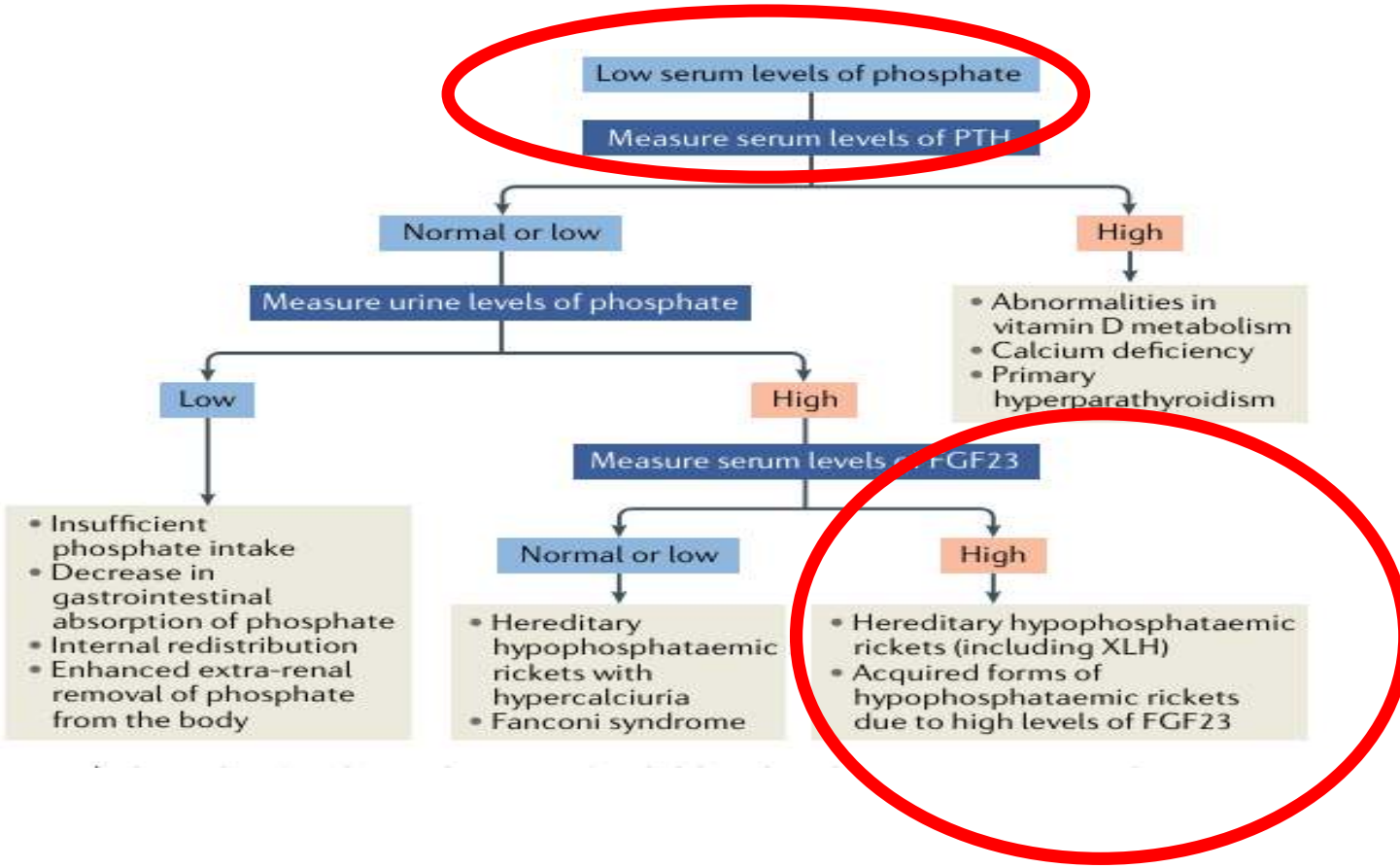


Algorithm for the diagnosis of Hypophosphatemia

Low S. Phosphate

Normal PTH

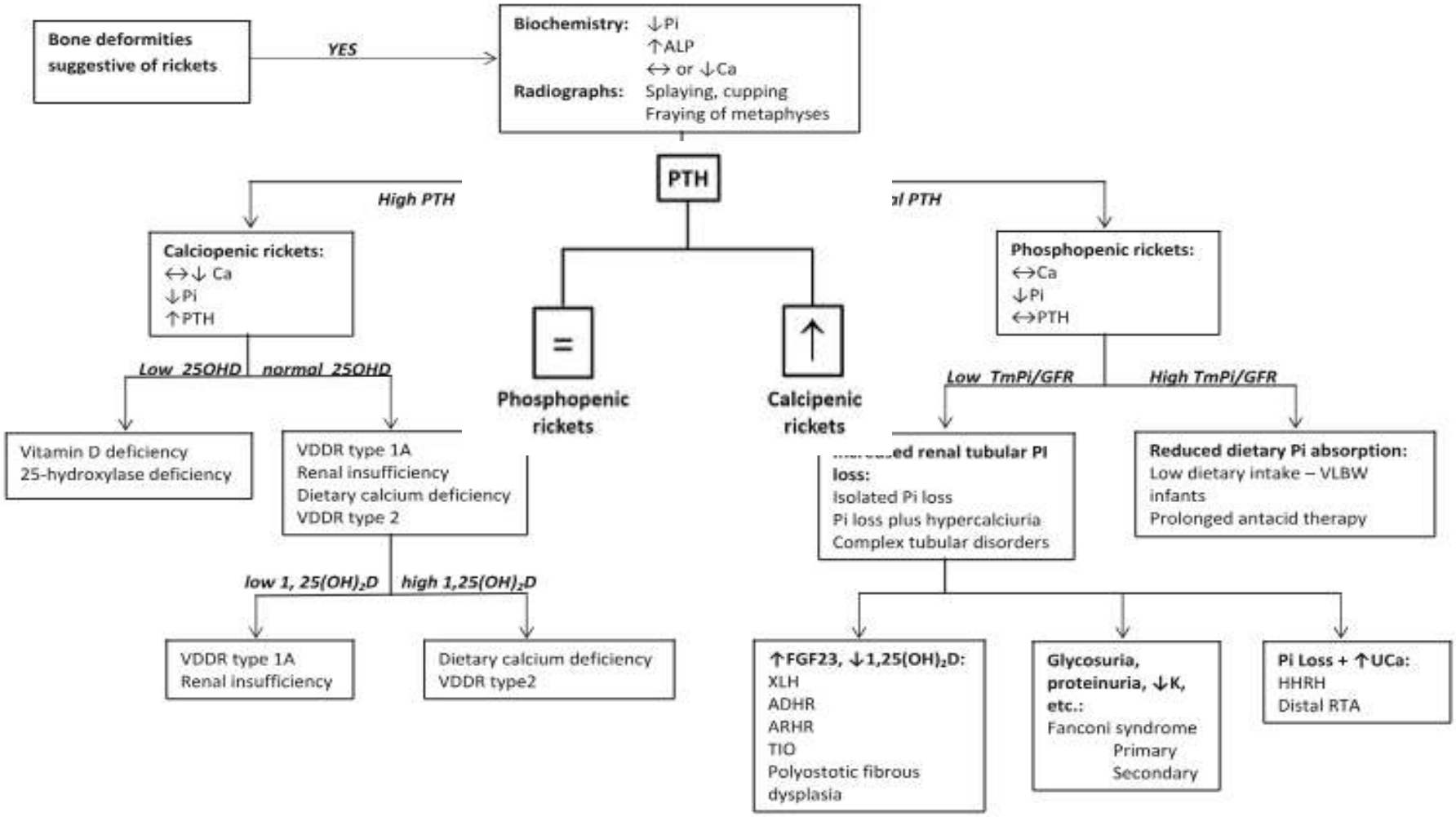
High FGF 23



Conformation of the diagnosis

- Genetic analysis is recommended in all cases

- If not feasible: High FGF23 with a positive family history in compatible clinical and biochemical scenario supports the diagnosis

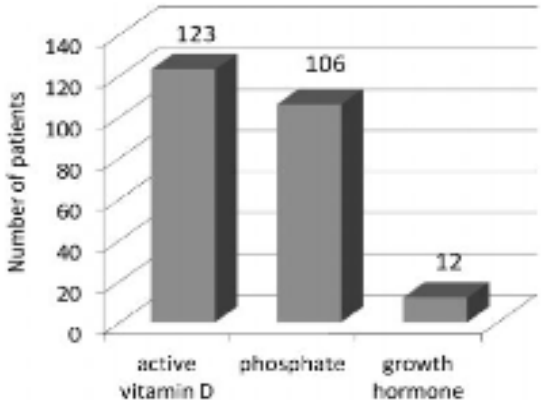


J. M. Pettifor et al.: Hypophosphatemic Rickets

Management of Hypophosphatemic Rickets Multidisplinary approach

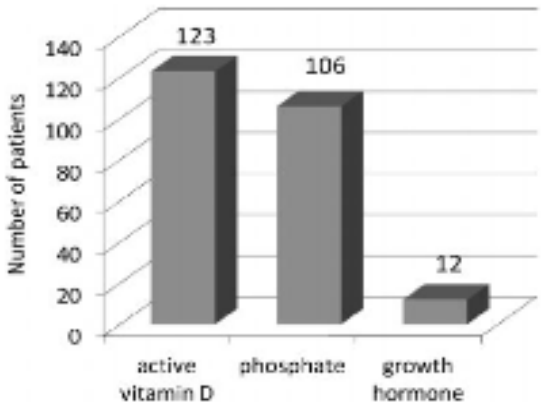
- General pediatrician
- Pediatric or adult nephrologist
- Radiologist
- Orthopedic surgeon
- Physical therapist
- Rheumatologist
- Dentist
- Neurosurgeon
- Otolaryngolist

Conventional treatment: Target is normalizing ALP & prevent side effect



Makoto Fujiwara. Clinical Pediatric Endocrinology 22(1):9-14

Conventional treatment: Target is normalizing ALP & prevent side effect



Phosphorous

- **Phosphorous: 20-50 mg/kg/day**
- **Promote growth, reduce bone pain, progressively correct deformities, improve dental health**

Calcitriol or alfacalcidiol

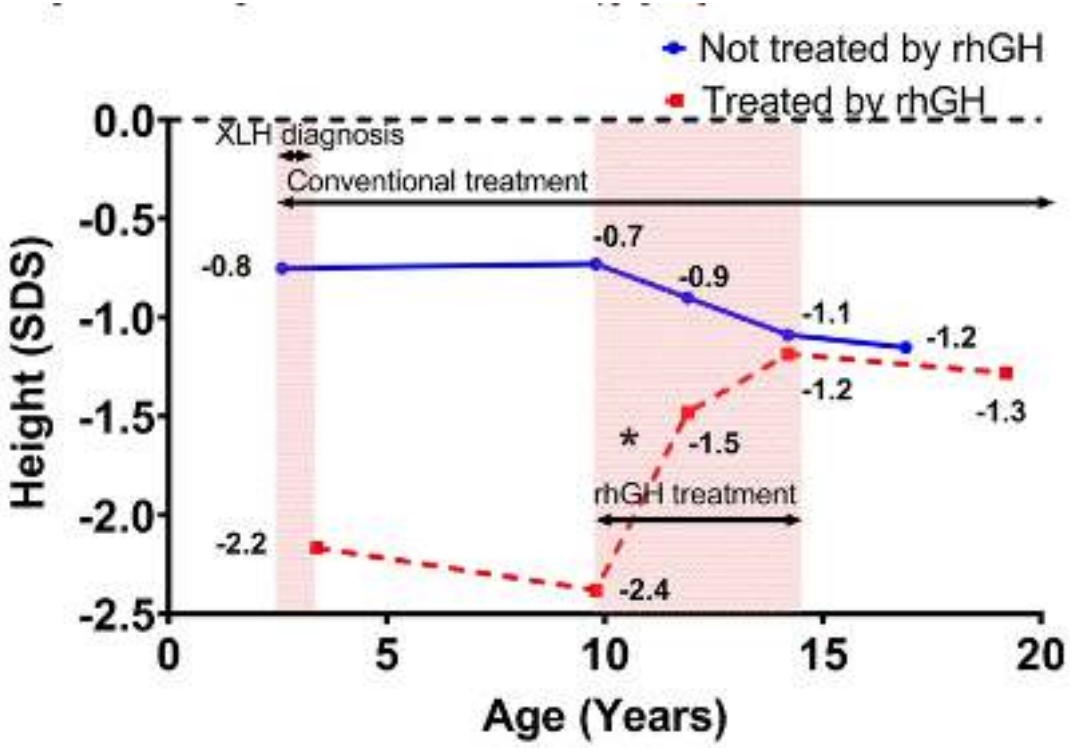
- **Prevent secondary hyperparathyroidism**
- **Increase phosphate absorption from GI**

Side Effect of treatment

- **GI upset**
- **Hyperparathyroidism**
- **Hypercalciuria and nephrocalcinosis**
- **Hypoparathyroidsm**

Makoto Fujiwara. Clinical Pediatric Endocrinology 22(1):9-14

Growth Hormone treatment improves final height in children with XLH



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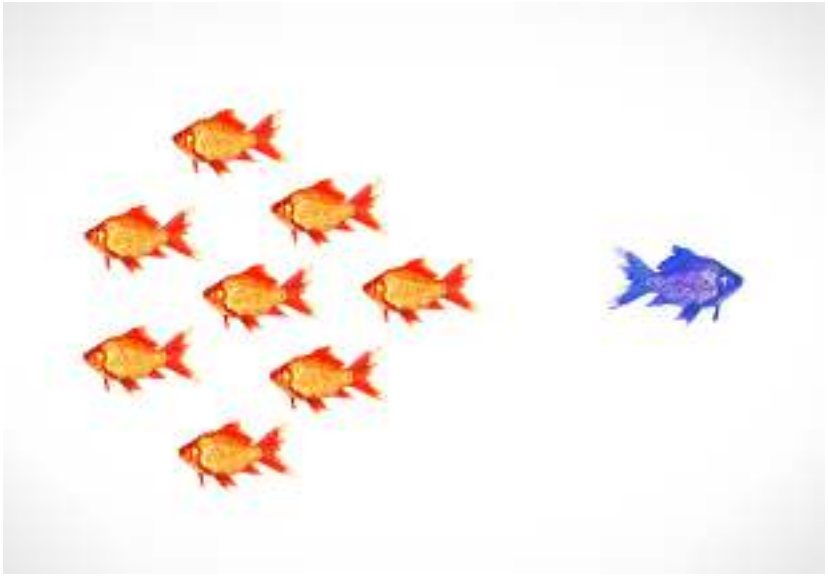


Burozumab: recombinant H IgG1 inhibits the activity of FGF 23

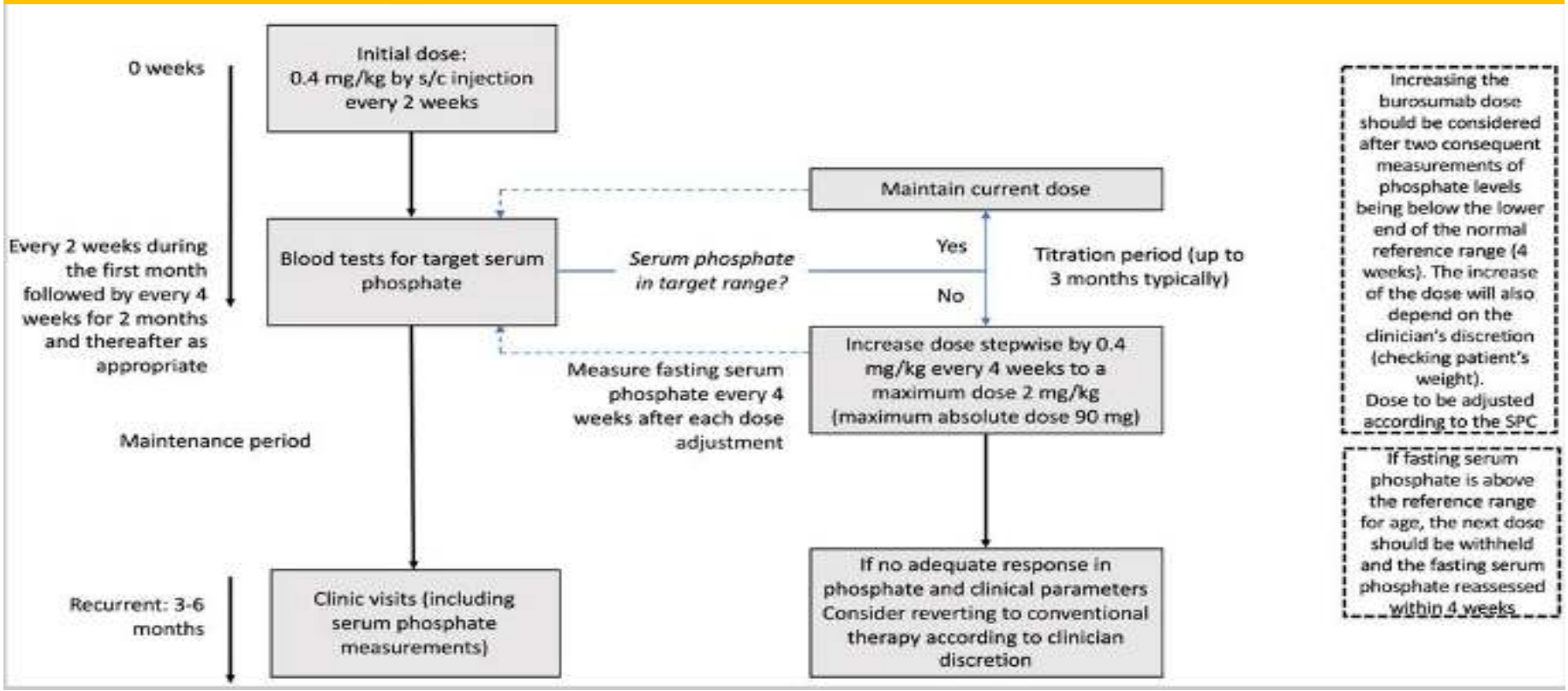
- 2018 Europe and USA for children > 1 year and adult
- 2 weekly injections 0.4 mg/kg to maximum of 2 mg/kg SC injection
- Should not be given with conventional treatment
- Monitored by fasting phosphate level on day 11 post dose
- improves bone mineral metabolism, heals rickets, increased growth and restore normal growth 1-4 y, mobility, and physical functioning & significantly alter the natural history of the disease

Recommendation of Burozumab Tx in children XLH and Adult

- ≥1 year and in adolescents with growing skeletons
- refractory to conventional therapy
- complications related to conventional therapy
- patient's inability to adhere to conventional therapy,

- Persistent bone and/or joint pain due to XLH
- Osteomalacia that limits daily activities
- Pseudo-fractures or osteomalacia-related fractures
- Insufficient response or refractory to conventional therapy
- Patients experience complications related to conventional therapy

Burozumab Dosing and Monitoring



Padidela R et alEndocr Connect. 2020 Oct;9(10):1051-1056

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Consensus Statement | Open access | Published: 08 May 2019

EVIDENCE-BASED GUIDELINE

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

Dieter Haffner ✉, Francesco Emma, Deborah M. Eastwood, Martin Biosse Duplan, Justine Bacchetta, Dirk Schnabel, Philippe Wicart, Detlef Bockenhauer, Fernando Santos, Elena Levtchenko, Pol Harvengt, Martha Kirchhoff, Federico Di Rocco, Catherine Chaussain, Maria Louisa Brandi, Lars Savendahl, Karine Briot, Peter Kamenicky, Lars Rejnmark & Agnès Linglart

Nature Reviews Nephrology **15**, 435–455 (2019) | Cite this article

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Haffner, D et al. *Nat Rev Nephrol* **15**, 435–455 (2019

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Consensus State

EVIDENCE-BASE

Clinical p

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Dieter Haffner

Schnabel, Philipp

Kirchhoff, Federi

Kamenicky, Lars

Nature Reviews N

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Endocrine CONNECTIONS

R Padidela *et al.* | XLH guidelines-BPABG recommendations | 9:10 | 1051–1056

RESEARCH

Clinical guidelines for burosumab in the treatment of XLH in children and adolescents: British paediatric and adolescent bone group recommendations

Raja Padidela[1], **Moira S Cheung**[2], **Vrinda Saraff**[3] and **Poonam Dharmaraj**[4]

[1]Royal Manchester Children's Hospital and Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[2]Evelina London Children's Hospital, London, UK
[3]Birmingham Women's and Children's Hospital, Birmingham, UK
[4]Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Correspondence should be addressed to R Padidela: raja.padidela@mft.nhs.uk

Abstract

X-linked hypophosphataemia (XLH) is caused by a pathogenic variant in the *PHEX* gene, which leads to elevated circulating FGF23. High FGF23 causes hypophosphataemia,

Key Words

▸ XLH

Cases 1 (ENPP1 deficiency)

- She has been involved in phase 3 clinical trial for enzyme replacement study

Cases

- Case 1 (ENPP1 deficiency) has been involved in phase 3 clinical trial for enzyme replacement study

Case 2

- Genetic testing by WES showed PHEX gene mutation positive

- Started in conventional therapy and looking forward to receive Burozumab Unfortunately not FDA approved in Jordan and very expensive

Case 3

- She is diagnosed properly as having Hypophosphatemic Rickets started on the treatment and stopped 25 hydroxy vitamine D and looking forward to do genetic testing and receive the targeted therapy

Conclusion: Hypophosphatemic rickets

- Sever disease affecting life style
- Proper & early Diagnosis is mandatory for control of the disease
- Long term treatment is mandatory and has side effect
- Multi-disciplinary team management is the key to give the best results
- Burozumab is promising drug in changing the outcome of the disease
- Clinical trials are still going on to find further treatment for other types


Thank you

Phosphorous homeostasis

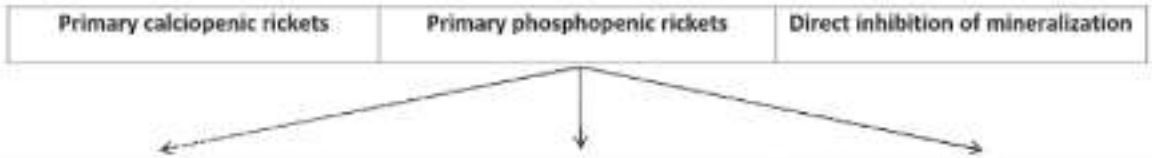
- 90% of total phosphorus is stored in bone, while the remainder is present in the soft tissues and less than 1% in extracellular fluid [2]. In serum, the majority of phosphorus exists as free ions of inorganic phosphate (Pi), such as HPO_4^{2-} and $H_2PO_4^-$,

- maintained by its intestinal absorption, renal excretion, and accumulation in and release from bone and soft tissue
- Since phosphate is indispensable for the formation of hydroxyapatite, its chronic deficiency or wasting leads to impaired skeletal mineralization, namely, rickets in children and osteomalacia in adults

Michigami, T.; Kawai, M.; Yamazaki, M.; Ozono, K. Phosphate as a Signaling Molecule

Hypophosphatemic rickets

- Disabling conditions
- Negatively impact physical functioning
- & mental health, social life, and leisure activities



Decrease gastrointestinal Pi absorption	Isolated renal phosphate leak	Renal tubular disorders associated with Pi leak
Decreased dietary intake • Breast fed very-low-birthweight infants **Impaired intestinal absorption** • Prolonged antacid use	**FGF23 related** **Isolated phosphaturia** • X-linked hypophosphatemic rickets (XLH) • Autosomal dominant hypophosphatemic rickets (ADHR) • Autosomal recessive hypophosphatemic rickets (ARHR) • Tumour induced rickets (TIO) • Polyostotic fibrous dysplasia and McCune Albright syndrome • Neurocutaneous syndromes (linear sebaceous naevus syndrome) • Hypophosphatemic rickets with hyperparathyroidism **FGF23 unrelated** **Phosphaturia plus calciuria** • Hereditary hypophosphatemic rickets with hypercalciuria	**Phosphaturia, calciuria plus acidosis** • Distal renal tubular acidosis **Phosphaturia, aminoaciduria, acidosis, glucosuria, plus electrolyte disturbances** • Fanconi syndrome (primary and secondary) • Dent disease • Lowe syndrome • Ifosfamide toxicity

Diagnosis of Rickets

- Clinical presentation: leg deformities, hypotonia and muscle weakness, delayed walking and teething, wide anterior fontanyl, ultimately nonproportional short stature and deformed bone

- Radiological abnormality: metaphyseal fraying cupping and widening, decreased bone density and varus or vulgus deformities

- Biochemical abnormality: high Alkaline phosphatase

- e FGF23-αKlotho axis plays a central role in phosphate homeostasis, its disruption causes hyperphosphatemic conditions, as described in the previous section. On the other hand, the excessive action of FGF23 underlies various hypophosphatemic diseases, which are characterized by urinary phosphate wasting, hypophosphatemia, and inappropriately low levels of serum 1,25(OH)2D
- chronic hypophosphatemia due to excessive FGF23 leads to rickets in children and osteomalacia in adults. The impaired production of 1,25(OH)2D contributes to the resistance of FGF23-related hypophosphatemic rickets/osteomalacia to native vitamin D. FGF23-related hypophosphatemic rickets/osteomalacia include various conditions such as genetic diseases

Burozumab NICE

- The NICE recommendation in UK is not population restricted beyond the indication of the EMA licence, so both newly diagnosed XLH patients and those currently on conventional therapy, irrespective of the disease severity, are eligible for treatment with burosumab
- agreed by the guardian/patient, responsible clinician, and tertiary metabolic bone specialist
- Stopping tx when final height is achieved and or when growth velocity fall<2cm/y

FGF 23 Related Hypophosphatemic Rickets

- X-Linked Hypophosphatemic Rickets (XLH)
- Autosomal Dominant Hypophosphatemic Rickets (ADHR)
- Autosomal Recessive Hypophosphatemic Rickets Type 1 (ARHR1)
- Autosomal Recessive Hypophosphatemic Rickets Type 2
- Raine Syndrome (RNS)
- Tumor-Induced Osteomalacia (TIO)
- McCune-Albright syndrome

Growth Hormone I Hypophosphatemic Rickets

- Recombinant human growth hormone (rhGH) increases phosphate tubular reabsorption and phosphate level in blood and, thus, constitutes an attractive but controversial therapy in short children with XLHR, those efficacy was demonstrated in small uncontrolled series.

Ariceta G, Langman CB. Eur J Pediatr. 2007 Apr;166(4):303-9.

Infections post kidney transplant Updates on CMV

Dr Ruba Saqer Al Assaf
Pediatrics nephrology senior fellow
Queen Rania children's hospital
Royal medical services
Amman/Jordan
June 2024

The outline

Introduction

Major risk factors

Infection timeline

prevention

CMV

Home massages

Mortality post kidney transplant

Although mortality among pediatric kidney transplant recipients has improved in recent years, it is not clear how cause-specific mortality has changed over time

With longer patient survival ,systemic complications of transplant as accelerated cardiovascular disease became more prominent

With more potent immunosuppression regimen , more infectious and non- infectious complications especially on long term has emerged

Cardiovascular causes (40%) : cardiac arrest, MI, stroke
Cancer (12%) : PTLD, cancers of GI tract
Infection (28%)
Other causes 31%)

The relative contribution of each cause of death varied depending on transplant status (functioning versus failed, on dialysis)/ incidence of death from CVD 10 times higher during dialysis

Infection is the most common cause of death in first year post transplant

Rates of cancer deaths remained unchanged

While acute rejection rates have fallen ,the community has seen the emergence of newer infection complications as PTLD and BKVAN

Infection hospitalization cumulative incidence is much higher at 47% in children in first 3 years post transplant than while on dialysis or in comparison to adults .

Unlike adults , total cumulative infection incidence in children didn't drop in recent years

Basic principles

- Net State of immunodeficiency
- Environmental exposure

Metabolic : uremic patient , diabetic , malnourished…

Underlying immunodeficiency : SLE, hypogamaglonulinemia , neutropenia/ lymphopenia

Prior treatment with chemotherapy , antibiotics

Muco-cutaneous barrier integrity : drains , catheters ,lines….

Viral co-infection : HBV,HCV,EBV

Greater infectious risk :

young age at transplant
(lack of prior exposure, more mismatch, vaccines)

related to surgery:

induction therapy- lymphocyte depletion / high dose steroid / plasmaphresis
high risk of rejection / early graft disfunction
latent / active donor related infection

Technical complications: anastomotic leak ,wound infection ,poor healing,
prolonged icu care , vascular and urinary catheters.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7123753/#

Lower infectious risk:

High HLA- matching

Good graft function

Technically successful surgery

Pre-surgical prophylaxis

Appropriate vaccination

Environmental exposure :

Donor derived infections

Recipient derived infection

community acquired infection

Nosocomial infections

Donor screening

- Epidemiologic history
- Serologic testing for VDRL, HIV,CMV, EBV, HSV, VZV, HBV
- (HBsAg, anti-HBsAg), and HCV
- Microbiologic testing of blood and urine
- Chest radiography
- Known infections (appropriate therapy?)
- Possible infections (e.g., encephalitis,sepsis)
- Special serologic testing, nucleic acid assays, or antigen detection based on epidemiological factors and recent exposures (e.g., toxoplasma,West Nile virus, HIV, HCV

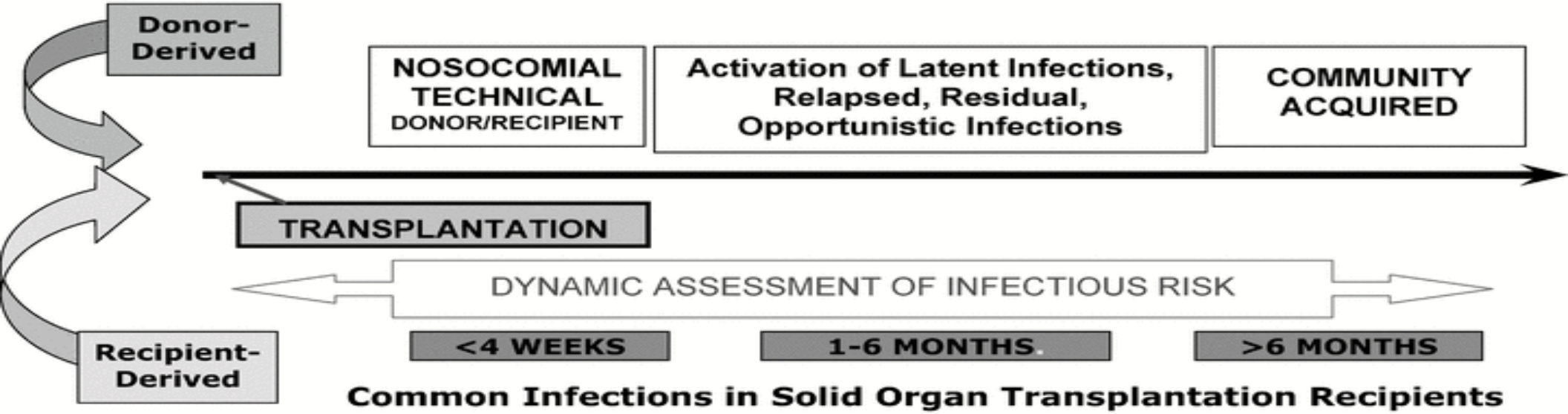
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7123753/#

Recipient screening

- Epidemiologic history
- Vaccination history, TB skin test
- Serologic testing for VDRL, HIV,
- CMV, EBV, HSV, VZV, HBV
- (HbsAg, anti-HbsAg), and HCV
- Microbiologic testing of blood and urine
- Chest radiography

The Timeline of Post-Transplant Infections

Modified from [1-3]



Common Infections in Solid Organ Transplantation Recipients

Antimicrobial-resistant species:
- MRSA
- VRE
- Candida species (non-albicans)

Aspiration
Line Infection
Wound Infection
Anastamotic Leaks/Ischemia
C. difficile colitis

Donor-Derived (Uncommon):
HSV, LCMV, rabies, West Nile

Recipient-Derived (colonization):
Aspergillus, Pseudomonas

With PCP and antiviral (CMV, HBV) Prophylaxis:
- BK Polyomavirus Nephropathy
- C. difficile colitis
- Hepatitis C virus
- Adenovirus, influenza
- *Cryptococcus neoformans*
- *M. tuberculosis*

Anastamotic complications

Without Prophylaxis Add:
Pneumocystis
Herpesviruses (HSV, VZV, CMV, EBV)
Hepatitis B virus
Listeria, Nocardia, Toxoplasma
Strongyloides, Leishmania, T. cruzi

Community Acquired Pneumonia
Urinary Tract infection
Aspergillus, Atypical moulds, *Mucor* species
Nocardia, Rhodococcus species
Late Viral:
- CMV (Colitis/Retinitis)
- Hepatitis (HBV, HCV)
- HSV encephalitis
- Community acquired (SARS, West Nile)
- JC polyomavirus (PML)

Skin Cancer, Lymphoma (PTLD)

Infections timeline 0-1 month

- Post-op Infections
  - Technical / anastamotic related infection
  - Nosocomial pneumonia, wound infection, UTI
  - MRSA, VRE, Candida, C. difficile

- Donor Derived Infection
  - These are rare but diagnosis can be missed

- Recipient derived infection
  - Ongoing pneumonia
  - Colonization to infection
- Most OI absent: exceptions include certain fungal infections, HSV, occasional others

Infections timeline 1-6 months

Account for CMV, PCP prophylaxis
BK viruria / viremia, BKVAN
CMV
EBV viremia D+/R-
HCV recurrence (OLTx)
C. difficile, fungal, mycobacterial, respiratory virus
VZV post-prophylaxis

Infections timeline > 6 months

Depends on outcome: good vs. bad graft function. Tapering immunosuppression vs. ongoing high level – problems with rejection

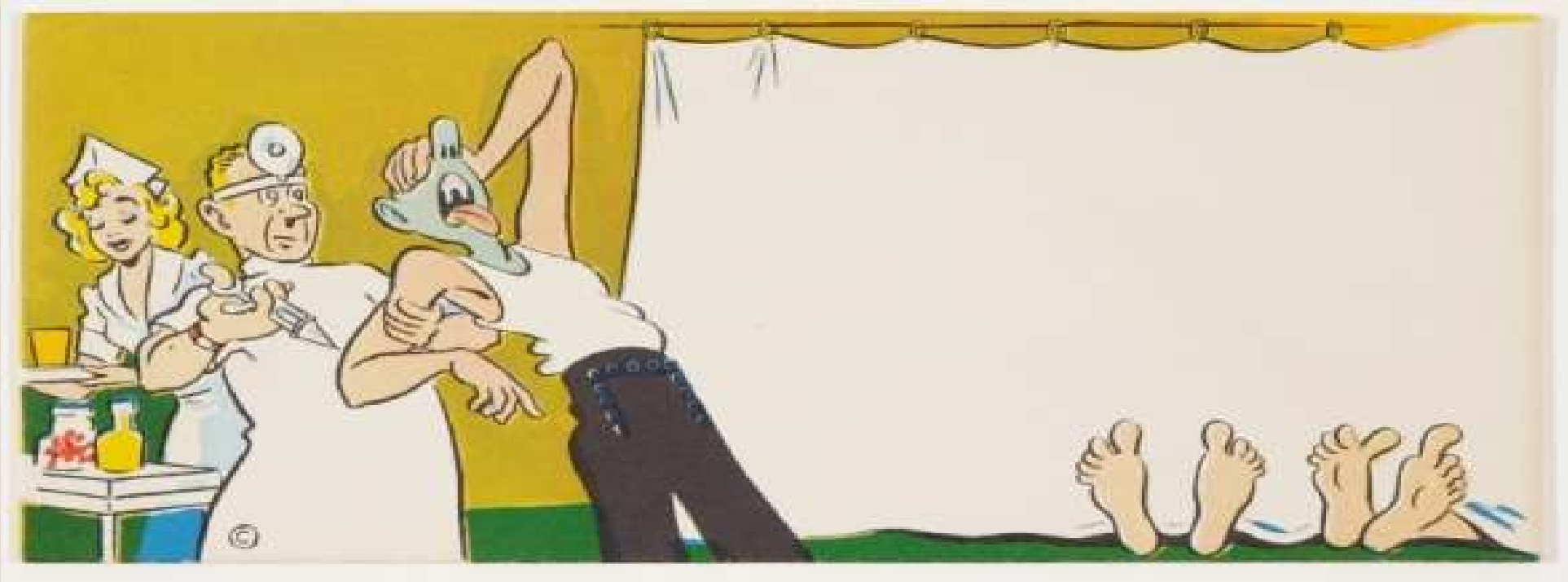
Some patients at ongoing risk of OI despite minimal exposures
Others only get OI if significant exposure

Mainly community acquired viruses as well as infections with chronic graft dysfunction

- Fungal infections.

- Growth from urine particularly if recurrent or from blood may signify invasive disease and unlikely to clear if associated with indewlling catheter.
- Candida and Aspergillus account for ~ 80% of invasive fungal infections.
- Other 20% cryptococcus, other molds, and endemic mycosis
- Beware of fluconazole increasing CNI levels .reduce dose if levels already high and recheck after 48-72 hours

VACCINATIONS IN TRANSPLANT RECIPIENTS



7 While vaccination in ESRD may be less effective and durable than in healthy patients a better response can be anticipated prior to transplant than after

odeh04670@gmail.com, 31/05/2024

PRETRANSPLANT VACCINATION BOOSTERS TO BE GIVEN TO ALL TRANSPLANT RECIPIENTS UNLESS RECENT ADMINISTRATION CAN BE DOCUMENTED

1. Td (Tetanus toxoid, diphtheria)
2. Pneumococcal vaccine
3. Hepatitis B
4. Influenza

VACCINES THAT MAY NOT BE GIVEN (LIVE ATTENUATED VACCINES)

1. Bacille Calmette-Guérin (BCG)
2. Measles
3. Mumps
4. Rubella
5. Oral polio, Oral typhoid
6- varicella
7. Yellow fever

CMV

- Largest known virus to infect human beings
- greek cyto-, "cell", and -megalo-, "large".
- In humans it is commonly as Human Herpesvirus 5 (HHV-5).
- belongs to the Betaherpesvirinae subfamily
- Other herpesviruses include Alphaherpesvirinae (HSV1/2 and VZV) Gammaherpesvirinae (including EBV).
- All herpesviruses share a characteristic ability to remain latent within the body over long periods.

One of the most frequent infections seen in solid organ transplant recipient

Pediatrics population is specifically at increased risk due to high prevelance of seronegativity in children and serpositivity in donors
Seroprevalence is age-dependent

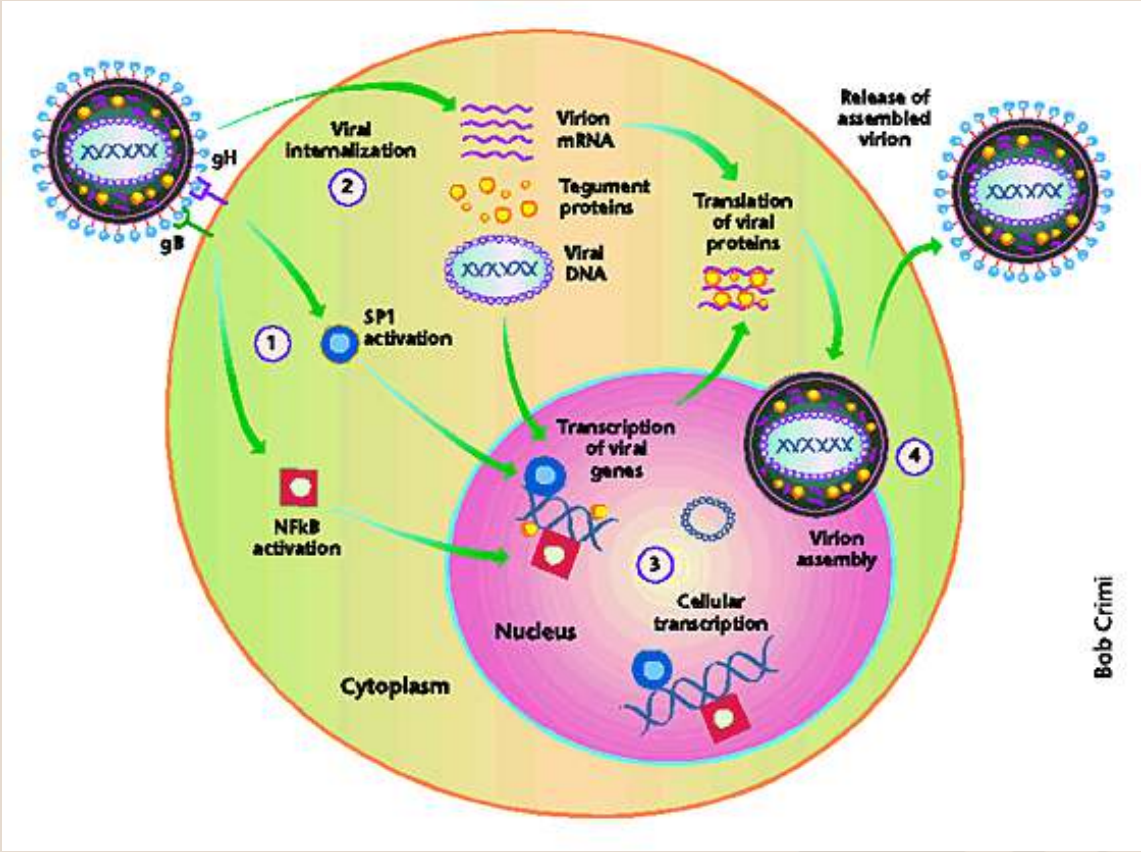
Causes morbidity and mortality through direct tissue invasive disease and indirect immunomodulatory effects

Pediatric data are scarce and many are extrapolated from adult literature

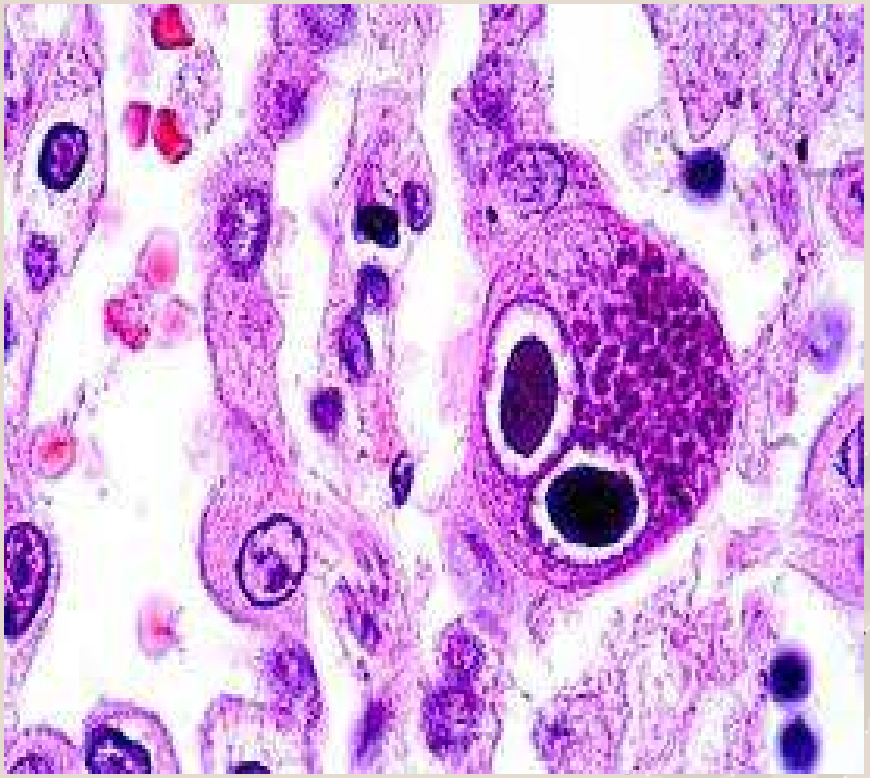
Controversies about type and duration of prophylactic therapy and optimal dosing of antiviral agents

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8837208/#

- In normal hosts: asymptomatic or causes an acute mono-like illness.
- Establishes latency in PMNs, T cells, endothelial cells, renal epithelium cells, and salivary gland.
- Wide spectrum of disease in immunocompromised hosts.



- CMV demonstrated by intranuclear inclusion bodies, showing the virus replicates in the nucleus rather than the cytosol. These inclusion bodies stain dark pink on an H&E stain, and are also called "Owl's Eye" inclusion bodies.
- Replicating virus disrupts the cytoskeleton, causing massive cell enlargement, which is the source of the virus' name.



Definitions

- CMV infection
  - Evidence of CMV replication regardless of symptoms
- CMV disease
  - Evidence of CMV infection with attributable symptoms
  - Viral syndrome with fever and/or malaise, leukopenia, thrombocytopenia, or tissue invasive disease

Impact of CMV disease

Direct effect :

Tissue invasive disease: Gi disease, hepatitis , penumonities , nephrities, CNS disease , retinitis pancreatities,cardities and others .

moratlity

Indirect effect:

Acute allograft rejection , chronic allograft failure, opportunistic infections as fungal ,bacterial , PTLD, hepatitis C recurrence ,HHV 6/7

NODAT

3 Although risk of tissue invasive disease has decreased it continues to cause morbidity through indirect immunmodulatory effect

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4 Causes bronciolities obliterates and chronic lung allograft dysfunction in lung reciepent

Causes coronary vasculopathybin heart reciepent

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Factors Influencing Reactivation of CMV and Progression to CMV Disease:

↑ CMV reactivation

Allograft rejection

Depleting antibodies

Stress- critical illness, surgical procedure, bacterial & fungal sepsis.

↑progression to disease

Lack of innate immunity (D+/R-)

IS: depleting antibodies,

MMF (> 2gm/day)

High dose methylprednione

Viral load

Mechanisms of Acquiring CMV Infection After transplantation

- Primary CMV infection (D+ /R-)- HIGH RISK
  (VIA TRANSPLANTED ORGAN OR TRANSUFION)
- Reactivation (D-/R+) -INTERMEDIATE RISK
- Superinfection (D+/R+) -INTERMEDIATE RISK
- Naïve (D-/R-) - LOW RISK
  (UNLESS TRANSFUSED D+ BLOOD PRODUCTS)

Therapeutic Strategies for CMV

1 –Universal prophylaxis :
Administration of anti-CMV therapy to all patients except seronegative recipient of a seronegative organ
* Targeted prophylaxis based on risk or selected recipient

2- Preemptive treatment:
Administration of anti-cmv therapy to patients at first sign of cmv infection

3- Standard therapy for those with the disease

	Universal Prophylaxis	Pre-emptive Therapy
Efficacy	Yes: large RCT	Yes: smaller trials, fewer D+/R-
Ease	Relatively easy to coordinate	More difficult to coordinate
Late onset disease	Potential problem	Less commonly seen
Cost	Higher drug costs	Higher lab costs
Toxicity	Potential for greater drug toxicity (myelosuppression)	Potential for less drug toxicity with shorter courses of antivirals
Indirect effects (graft loss, mortality, & opportunistic infections)	Consistent and positive impact based on meta-analyses and limited comparative trials	Limited data

Categories risk of CMV based on serostatus of recipient and donor
(highest risk for D+R-)
Induction with lymphocyte depletion agent

Chemoprophylaxis with Valganciclovir was associated with 64% lower risk of CMV

Duration of chemo prophylaxis for 6 month in all high risk patients and 3 months for intermediate risk

Earlier cessation of prophylaxis was associated with higher incidence of cmv disease

Main concern about extending treatment is drug toxicity

American society of transplantation / pubmed 2022. KDIQO guidlines

Even CMV D-/R- are at risk of nosocomial or community acquisition of CMV.

Additional risk factors:

- Use of unfiltered blood products/ not leukodepleted
- * increased immune suppression leading to activation of latently infected cells
- (ATG, anti-rejection trx in past 14 days)

- We recommend that KTRs (except D-R-)receive Chemoprophylaxis for CMV with oral Valganciclovir for at least 3 months after transplantation and for 6weeks after treatment with T cell depleting antibody

It’s recommended that patients with any of the following conditions be evaluated for CMV by examination , whole blood PCR and end organ histology if indicated by clinical suspicion:
Fever , muscle pain, , leukopnia,thrombocytopenia anemia
,hepatitis,gastroenterology,pneumonities and retinitis.

It’s recommended to use age and BSA- based antiviral dosing to optimize therapy

It’s recommended that Valganciclovir be dosed around a meal for best absorption

Consider re-initiation of prophylaxis for a minimum of 3months for patient who undergo trx for acute rejection with anti lymphocyte antibodies who are serologically at risk D+ Or R+.

Slide 33

5 FDA approved dosing algorithm of vgnc based on bsa .this may result in higher doses than weight based formula in younger patient with low bsa and nl kft

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Table 4: Valganciclovir and Ganciclovir

A. Valganciclovir and Ganciclovir Dosing by Age

Age	Valganciclovir (oral)	Ganciclovir (IV)
< 3 years	7 × BSA × GFR* daily Monitor for signs of toxicity†	All ages: 5 mg/kg IV every 24 hours‡
3 to 18 years	7 × BSA × GFR* daily Up to 900 mg daily‡	
≥ 18 years	900 mg daily‡	

* See GFR calculations below
† Toxicity includes neutropenia, thrombocytopenia and renal dysfunction
‡ Requires dose adjustments with renal dysfunction, see below

B. *GFR Calculations:

Patient	Equation	Comment
Less than 18 years	Bedside Schwartz equation: • 0.413 × height (cm) / SCr (mg/dL) ◦ For less than 12 months: calculate to a maximum GFR of 100 mL/min/1.73m^2 ◦ Ages 1-18 years: calculate to a maximum GFR of 120 mL/min/1.73m^2	• This equation has not been validated below age 2 years. It was developed in children with chronic kidney disease but is reasonable to use in this population. • For patients less than 12 months old, there is no validated equation to estimate GFR. For VCV dosing, the Schwartz equation has been used but likely overestimates clearance. By 1 year of age normal GFR is in the range of 100 mL/min/1.73 m^2 therefore recommend maxing at this for dose calculations. Consultation with nephrology may be appropriate to help assess GFR. • This equation will overestimate GFR in children with markedly decreased muscle mass (see cystatin C-based alternative below)

Surveillance for CMV:

On day 1 post transplant and weekly thereafter for 12 weeks screen for CMV by PCR.

If CMV DNA detected in blood by PCR, pre-emptive treatment should start as 60% will go on to develop disease within 10 days

The viral load threshold for initiation of treatment varies between centers . Initiate Valganciclovir and reduce dose of immunosuppressant . If titers continue to rise despite this therapy ,then IV ganciclovir is commenced.

This should continue until PCR is negative. Most centers advice to have two negatives results.

We recommend that all CMV disease in pediatrics KTRs be treated with intravenous ganciclovir

We suggest continuing therapy until CMV no longer detectable by plasma NAT or pp65 antigenemia

We suggest reducing immunosuppressive medication in life threatening CMV disease that persist in face of treatment until CMV disease has resolved

We suggest monitoring graft function closely during CMV disease.

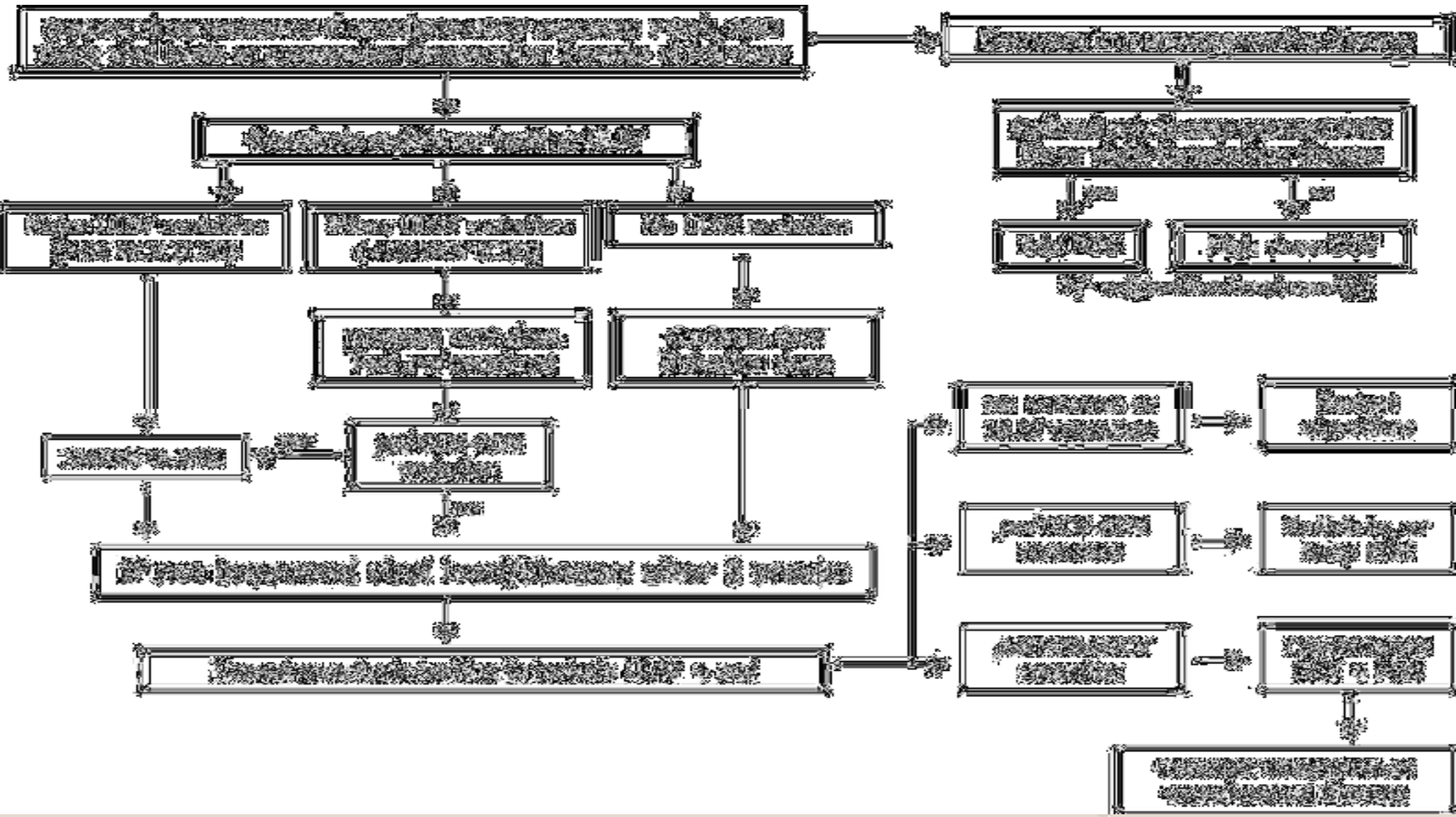
The presence of CMV infection and disease has been associated with the development of rejection independent of reduction of immunosuppression

Oral Valganciclovir Is Noninferior to Intravenous Ganciclovir for the Treatment of Cytomegalovirus Disease in Solid Organ Transplant Recipients

Baseline viral loads were not different between groups and decreased exponentially with similar half-lives and median time to eradication .

CMV Resistance

- Risk factors
  - Prolonged antiviral drug exposure
  - Ongoing active viral replication
  - Lack of prior CMV immunity
  - Inadequate antiviral drug delivery
- Ganciclovir resistance incidence 5-10%
- 90% ganciclovir resistant CMV isolates contain UL97 mutations
- Less common UL54, pol mutation



Home message:

Be aware of donor-transmitted infection
That are often(not always) occur in early post transplant and might be difficult to diagnose

CDC high risk behavior

Be aware of subclinical reactivation

Most of the data in regards to management of CMV are derived from adult literature and the filed is broad for research

Thank you