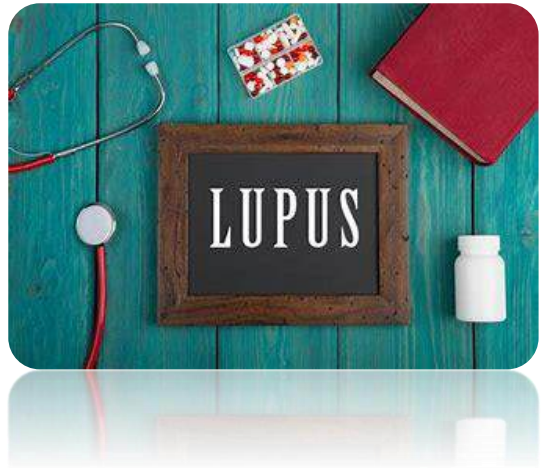
Lupus nephritis: Pathophysiology

Basics and beyond…..

Devi S. Sruthi.

Epidemiology



- Childhood onset SLE(c SLE): 20% of all SLE cases (<16 years)

  65% (16-55 years)

  15% (>55 years)

- Clinically significant lupus nephritis occurs in 50-75% in pediatric SLE cases within first 2 years

- Severity of nephritis is more in children

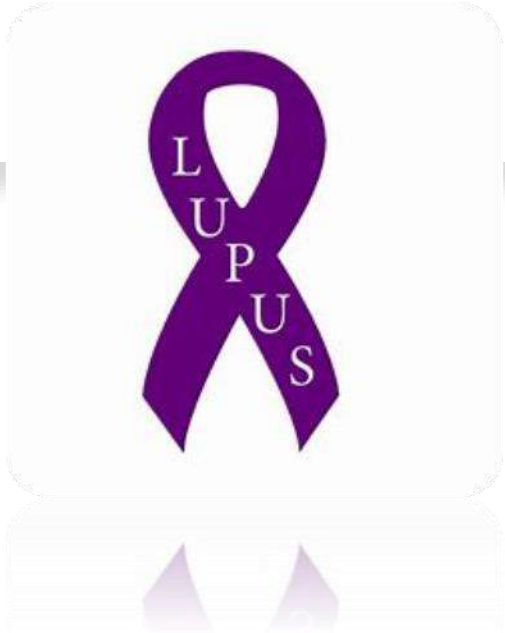
Sex: Female-male ratio→ in children 3:1

Prepubertal age 2:1

Adolescents 4.5:1

Adults 7:1 to 15:1

Severity of nephritis ↑males



Race: high in Asians, Africans & Hispanics

Risk factors

Genetic factors polygenic vs monogenic ??

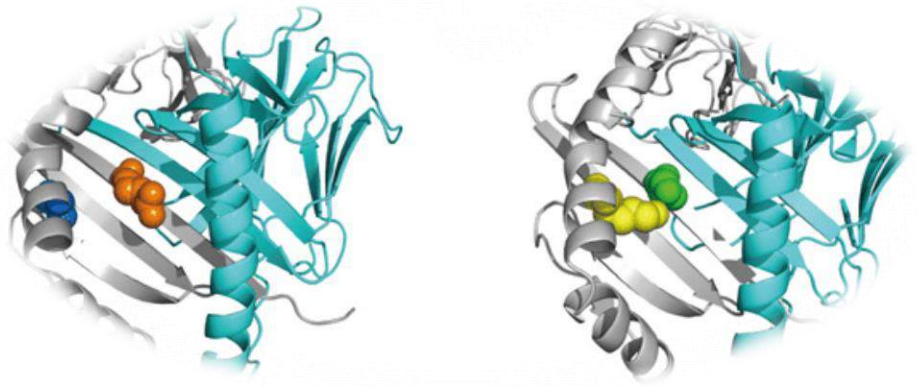
Environmental Factors

Hormonal factors

Genetics

- Polygenic
- GWAS - Over 100 loci
- Genes affecting
  - B cell signalling
  - Neutrophil function
  - Interferon regulation
  - Immune complex clearance
  - Toll like receptors
  - B cell survival factor(BAFF)

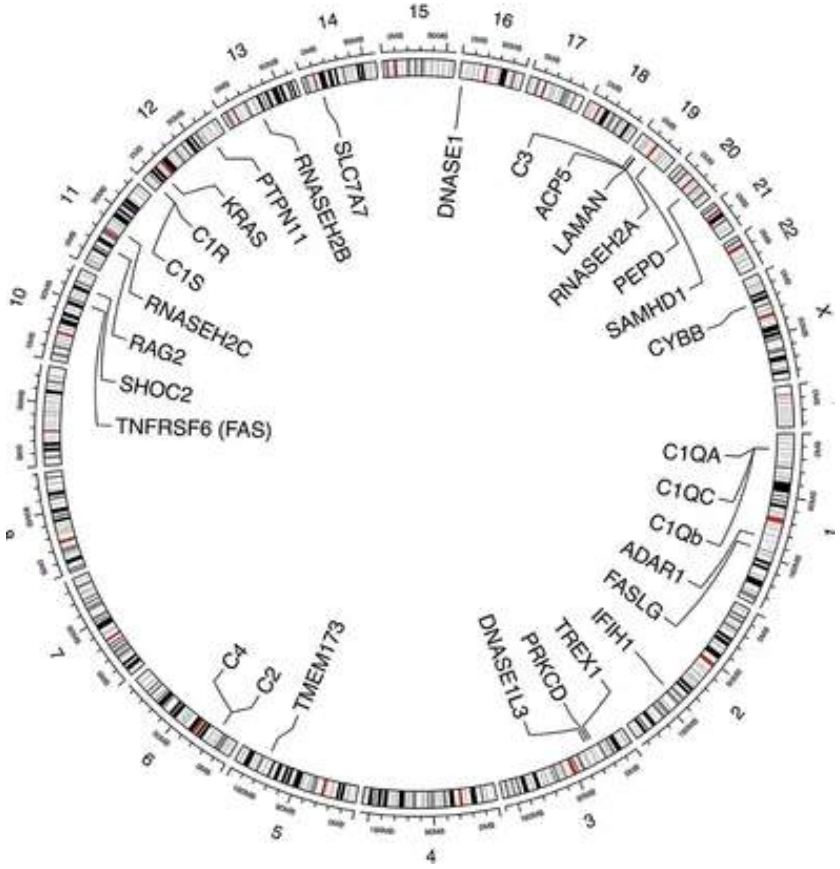
Genetics



- HLA DR2 DR3 and HLA DR 15 increased risk
- HLA DR4 and HLA DR 11 protective effect

Monogenic lupus

- Pediatric lupus<5 years
- pathogenic variants in a single gene
- Familial clustering-dominant/recessive inheritance
- High penetrance
- Severe disease manifestation
- Eg:
  - C1q, C2, C4 deficiency
  - Type 1 IFN pathway
  - TREX 1 gene-exonuclease that degrades ss RNA (familial chilblain lupus)

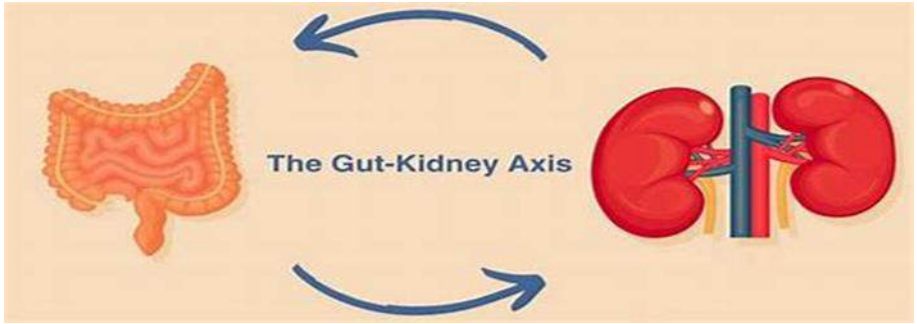


Environmental triggers

- UV exposure – **“skin-kidney axis”**
- ↑ keratinocyte apoptosis
- stimulate keratinocytes to secrete cytokines(IL-1) - B cells activation –antibody production.
- systemic autoimmunity –promotion of macrophage activation, antigen processing, autoreactive T cells (DNA hypomethylation)

Environmental triggers

- Psychosocial stress & Trauma
- Infections- EBV
- Smoking
- Drugs like hydralazine, procainamide, anti TNF biologics, quinidine
- Gut microbiome dysbiosis

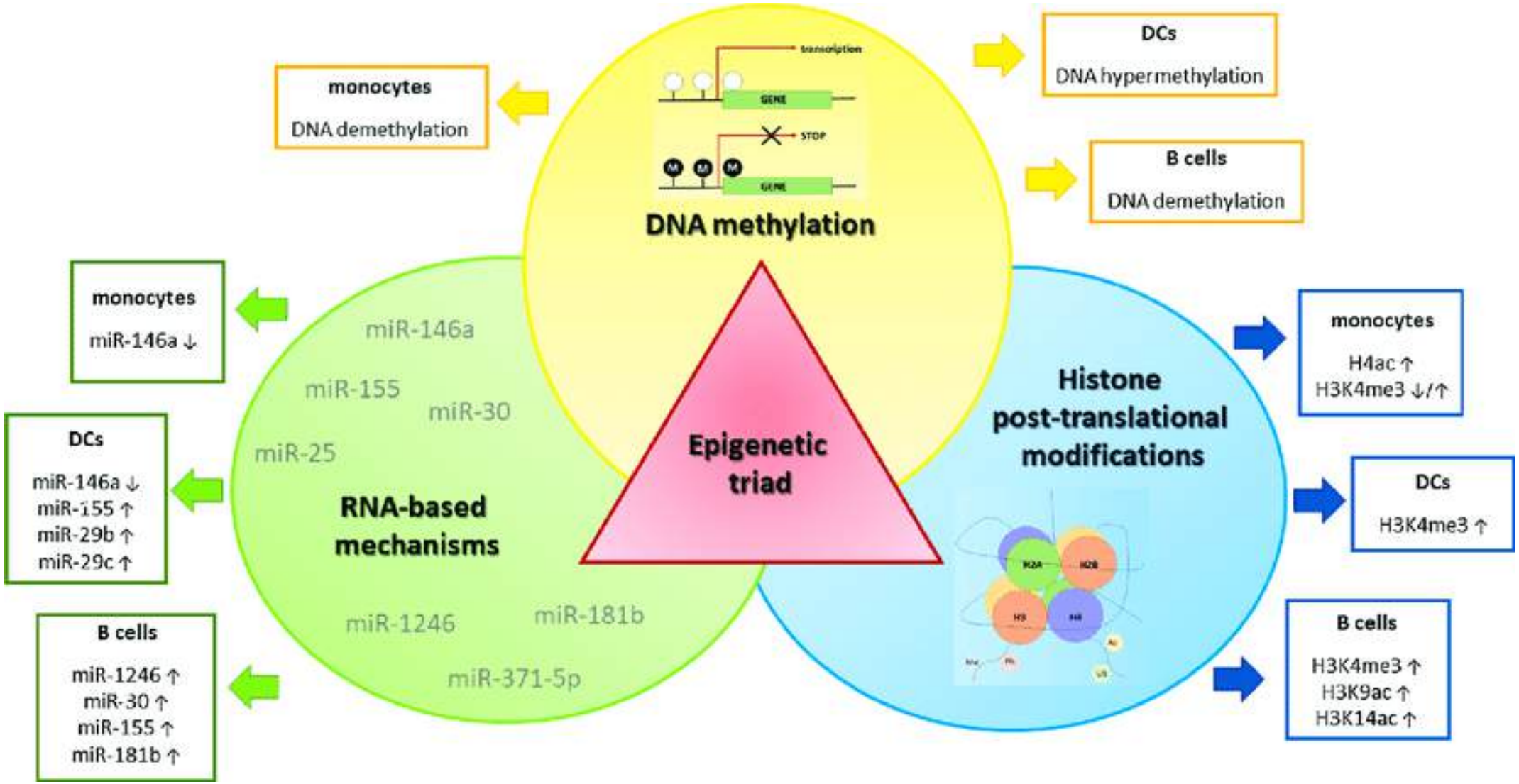


Hormonal factors

Estrogen

- early menarche, treatment with estrogen-OCP s ,HRT
  - stimulate the type 1 IFN pathway, IL1 & cytokine release
  - ↑ T cells, B cells, macrophages , ↓apoptosis of self reactive cells
  - Both progesterone & estrogen promotes Th2 response

- **Androgens** – tend to be immunosuppressive


monocytes
DNA demethylation
DCs
DNA hypermethylation
B cells
DNA demethylation
DNA methylation
monocytes
miR-146a ↓
DCs
miR-146a ↓
miR-155 ↑
miR-29b ↑
miR-29c ↑
B cells
miR-1246 ↑
miR-30 ↑
miR-155 ↑
miR-181b ↑
miR-146a
miR-155
miR-30
miR-25
RNA-based mechanisms
miR-1246
miR-181b
miR-371-5p
Epigenetic triad
Histone post-translational modifications
monocytes
H4ac ↑
H3K4me3 ↓/↑
DCs
H3K4me3 ↑
B cells
H3K4me3 ↑
H3K9ac ↑
H3K14ac ↑

Why more in females?

- Hormonal effect of estrogen
- X chromosome(atleast 3 genetic variants) “gene dose effect”
- Sex specific epigenetic modifications -DNA hypomethylation- X chrom.
- Difference in gut microbiota b/w sexes
- Pregnancy→ hormonal changes, increase in complement levels, microchimerism.

Pathogenesis

- What distinguishes the pathogenesis of SLE from other auto immune disorders?

- Disease heterogeneity

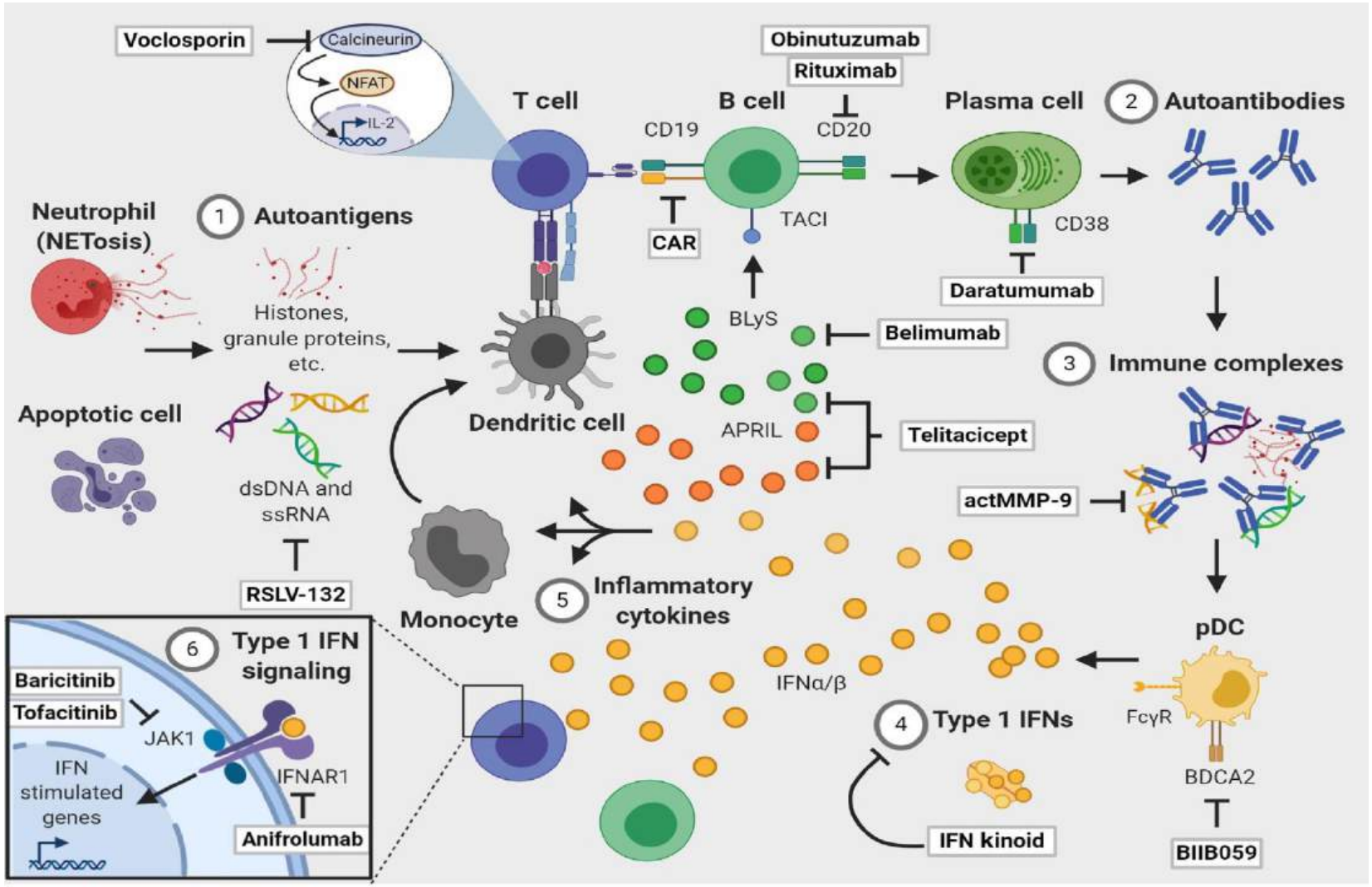
“rather a clinical syndrome”

different combinations of genetic alterations that cause systemic autoimmunity through different avenues of immune dysregulation.

Pathogenesis

- Why is it currently relevant?

Bench to bedside-the novel therapies



Pathogenesis

Loss of self tolerance for nuclear auto antigen

Aberrant activation of innate and adaptive immunity

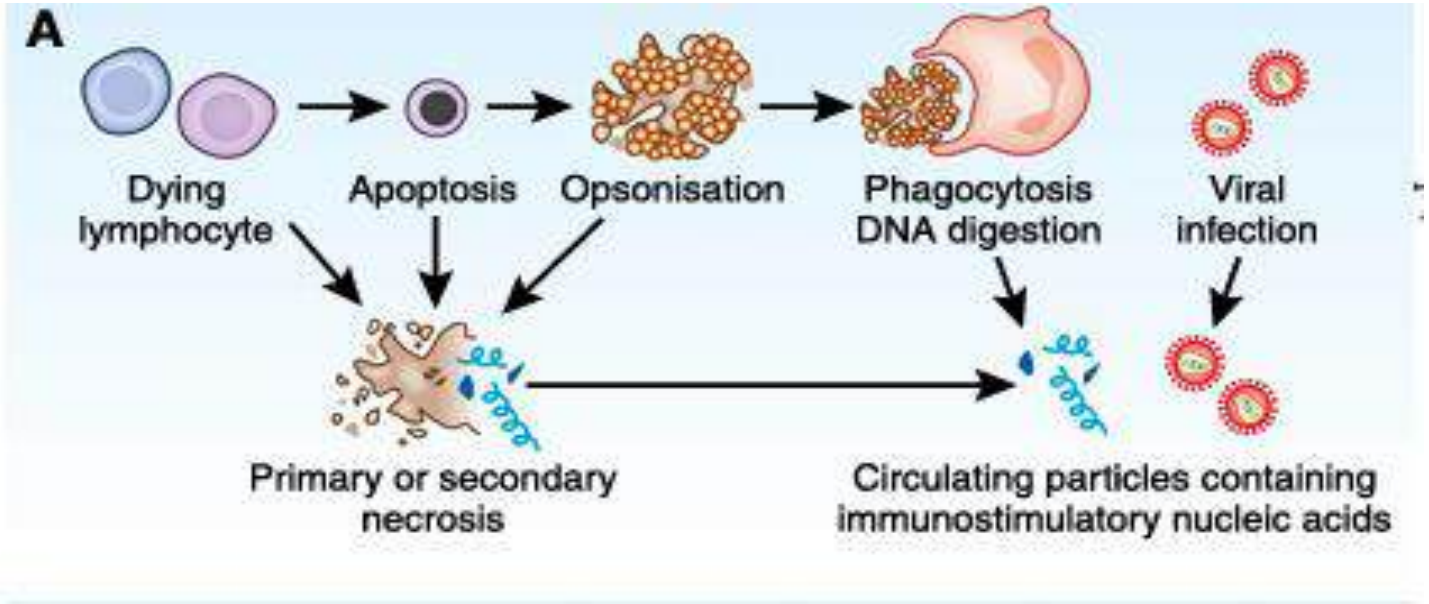
Immune complex formation

Immune mediated tissue injury, aberrant cytokine expression and healing

Loss of self tolerance to nuclear autoantigens

- Abnormal regulation of apoptosis
- defective clearance of apoptotic material as in C1q, C2 ,C4 def

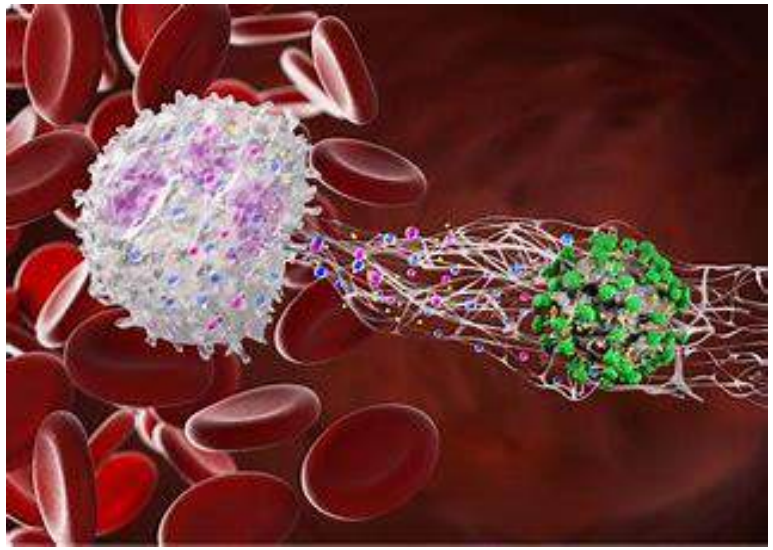
  increased levels of nuclear materials in blood " auto antigens"

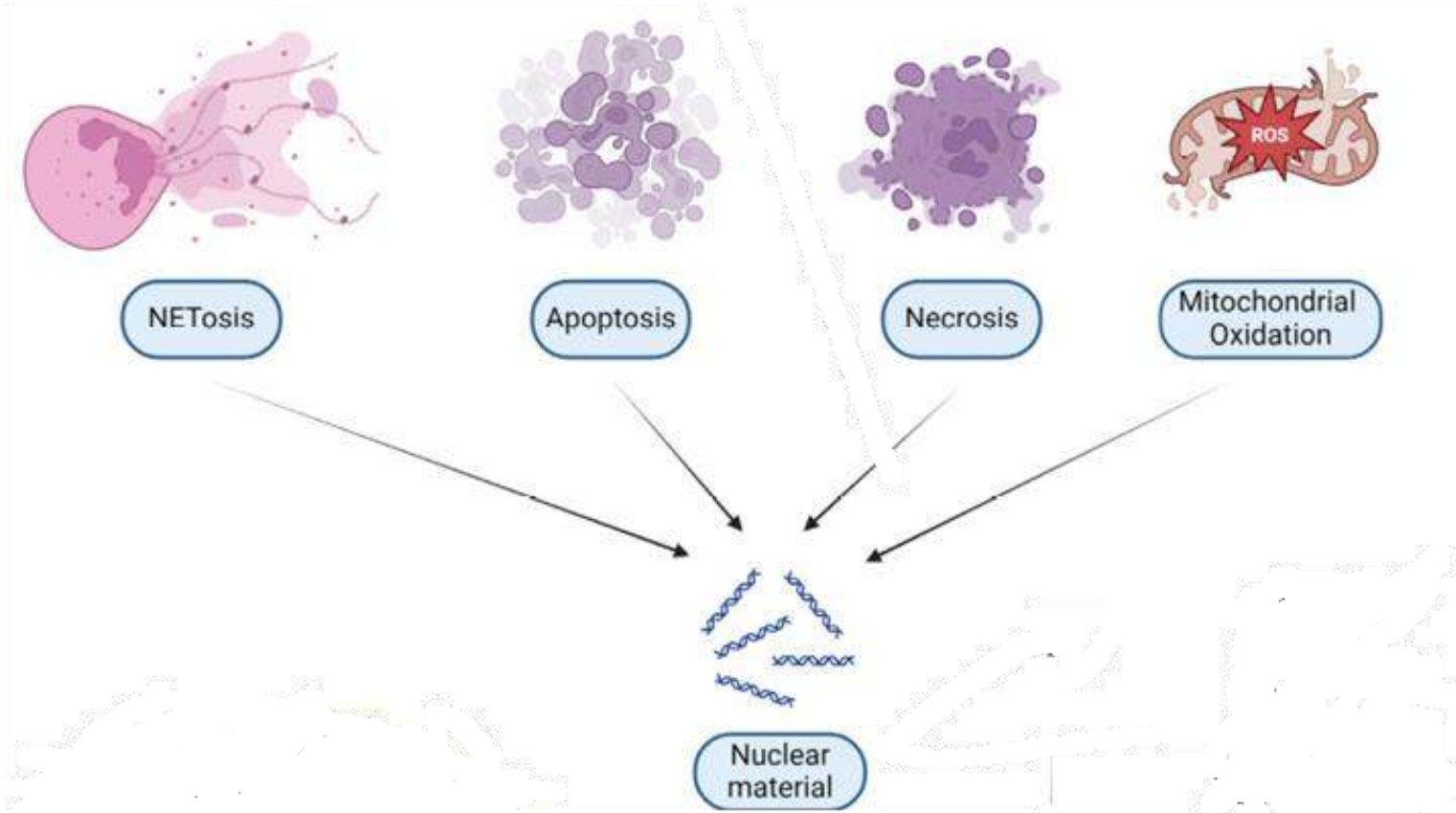


Role of neutrophils-NETosis

- In SLE
  - associated with ↑ no of circulating neutrophils undergo NETosis
  - impaired NETs degradation by endonucleases
  - NET covered by antimicrobial peptides-LL-37 &HNP
  - source of antigen - stimulate production of IFNα & antibodies

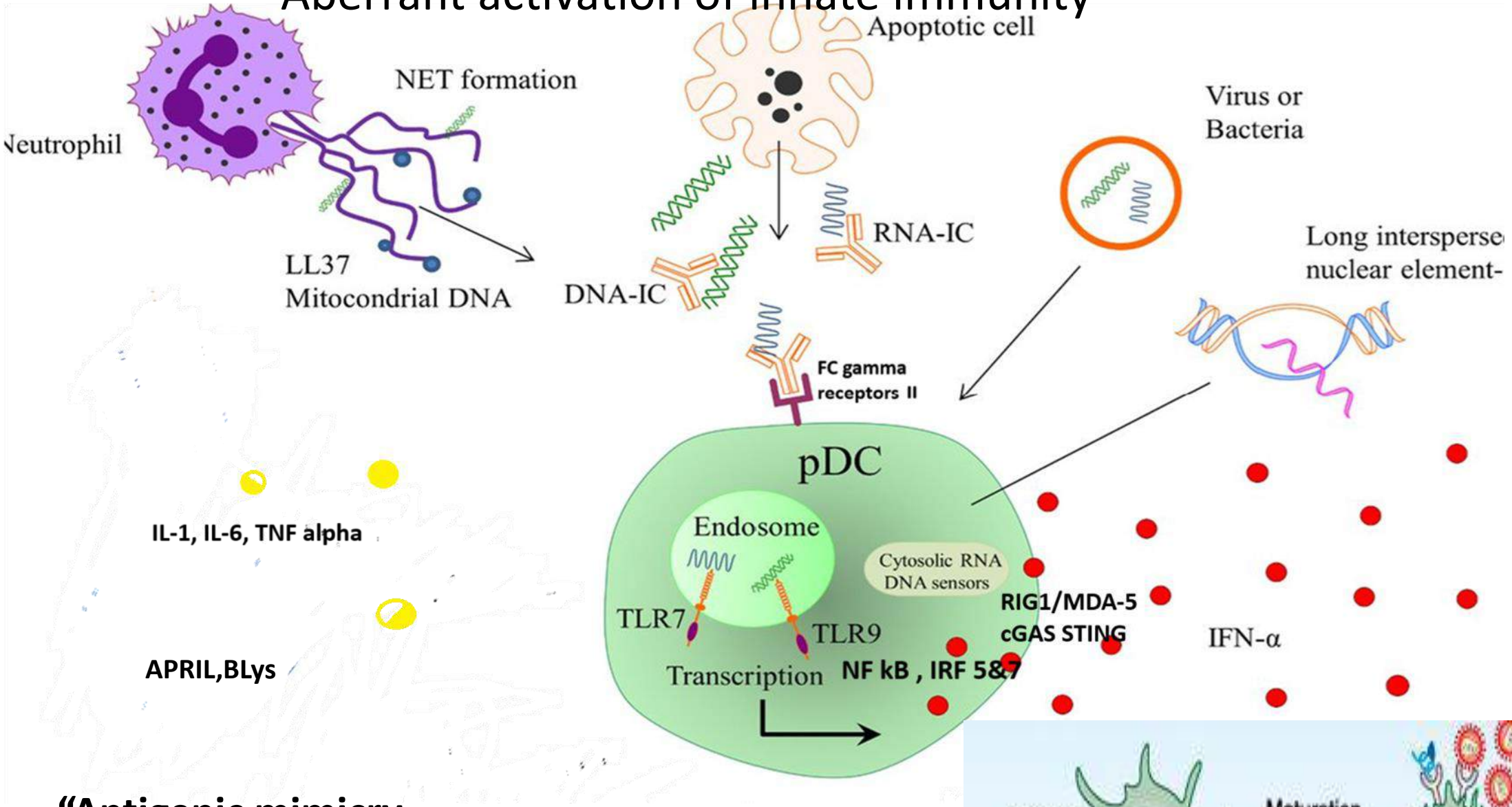
Nuclear Extracellulat Traps-
NET osis

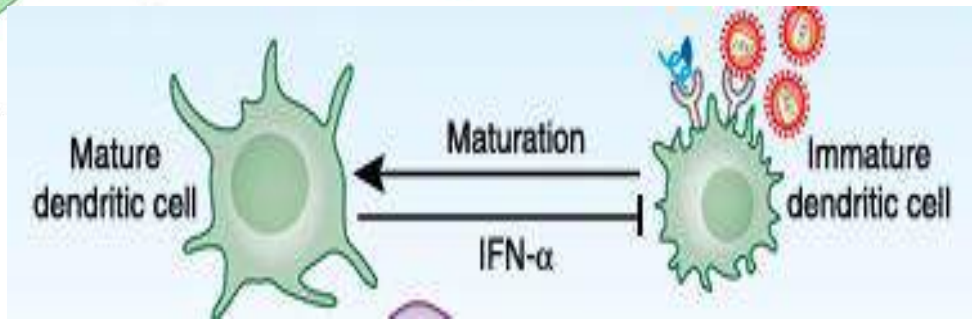




increased levels of nuclear materials in blood “ auto antigens”

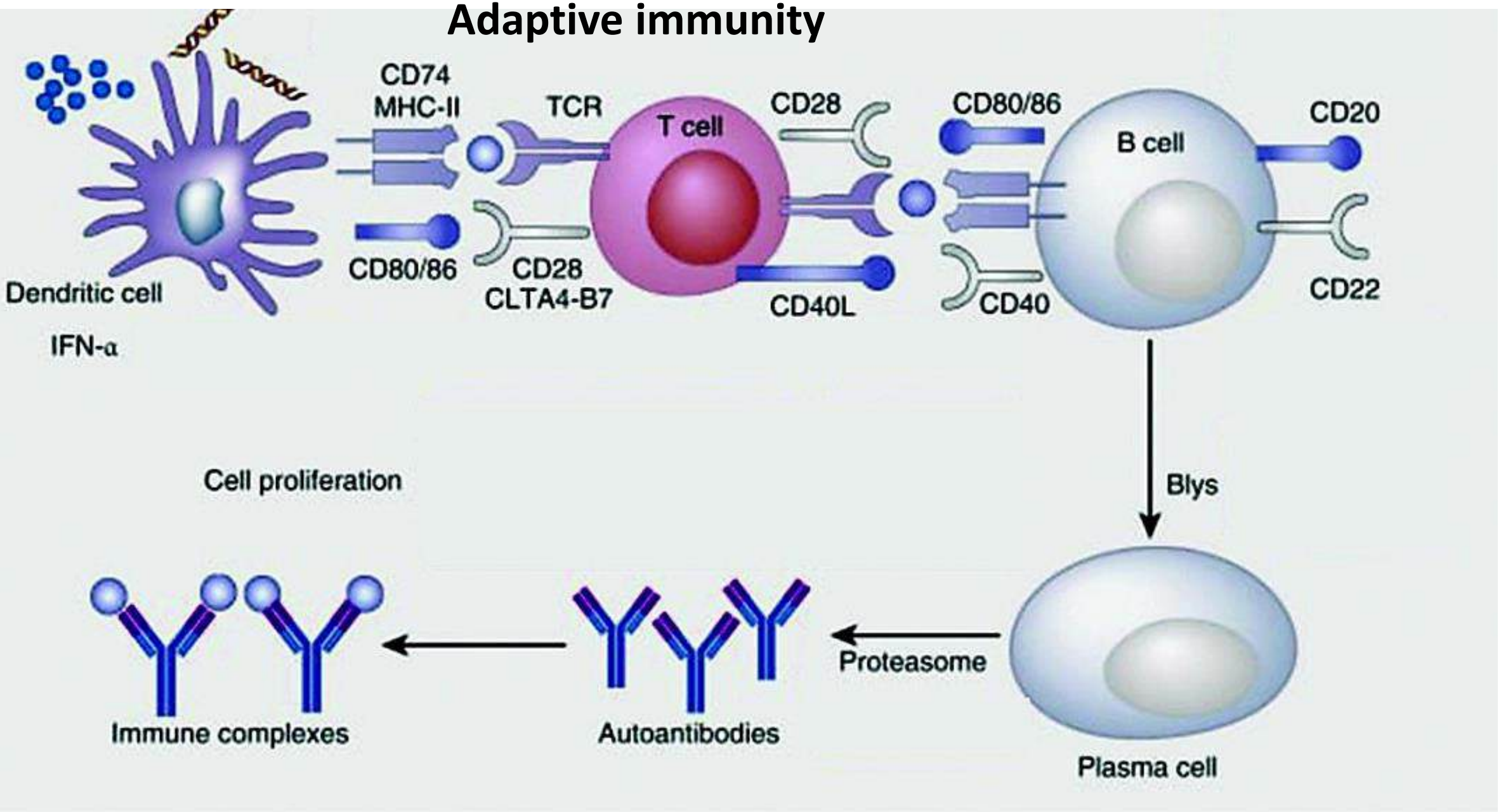
Aberrant activation of innate immunity

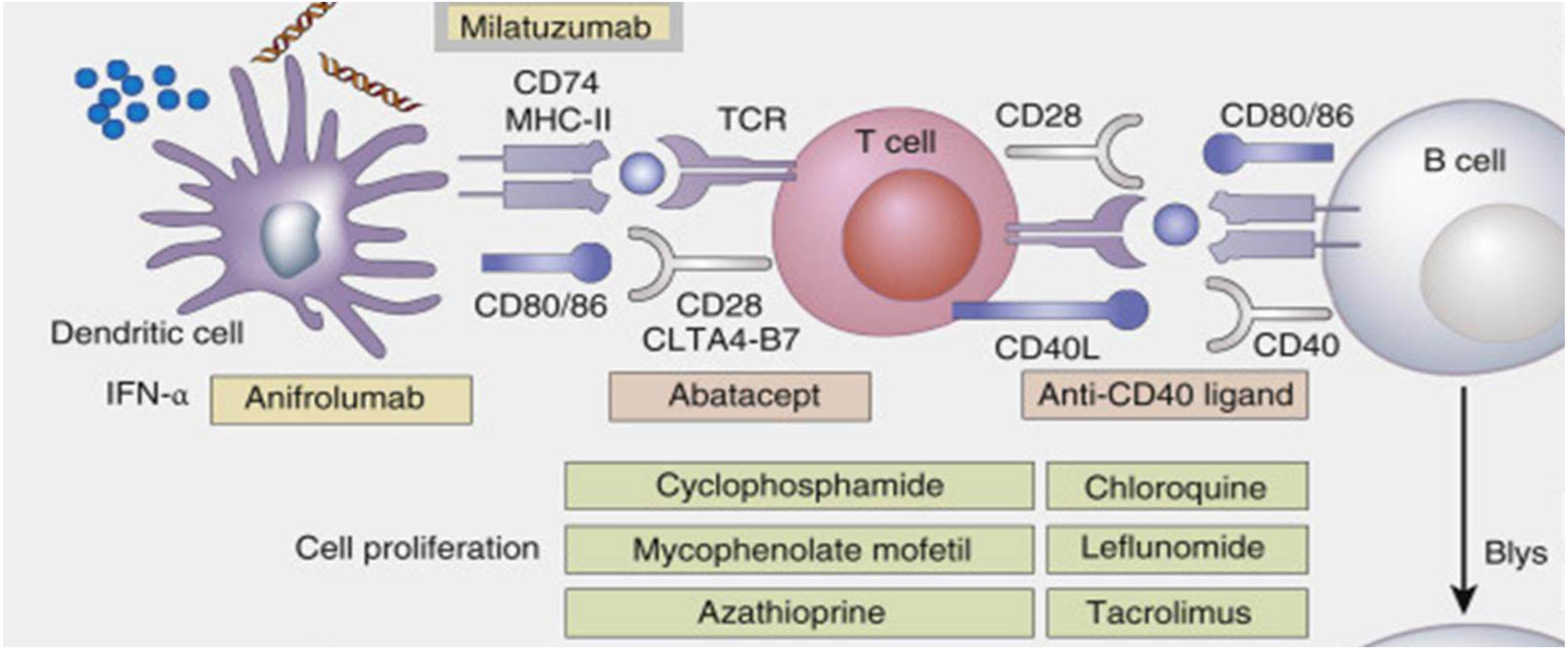




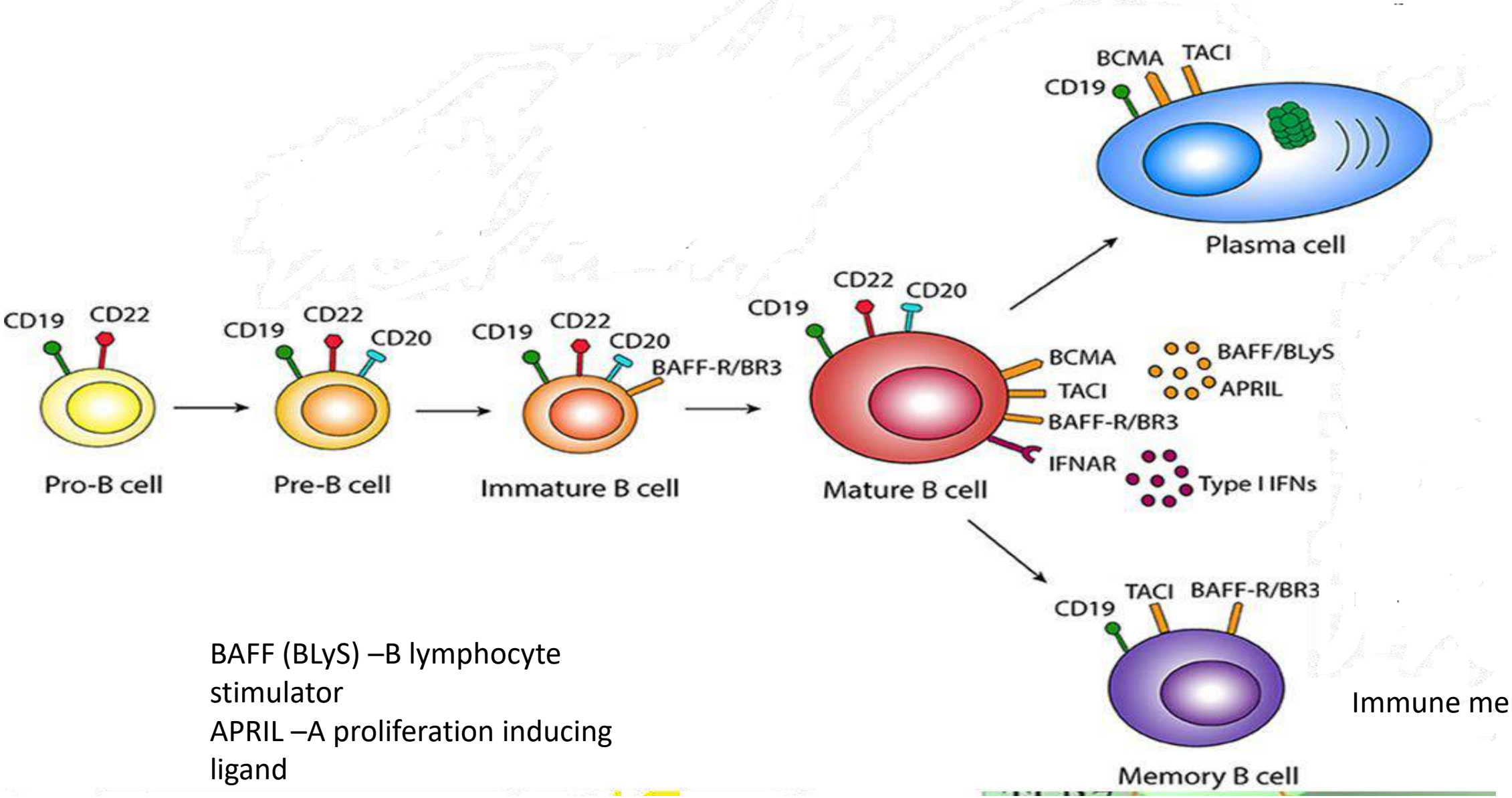
“Antigenic mimicry
-pseudo antiviral response”

Adaptive immunity



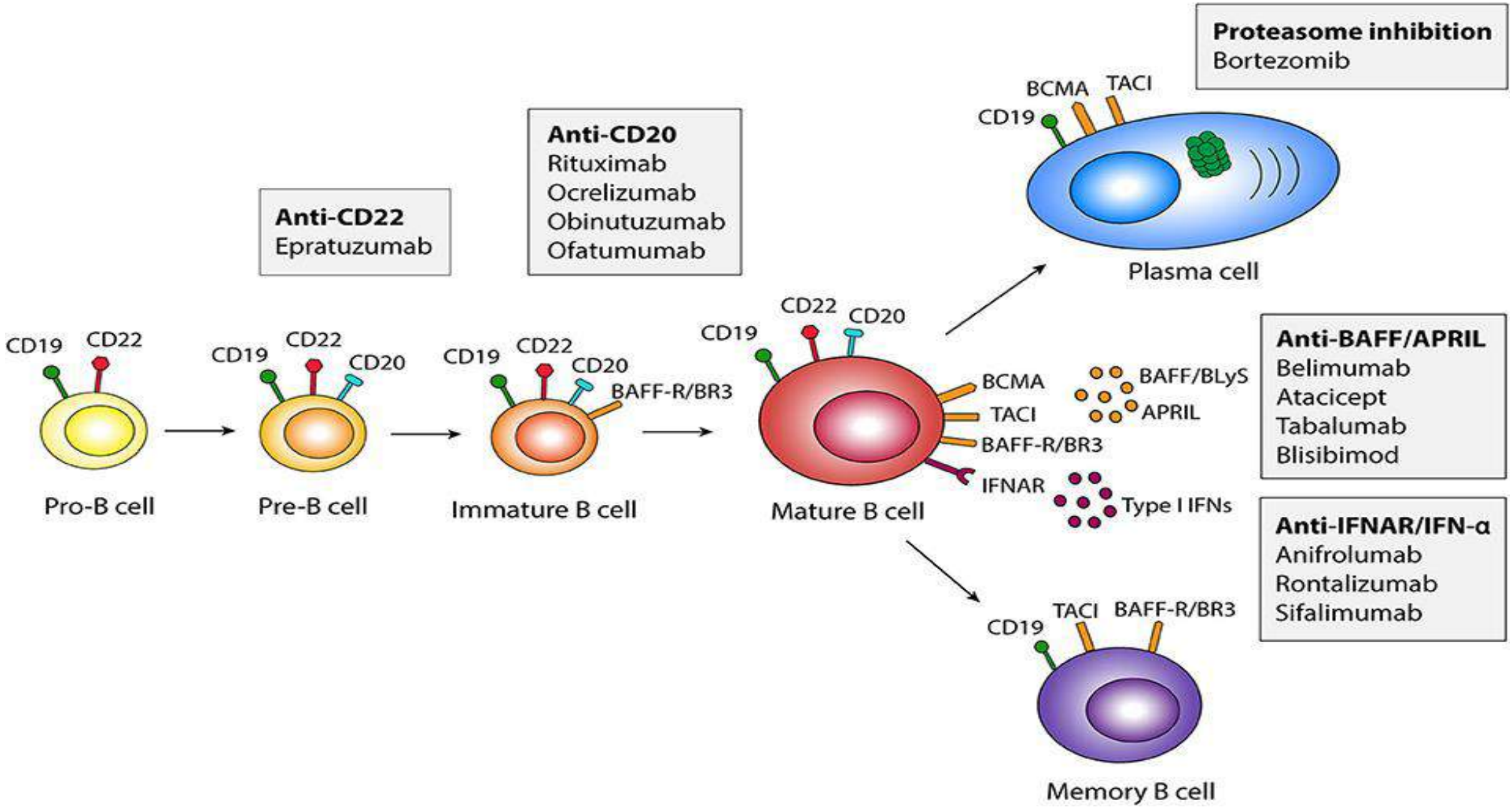

Milatuzumab
CD74
MHC-II
TCR
T cell
CD28
CD80/86
B cell
Dendritic cell
CD80/86
CD28
CLTA4-B7
CD40L
CD40
IFN-α
Anifrolumab
Abatacept
Anti-CD40 ligand
Cyclophosphamide
Chloroquine
Cell proliferation
Mycophenolate mofetil
Leflunomide
Azathioprine
Tacrolimus
Blys

Blvs . APRIL & role of B cells



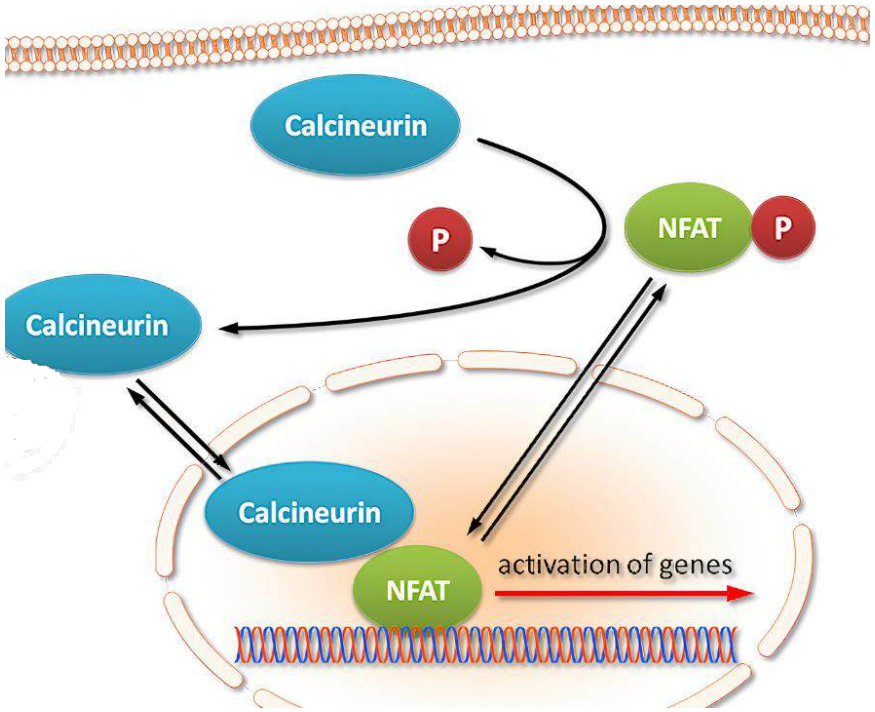
BAFF (BLyS) –B lymphocyte stimulator
APRIL –A proliferation inducing ligand

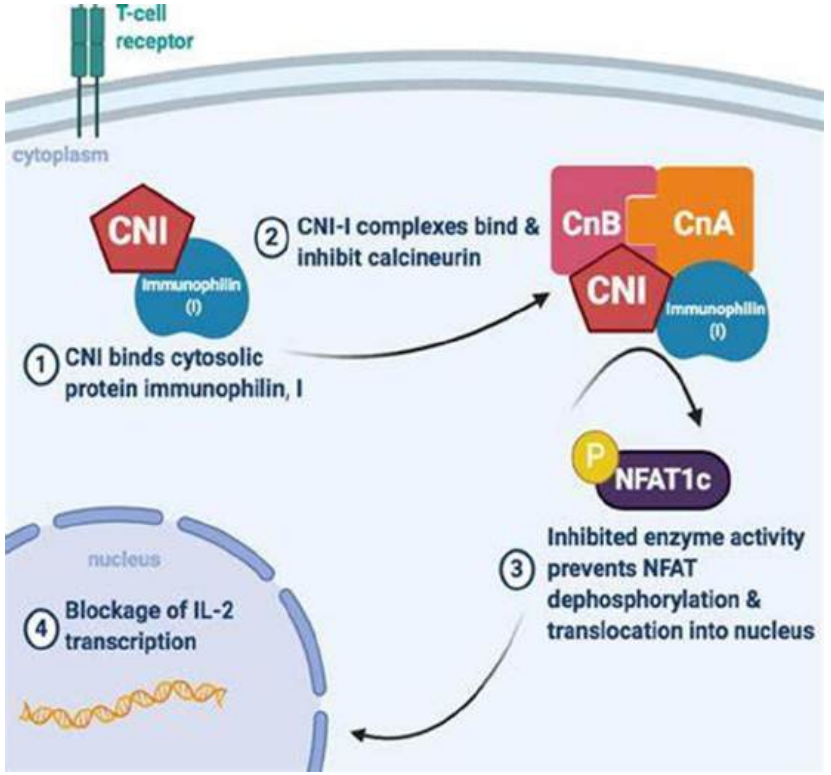
Immune memory


Proteasome inhibition
Bortezomib
BCMA
TACI
CD19
Plasma cell
Anti-CD22
Epratuzumab
Anti-CD20
Rituximab
Ocrelizumab
Obinutuzumab
Ofatumumab
CD19
CD22
CD20
BAFF-R/BR3
BCMA
TACI
BAFF-R/BR3
IFNAR
BAFF/BLyS
APRIL
Type I IFNs
Anti-BAFF/APRIL
Belimumab
Atacicept
Tabalumab
Blisibimod
Anti-IFNAR/IFN-α
Anifrolumab
Rontalizumab
Sifalimumab
Pro-B cell
Pre-B cell
Immature B cell
Mature B cell
Memory B cell

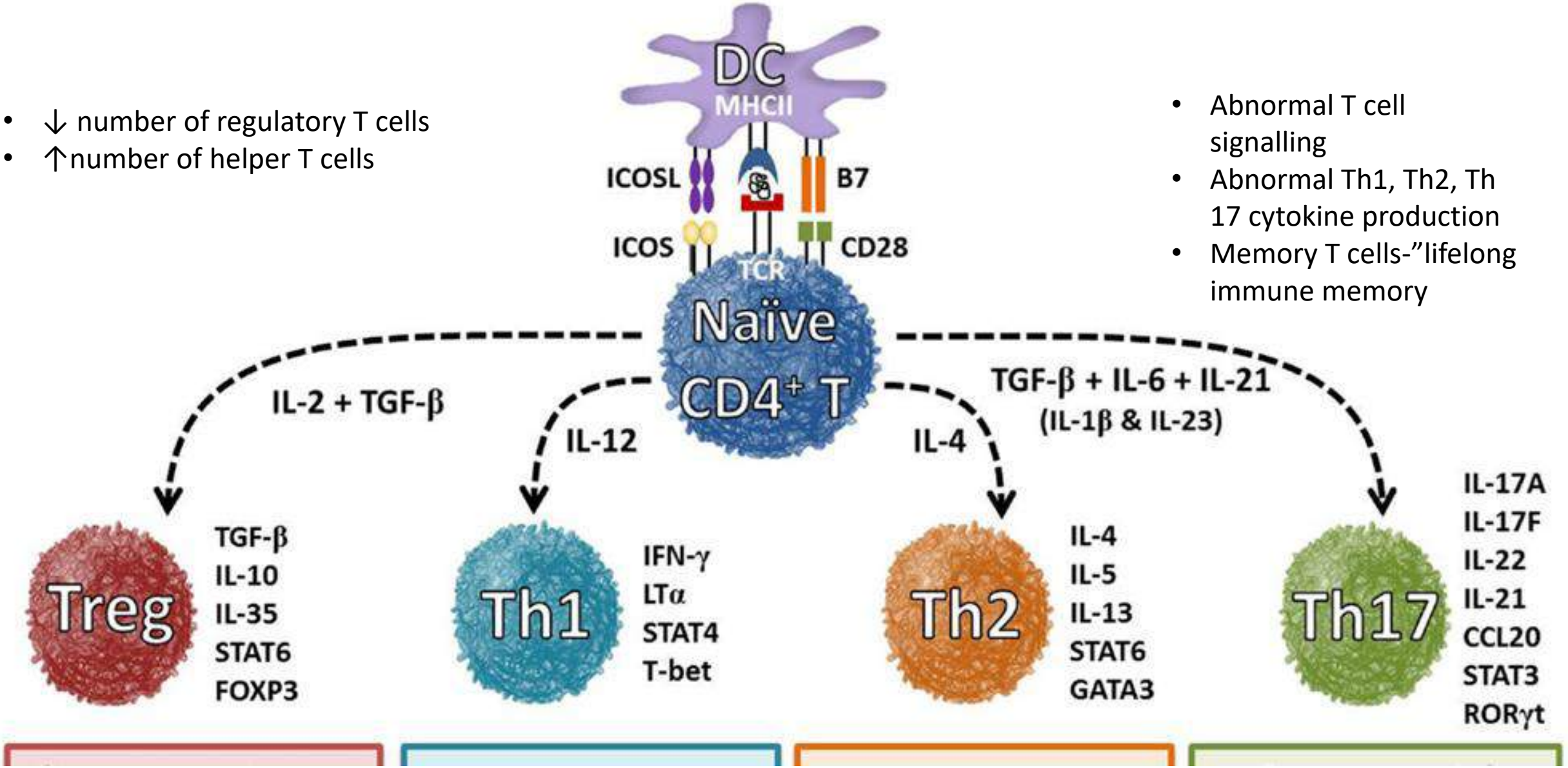
Role of T cells

- TCR activation-calcineurin activation- dephosphorylation & nuclear translocation of NFAT(nuclear factor of activated T cells)
- Downstream induction of cytokines





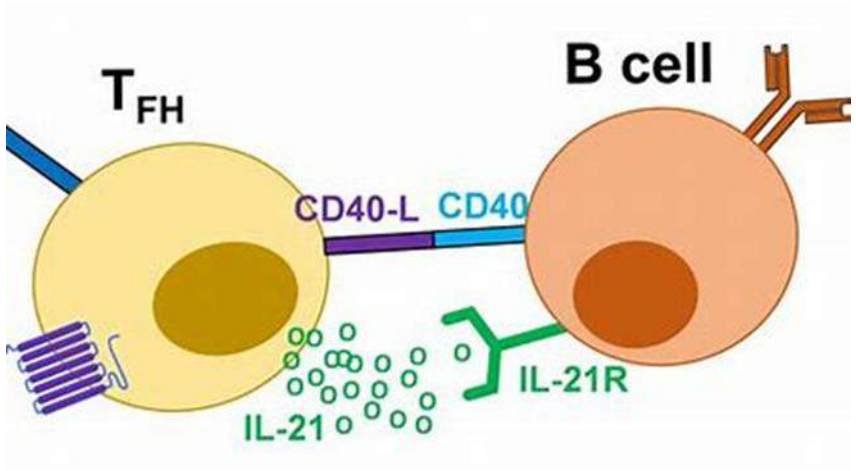
- ↓ number of regulatory T cells
- ↑number of helper T cells

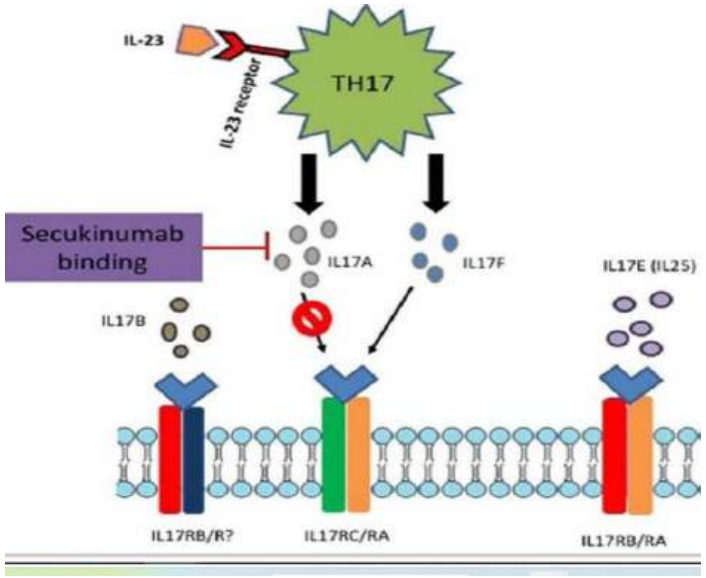


- Abnormal T cell signalling
- Abnormal Th1, Th2, Th 17 cytokine production
- Memory T cells-”lifelong immune memory

Tertiary lymphoid organ formation

- Follicular helper T cells (Tfh) Tfh support high-affinity autoreactive B cells and lymphoid germinal center formation
- Th 17 cells promote autoantibody formation in renal tissue





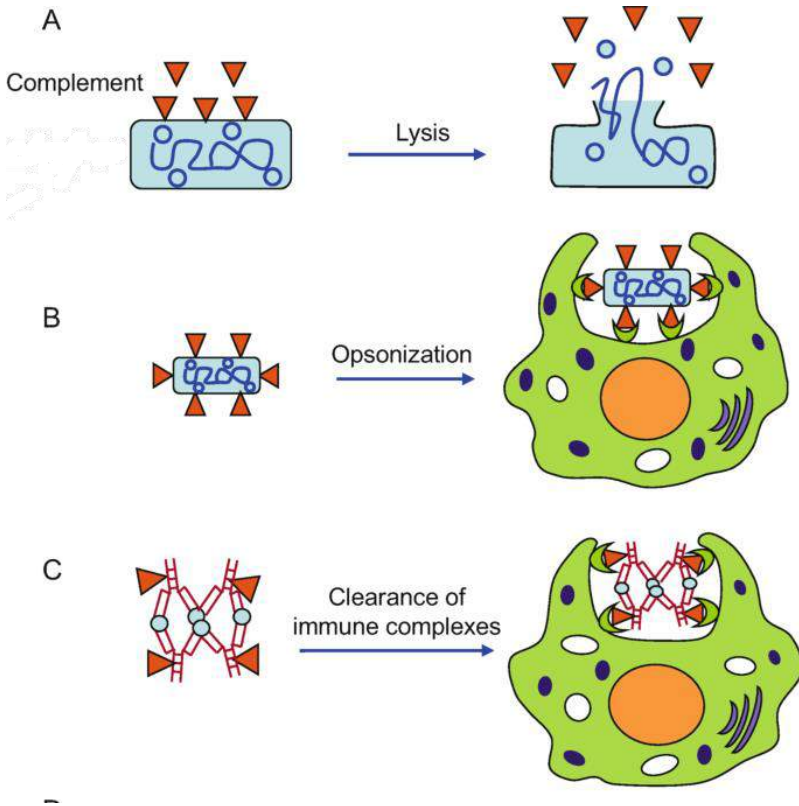
Antibodies

- 2 classes based on reactivity
  - components of the nucleosome (a complex of DNA and histones) – anti ds DNA, anti ss DNA
  - RNA-binding proteins (RBPs)- anti smith antibody

    anti Ro/SSA and anti La/SSB(neonatal lupus & congenital heart block), anti U1RNP

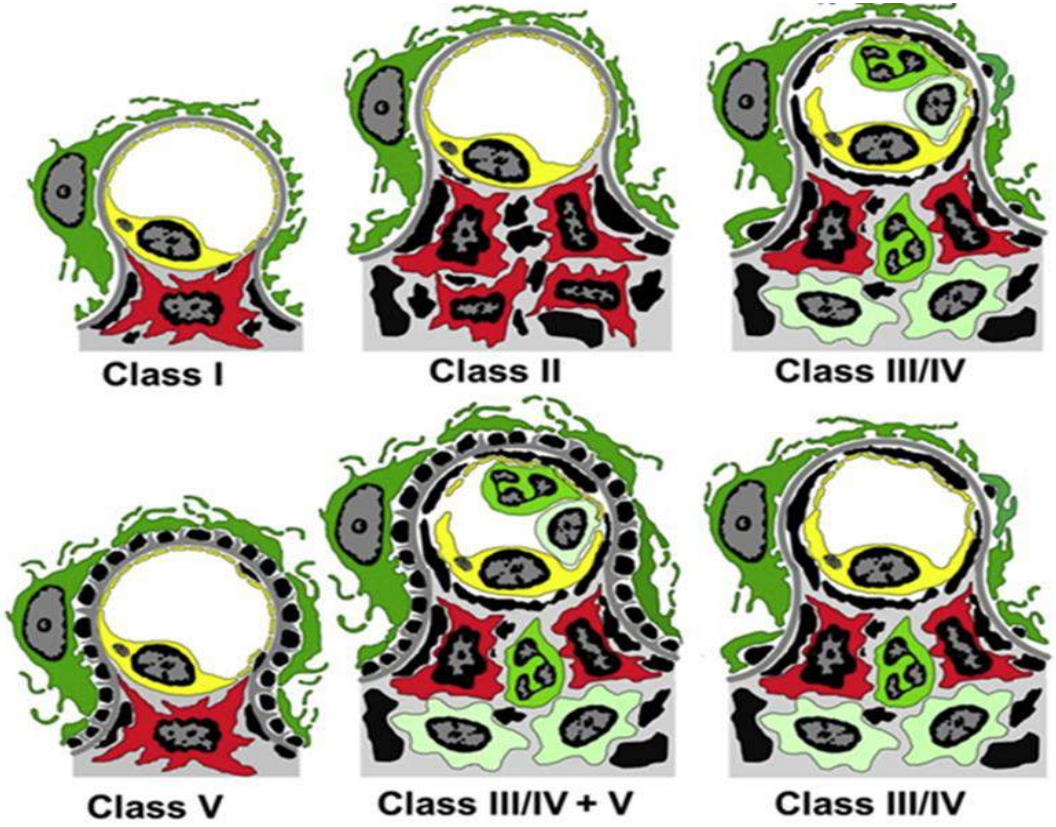
Immune complex formation

- Autoantibodies and antigens combine to form immune complexes, which persist in patients with SLE
  - Defective complement mediated solubilization and clearance
  - Defective FC receptor mediated phagocytosis by monocytes/macrophages



From antibody to injury

- combine with their target antigens - localize to compartments within the glomerulus



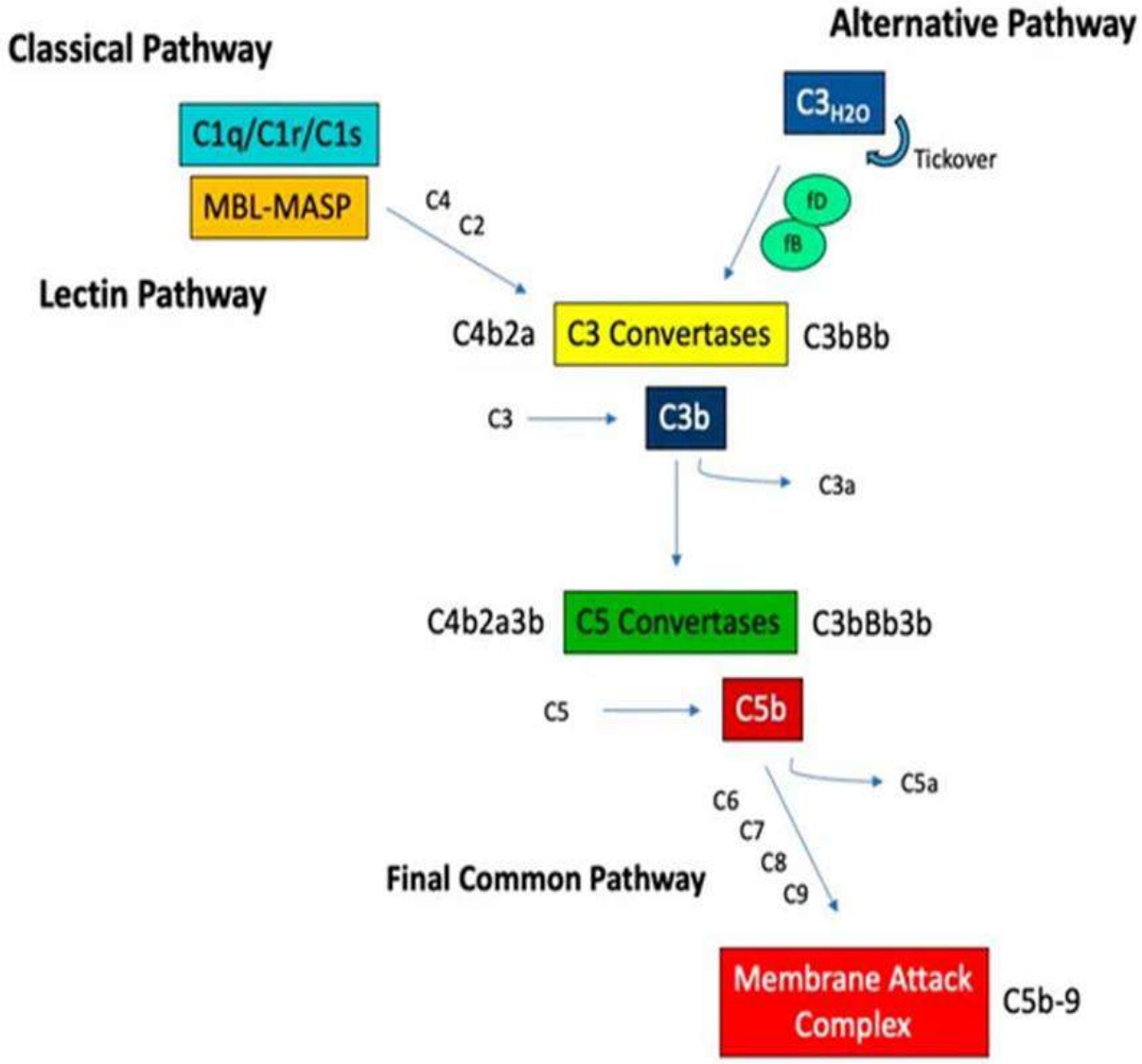
Potential autoantigens

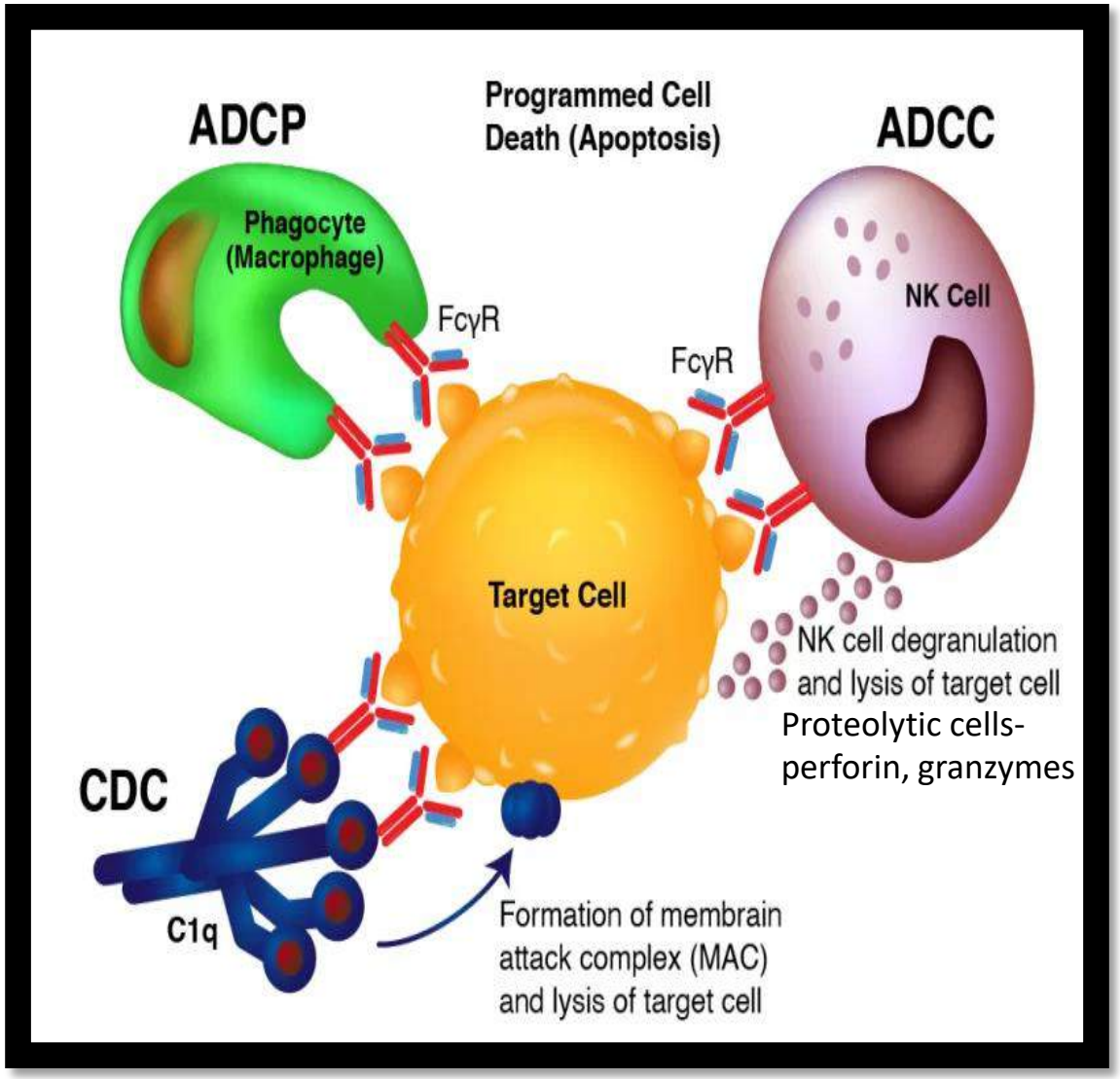
- Annexin –A 1-proliferative lupus
- NCAM, **EXOSTOSIN 1/2-membraneous lupus**

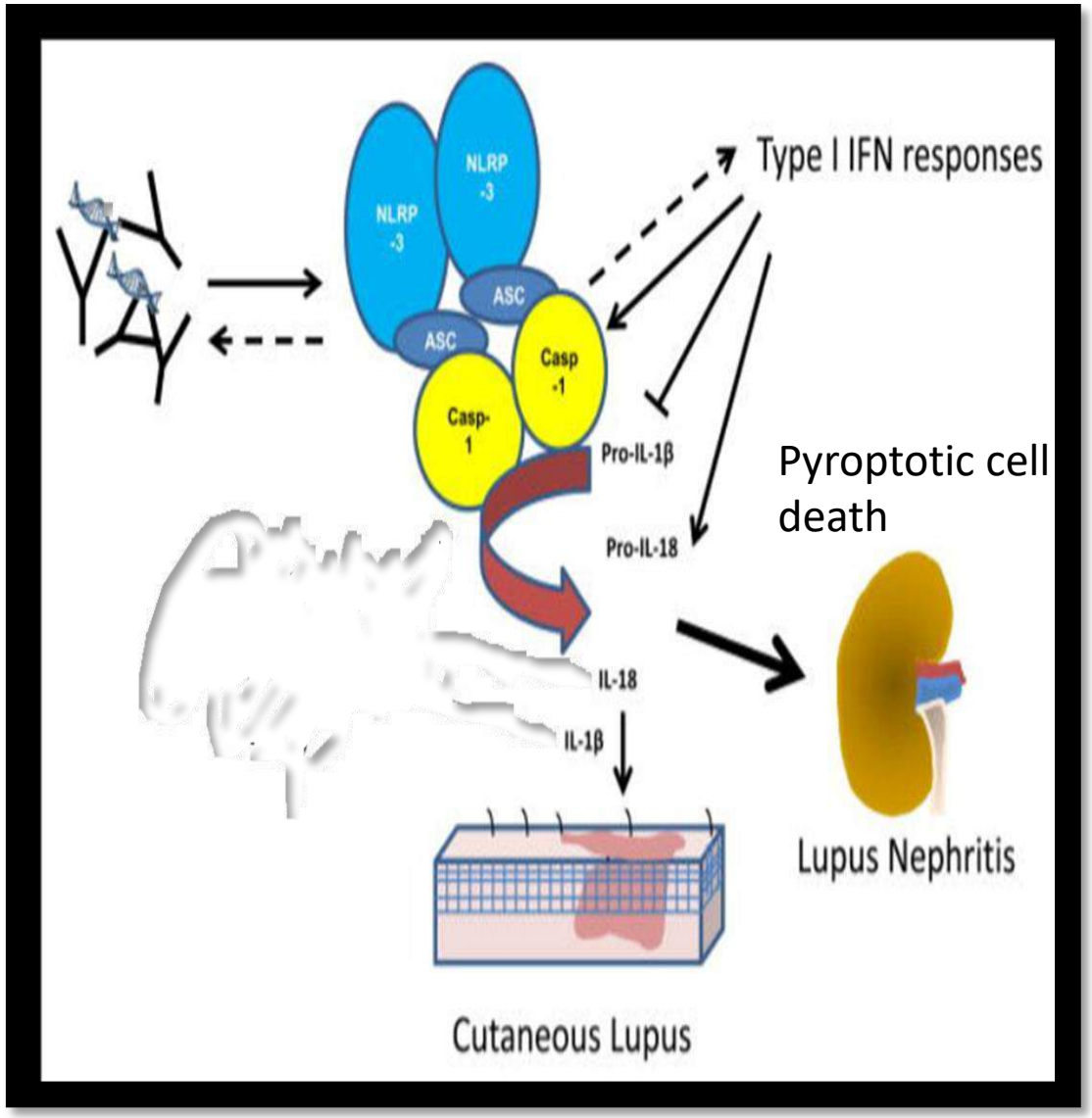
The complement system

- dual role
  - protective role - apoptotic debris removal.
  - Mediating tissue injury
- anti-C1q antibodies- acquired amplification loop the classical pathway

Avacopan	C5 a R
Eculizumab	c5
Factor b/MASP 2	inhibitor




ADCP
Programmed Cell Death (Apoptosis)
ADCC
Phagocyte (Macrophage)
FcγR
FcγR
NK Cell
Target Cell
NK cell degranulation and lysis of target cell
Proteolytic cells- perforin, granzymes
CDC
C1q
Formation of membrain attack complex (MAC) and lysis of target cell


NLRP -3
NLRP -3
ASC
ASC
Casp -1
Casp-1
Type I IFN responses
Pro-IL-1β
Pro-IL-18
Pyroptotic cell death
IL-18
IL-1β
Lupus Nephritis
Cutaneous Lupus

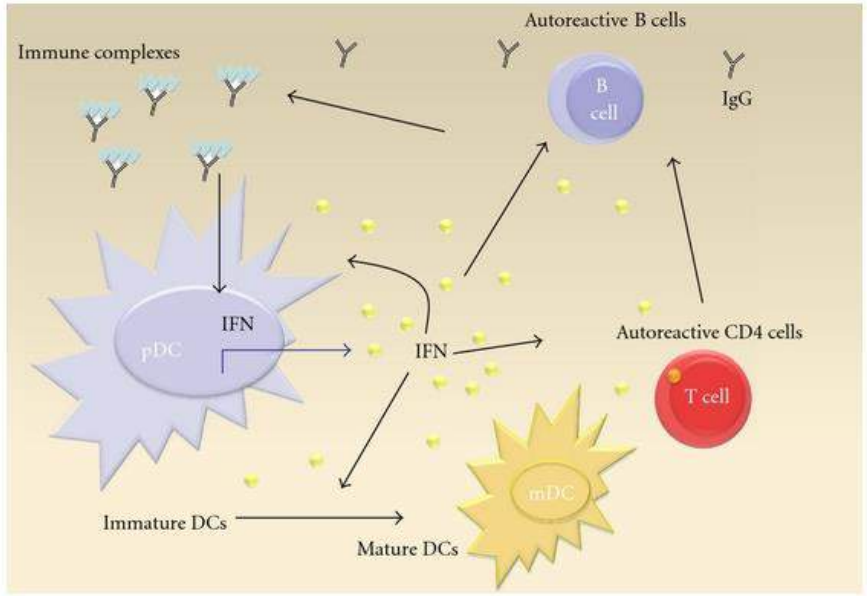
From antibody to injury

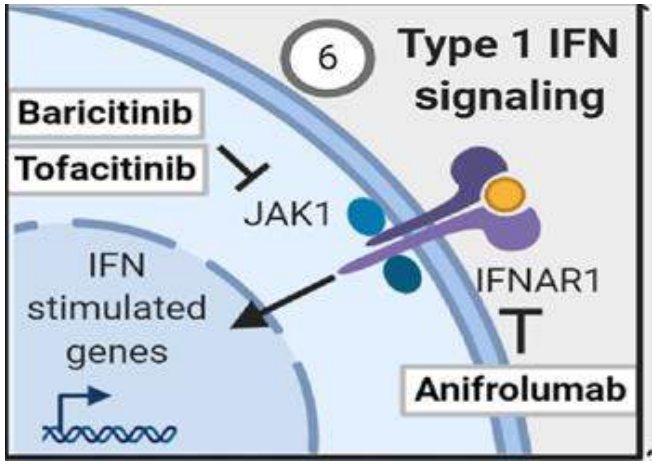
- Leucocyte Fc receptor activation → recruit leukocytes - amplification of tissue injury
- Release of cytokines, chemokines and adhesion molecules (TNF α,IL-6, 12, 17,TWEAK)→ cellular proliferation & matrix synthesis
- Repair, healing &fibrosis.

TNF α	Infliximab
IL-6	Tocilizumab
IL-12	Ustekinumab
IL17	Secukinumab
TWEAK	BIIB023

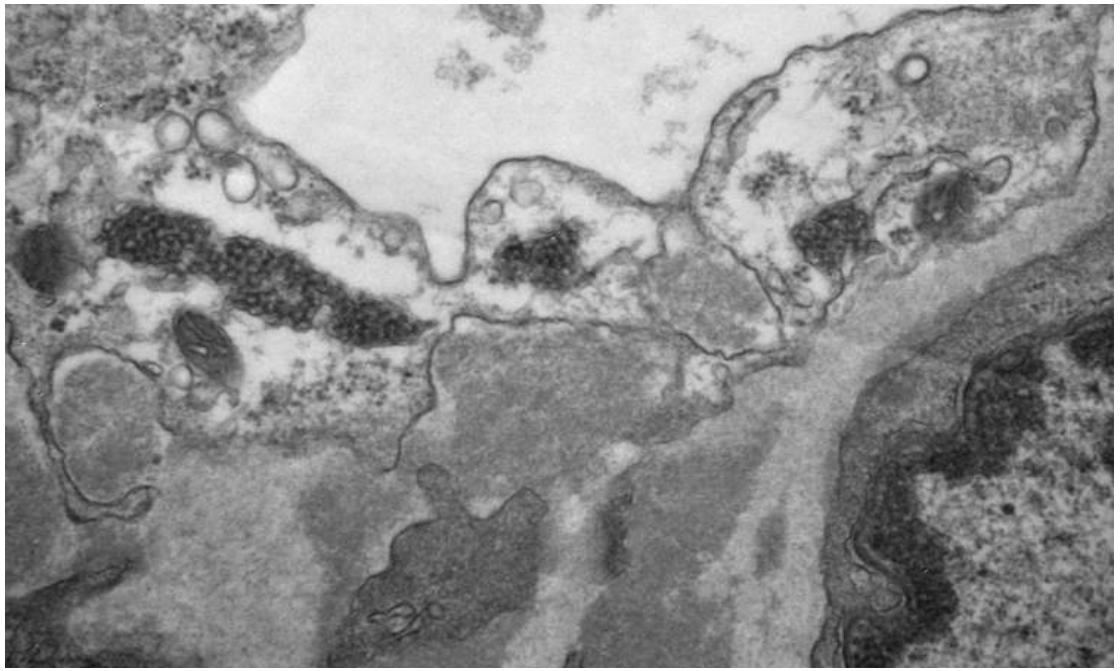
“IFN signature”

- SLE - increased IFN levels & expression of IFN-inducible transcripts esp in flare
- Stimulation of APC s, survival of B/T cells,memory cells, B cell differentiation, class switching,T reg suppression

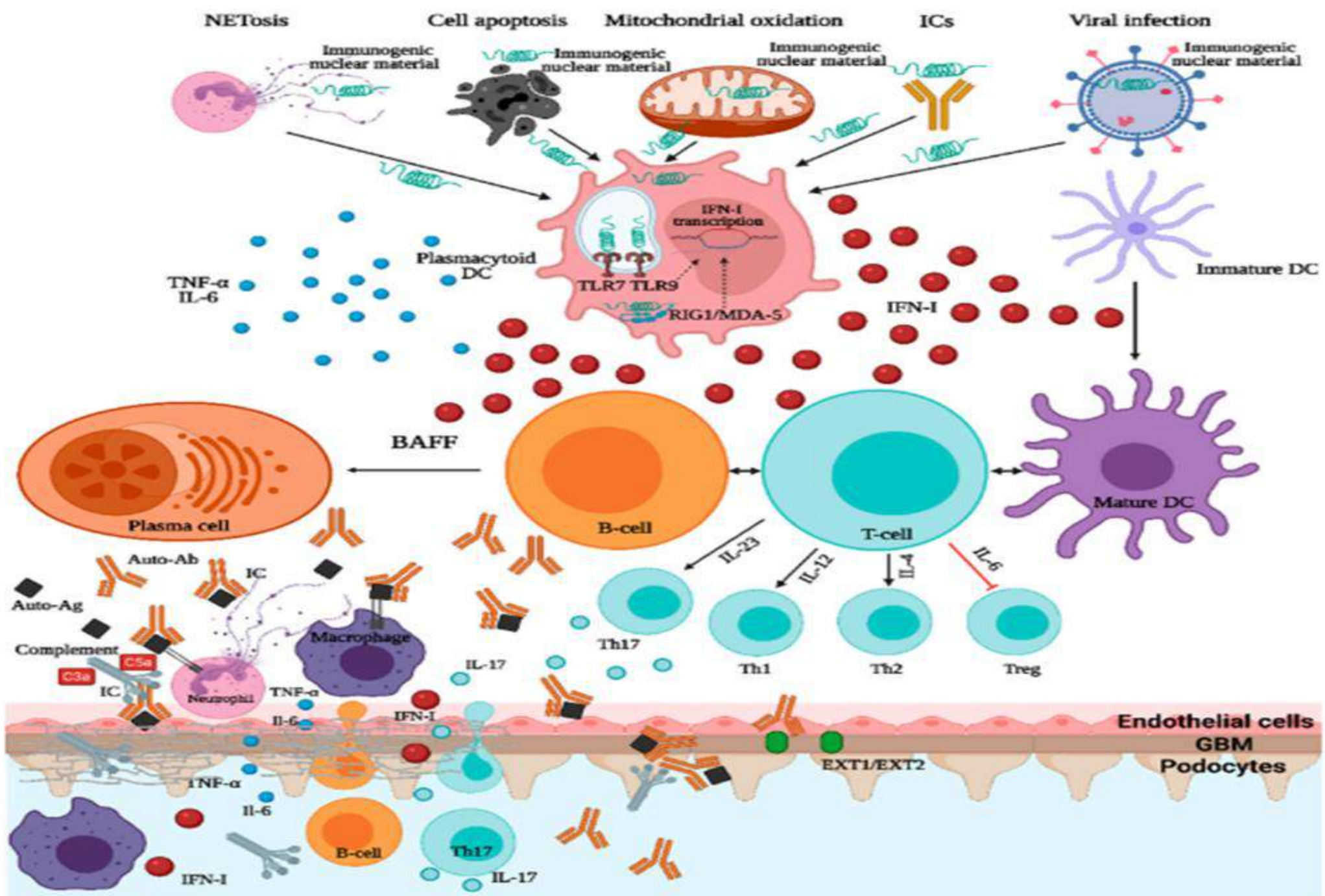


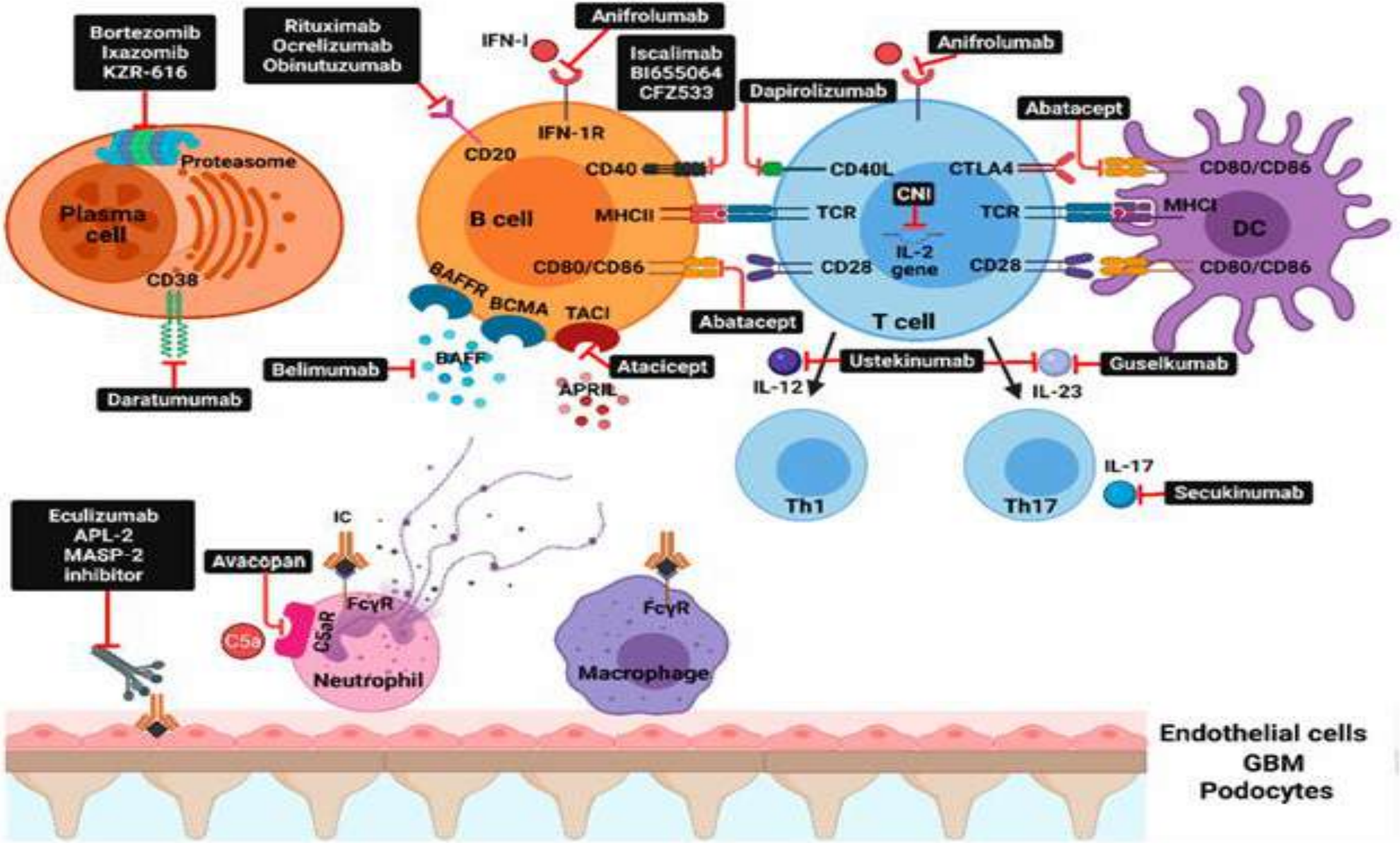


Tubuloreticular inclusions- “interferon footprint”



Also produced in intra renal cells like endothelial cells


NETosis
Cell apoptosis
Mitochondrial oxidation
ICs
Viral infection
Immunogenic nuclear material
Immunogenic nuclear material
Immunogenic nuclear material
Immunogenic nuclear material
IFN-I transcription
TLR7 TLR9
RIG1/MDA-5
Plasmacytoid DC
TNF-α
IL-6
IFN-I
Immature DC
BAFF
Plasma cell
B-cell
T-cell
Mature DC
Auto-Ab
IC
Auto-Ag
Complement
C5a
C3a
IC
Neutrophil
Macrophage
TNF-α
Il-6
IFN-I
IL-17
Th17
IL-23
IL-12
IL-4
IL-6
Th1
Th2
Treg
Endothelial cells
GBM
Podocytes
EXT1/EXT2
TNF-α
Il-6
IFN-I
B-cell
Th17
IL-17


Bortezomib
Ixazomib
KZR-616
Rituximab
Ocrelizumab
Obinutuzumab
IFN-I
Anifrolumab
Iscalimab
BI655064
CFZ533
Anifrolumab
Dapirolizumab
Abatacept
Proteasome
Plasma cell
CD38
Daratumumab
IFN-1R
CD20
CD40
B cell
MHCII
CD80/CD86
BAFFR
BCMA
TACI
BAFF
APRIL
Belimumab
Atacicept
Abatacept
CD40L
CTLA4
CD80/CD86
CNI
TCR
TCR
MHCI
DC
IL-2 gene
CD28
CD28
CD80/CD86
T cell
IL-12
Ustekinumab
IL-23
Guselkumab
Th1
Th17
IL-17
Secukinumab
Eculizumab
APL-2
MASP-2
inhibitor
IC
Avacopan
C5a
C5aR
FcγR
Neutrophil
FcγR
Macrophage
Endothelial cells
GBM
Podocytes

Take home messages

- Complex interplay of genetic, hormonal, environmental factors
- Key pathogenic pathways involve the cellular players-dendritic cells , neutrophils, B cells and T cells
- Role of cytokines-type 1 IFN
- Therapeutic insights & future directions

NATIONAL PEDIATRIC NEPHROLOGY CONCLAVE 2024

Diagnosis and evaluation of SLE

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Assistant Professor
Dept of Paediatrics
JIPMER, Puducherry

Case 1

- 14y/M presented 3 yrs back with gradually progressive easy fatigability and lethargy associated with on & off fever for the preceding 3-4 months
- No history of bleeding from any site
- O/E: Severe pallor, mild icterus, no rash, no LAP/HSM
- Ix: Hb 2.8, TLC 5600, Plt 1.7 L; DCT 2+, LDH 1272, TSB/Direct 4.3/0.4
- Recd blood transfusions and oral steroids x 3 mo
- Now presents again with dyspnea and easy fatigability

Is this SLE?

Case 2

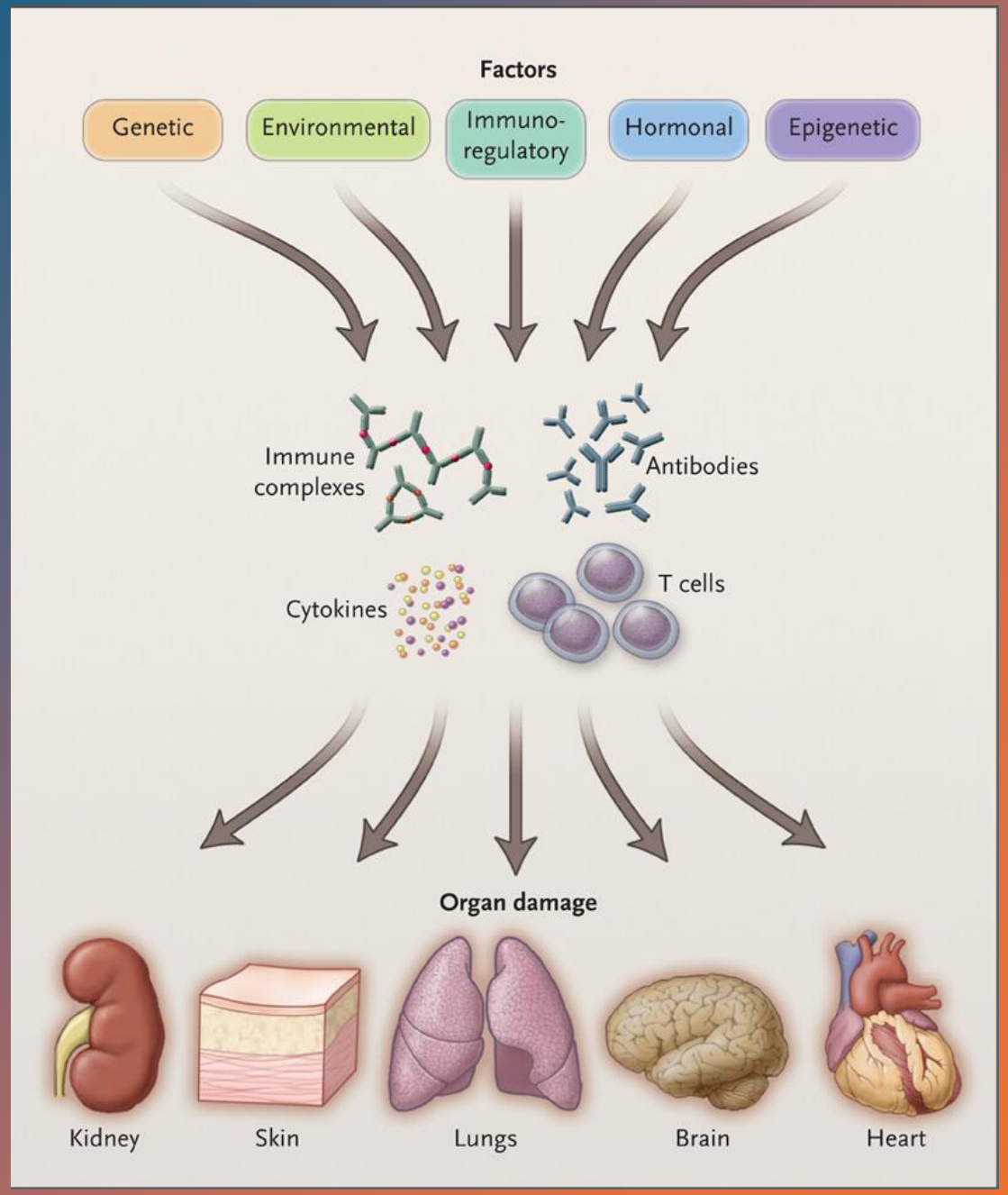
- 12y/F brought with seizures and abnormal dance-like movements for the past 1 month
- H/o on & off fever and headache for the past 6 months and progressive forgetfulness
- No h/o cough/weight loss/anorexia/vomiting/blurred vision/head injury/ vaccine/dog bite/travel history
- O/E Rash over face, oral ulcers, choreiform movements
- Tone, reflexes normal, plantar flexor, No FND/cerebellar/meningeal signs

Could this be SLE?

Case 3

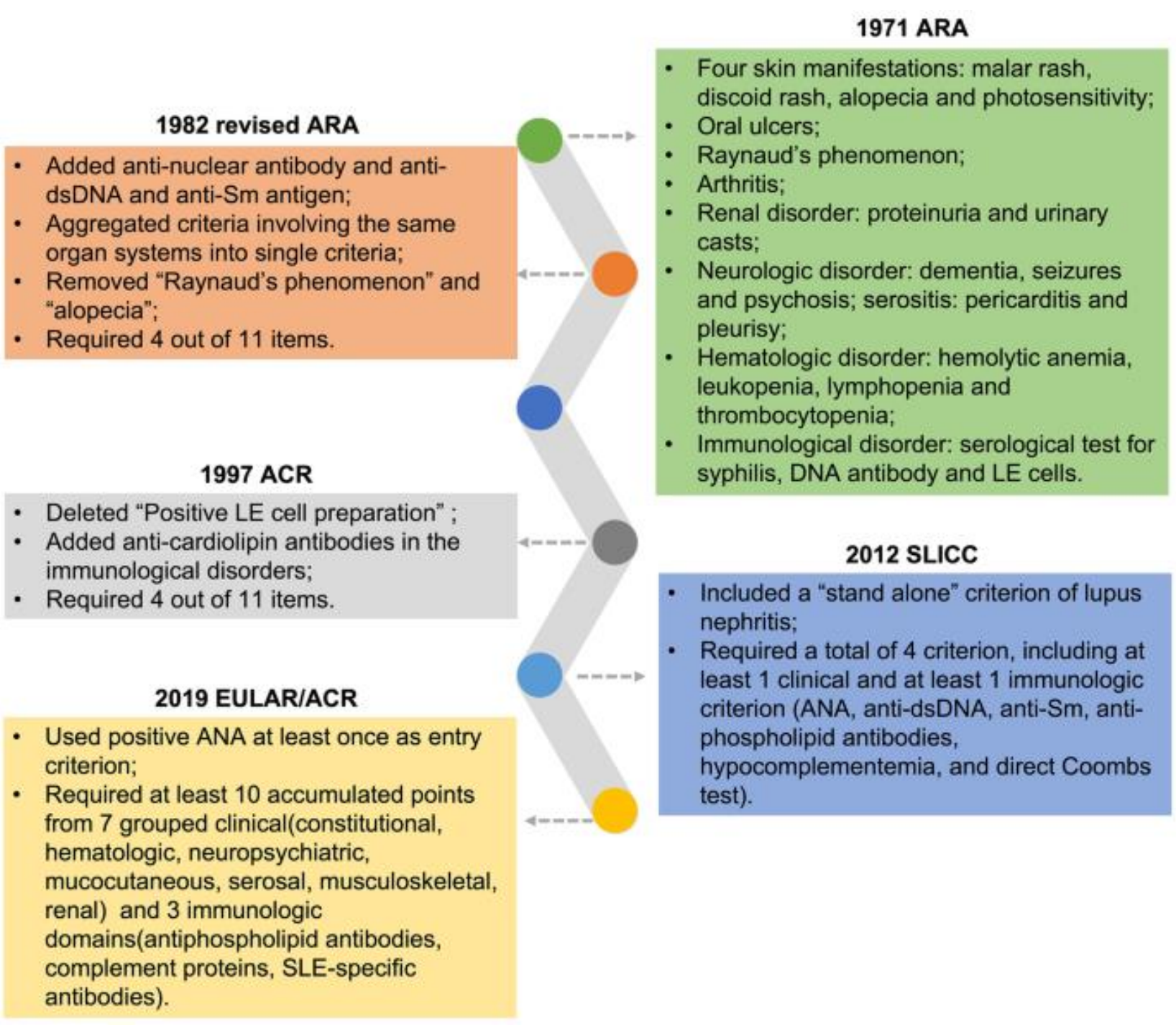
- 8y/M presented with periorbital puffiness and pedal edema for the past 1 month
- Of late, he has observed frothy urine but no h/o gross hematuria/ oliguria
- H/o on and off swelling and pain in wrist and small joints of the hand for the past 4-5 months
- O/E Alopecia, reduced air entry with dull note on right hemithorax
- Ix: creat 0.5, albumin 2.7, Urine: 25-30 RBCs/HPF, UpUC 2.8

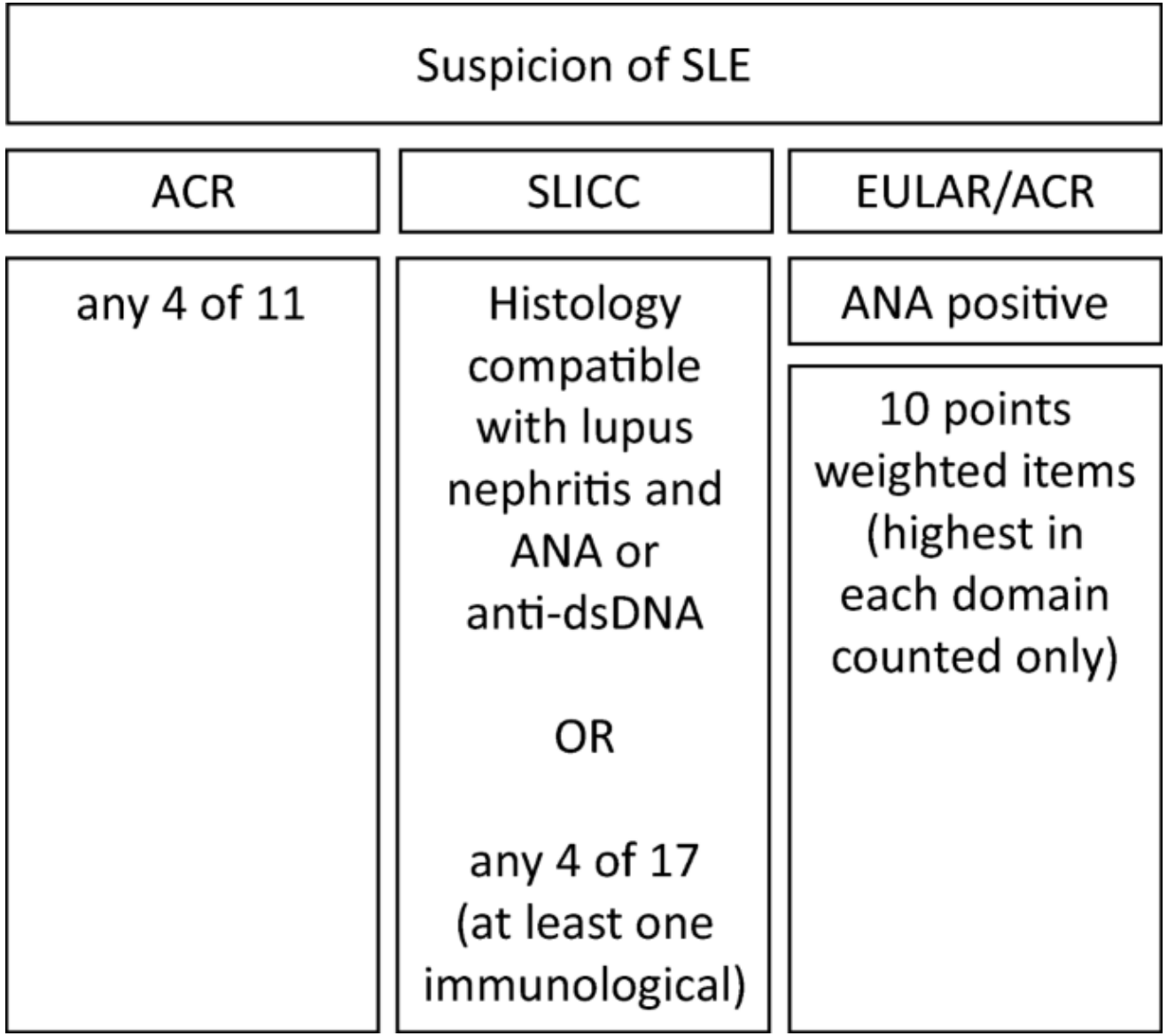
Can this be lupus nephritis?



SLE is a disease with diverse manifestations!

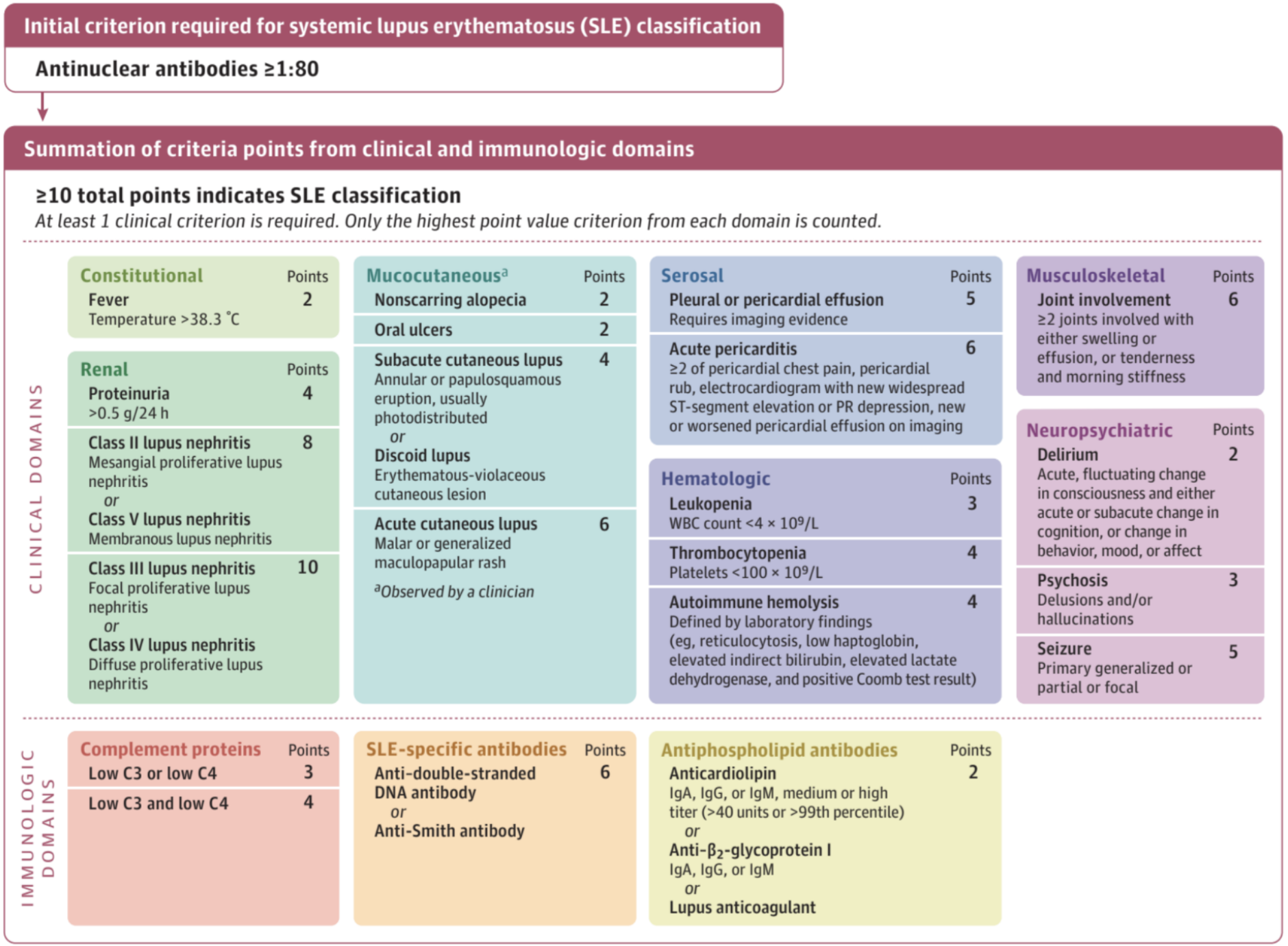
Classification criteria for SLE



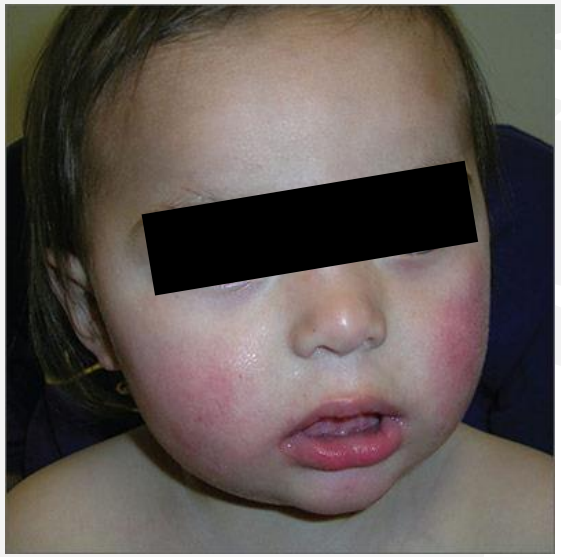


Sensitivity	70%	89%	88%
Specificity	83%	81%	67%

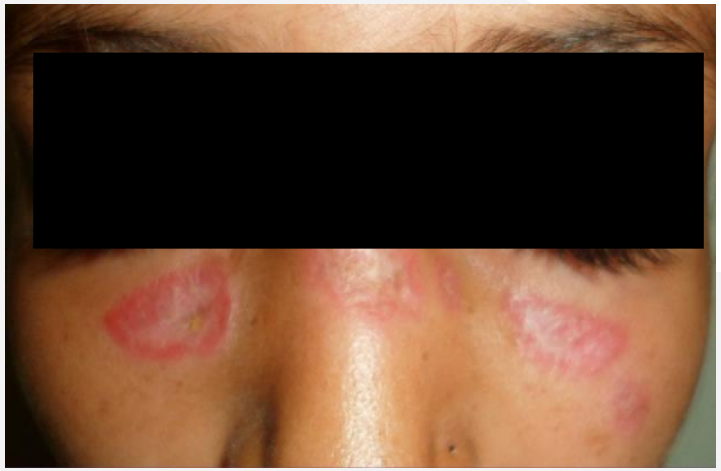
ACR/EULAR 2019 classification criteria



Cutaneous manifestations of SLE



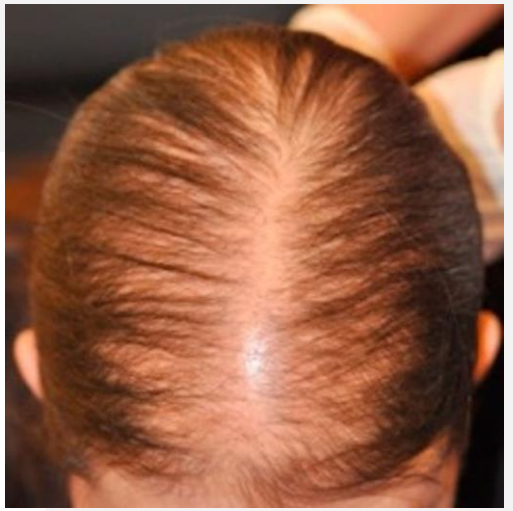
Erythematous
Photosensitive
Non-scarring



- Malar rash
- Bullous rash
- Maculopapular rash
- Photosensitive rash
- Toxic epidermal necrolysis (variant of SLE)

Acutecutaneous lupus 1

Subacute cutaneous lupus erythematosus (they are erythematous, annular/polycyclic papulosquamous lesions that are photosensitive and resemble psoriasis, they resolve leaving hypo/hyperpigmentation)



- Classic discoid rash
- Hypertrophic verrucous lupus
- Lupus panniculitis
- Mucosal lupus
- Lupus erythematosus tumidus
- Chilblains lupus

Chronic cutaneous lupus 2

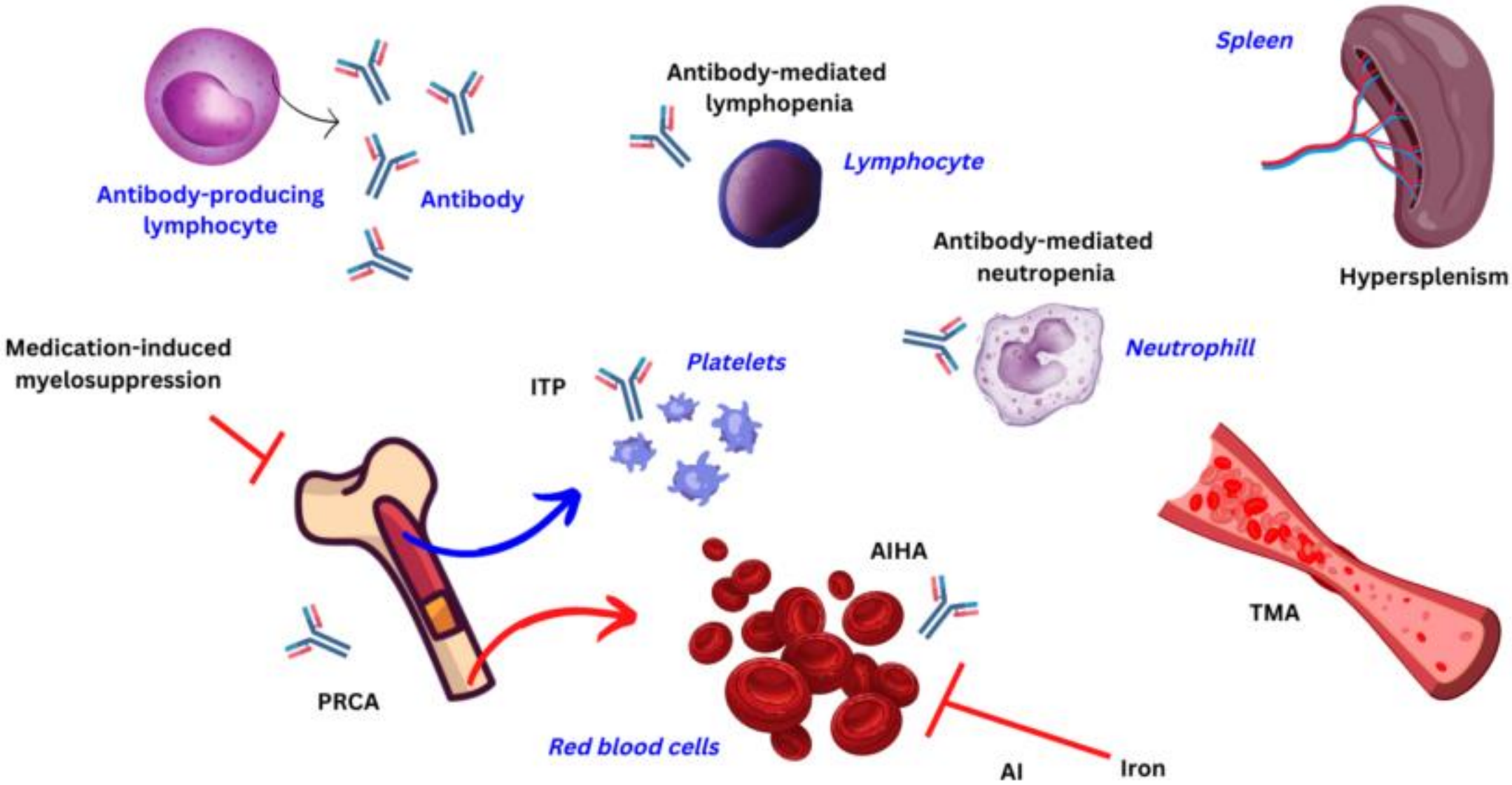
Non-scarring alopecia 3

Discoid lupus/lichen planus overlap

Nasal or oral ulcers 4

Oral ulcers are painless so look for them rather than asking history

Hematological manifestations of SLE

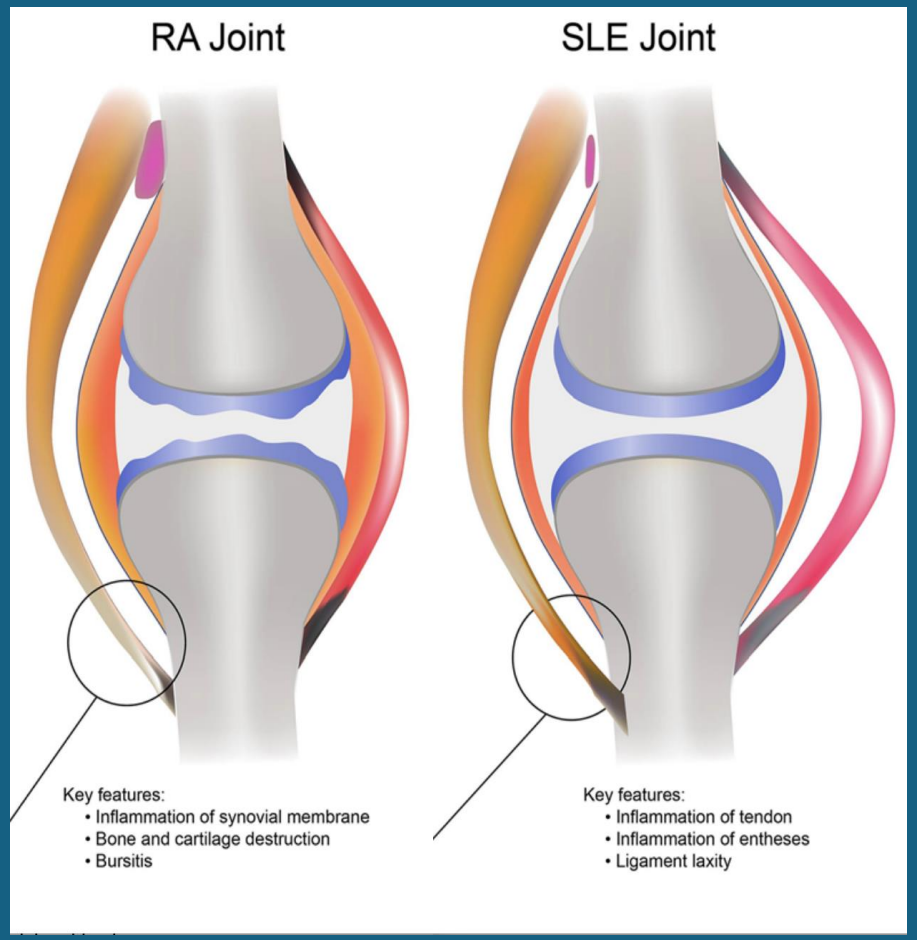


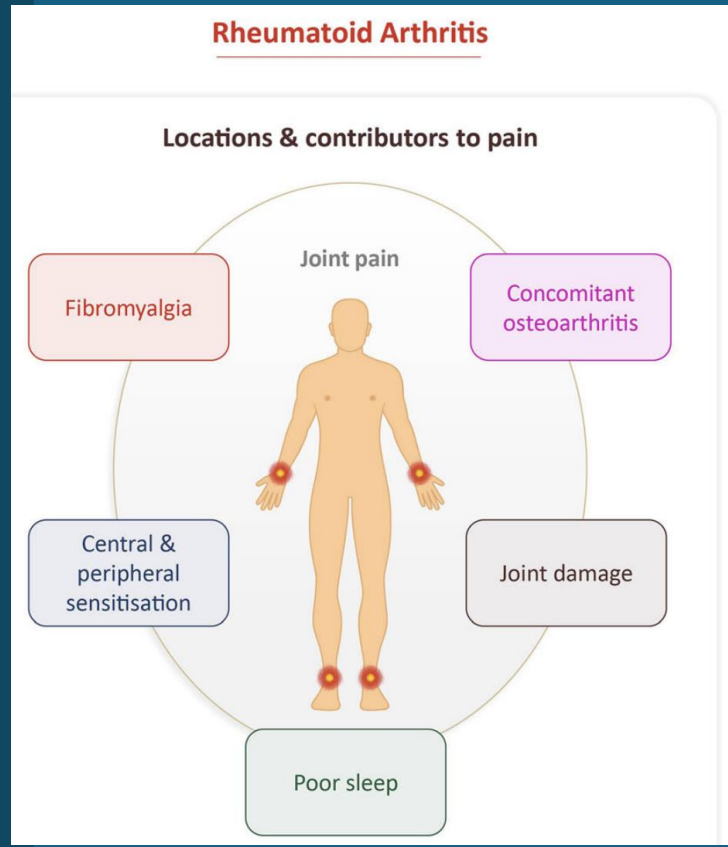
Neuropsychiatric manifestations of SLE

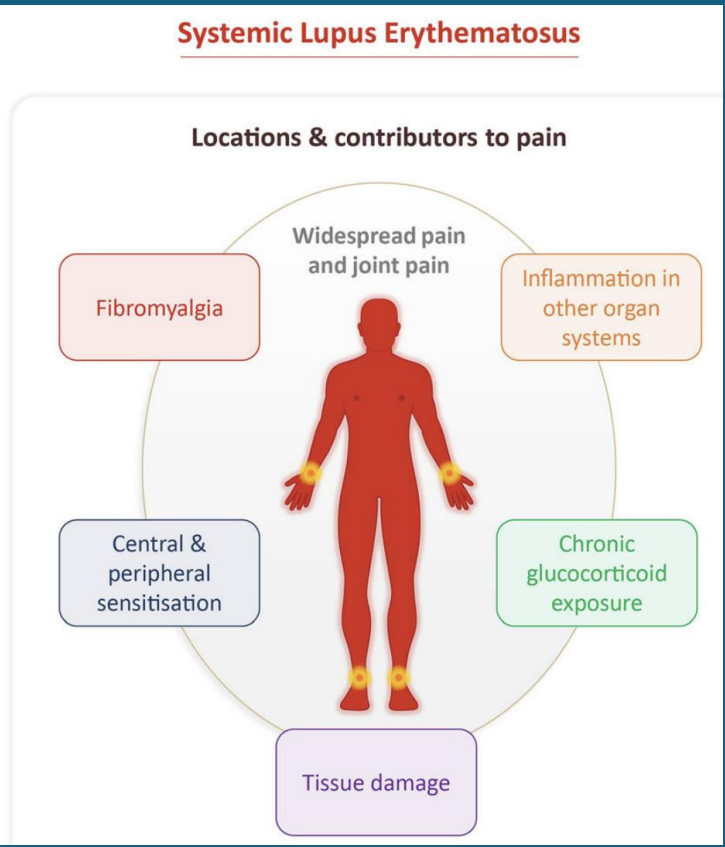
NPSLE associated with the central nervous system	NPSLE associated with the peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating
Cerebrovascular disease	Syndromes (Guillain-Barré syndrome)
Demyelinating syndromes	Autonomic neuropathy
Headaches	Mononeuropathy, single or multiplex
Movement disorders (chorea)	Myasthenia gravis
Myelopathy	Cranial neuropathy
Seizure disorders	Plexopathy
Anxiety disorders	Polyneuropathy
Cognitive dysfunction	
Mood disorders	
Psychosis	

NPSLE = neuropsychiatric systemic lupus erythematosus.

Musculoskeletal involvement in SLE







Arthritis in SLE

Not deforming

Not painful

SLE + RA = Rhupus

Lupus nephritis

Renal involvement seen in 50-67% children; 80-90% within the first yr of diagnosis

Manifestations

Hematuria

Proteinuria/nephrotic syndrome

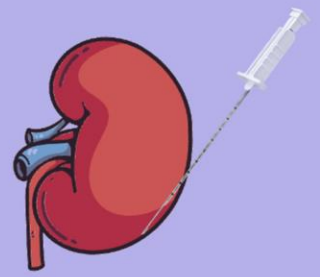
Deranged renal function/RPGN

CKD

Hypertension

Indications for kidney biopsy:

- RPGN/elevated creatinine
- Proteinuria (24UP > 500 mg/ UpUC >0.5)
- Hematuria (>5% acanthocytes/RBC cast)



INITIAL DIAGNOSIS

At initial presentation

PROVIDED INFORMATION

Diagnosis

- Disease activity/chronicity
- ISN/RPS classification
- Non-classical etiologies
- Selection for clinical trials

Prognosis

- Limited prognostic value

LACK OF RESPONSE

After 3 to 6 months of initial therapy

PROVIDED INFORMATION

Diagnosis

- Evaluation for resistant LN
- Irreversible damage
- Non-classical etiologies
- Change of therapy

Prognosis

- Long-term prognosis

POST-THERAPY

After 12 to 18 months of initial therapy

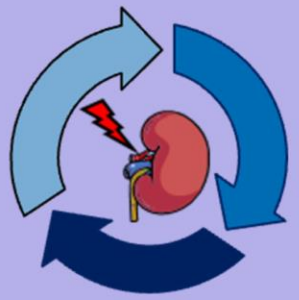
PROVIDED INFORMATION

Diagnosis

- Histological response
- Proteinuria from activity or chronicity (“*residual*”)
- Therapy adjustment

Prognosis

- Risk of kidney relapse
- Long-term prognosis



KIDNEY RELAPSE

At a new flare diagnosis

PROVIDED INFORMATION

Diagnosis

- ISN/RPS class switch
- Disease activity/chronicity
- Non-classical etiologies

Prognosis

- Long-term prognosis

DRUG WITHDRAWAL

After 36 months of remission

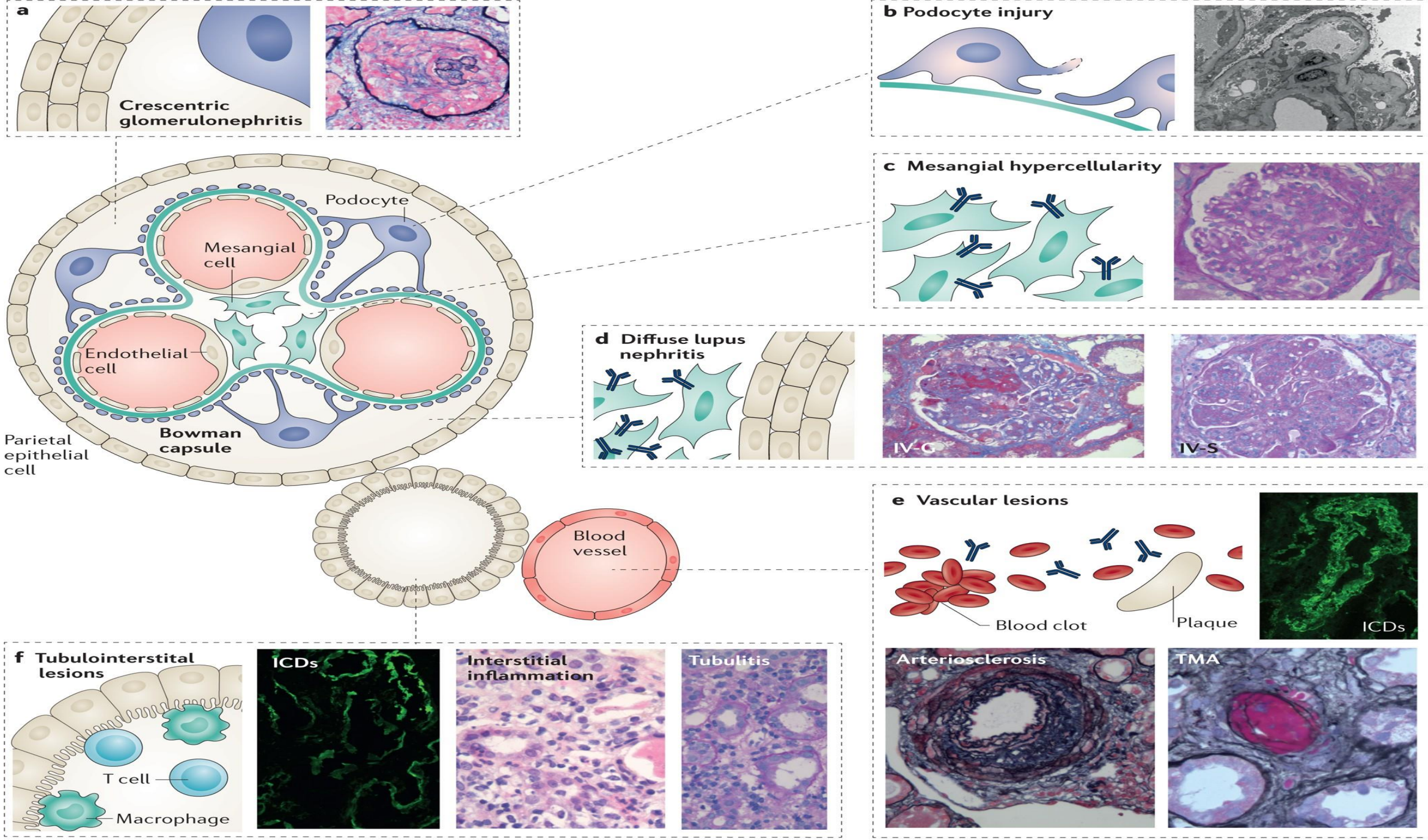
PROVIDED INFORMATION

Diagnosis

- Histological remission
- Decision-making support for therapy tapering and/or suspension

Prognosis

- Risk of kidney flare during tapering or suspension


a
Crescentric glomerulonephritis
b Podocyte injury
c Mesangial hypercellularity
Podocyte
Mesangial cell
Endothelial cell
Bowman capsule
Parietal epithelial cell
d Diffuse lupus nephritis
IV-G
IV-S
Blood vessel
e Vascular lesions
Blood clot
Plaque
ICDs
f Tubulointerstital lesions
T cell
Macrophage
ICDs
Interstitial inflammation
Tubulitis
Arteriosclerosis
TMA

Histological classes of Lupus nephritis

Class of Lupus Nephritis		Histopathology
Class I	Minimal Mesangial	LM normal; IC visible in mesangium by IF or EM
Class II	Mesangial Proliferative	Mesangial proliferation visible on LM
Class III	Focal Proliferative	Thickened capillary loops on LM, **<50%** glomeruli affected, subendothelial IC seen on EM
Class IV	Diffuse Proliferative	Thickened capillary loops on LM, **>50%** glomeruli affected, subendothelial IC on EM
Class V	Membranous	Subepithelial IC deposition and GBM thickening
Class VI	Advanced Sclerosing	>90% globally sclerotic glomeruli

Activity index

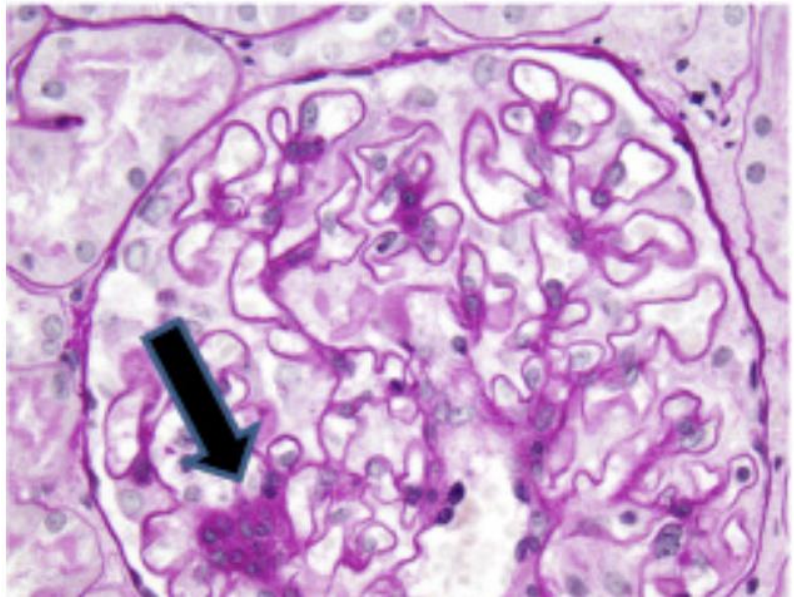
- Endocapillary hypercellularity
- Neutrophils
- Fibrinoid necrosis
- Hyaline deposits
- Crescents
- Interstitial inflammation

24

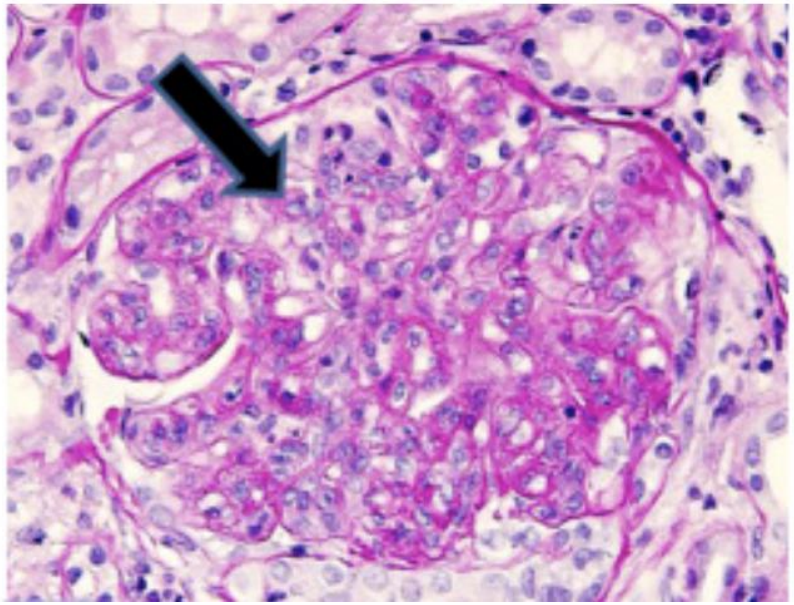
Chronicity index

- Glomerulosclerosis
- Fibrous crescents
- Interstitial fibrosis
- Tubular atrophy

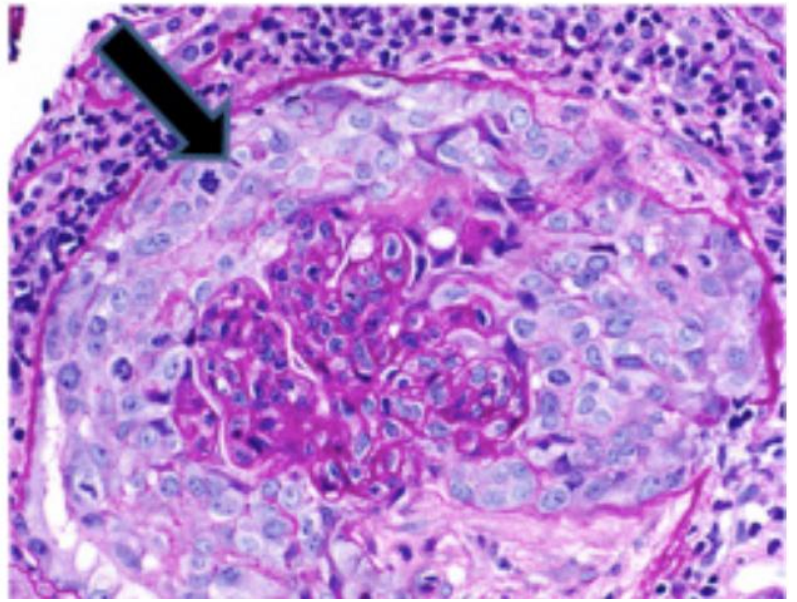
12



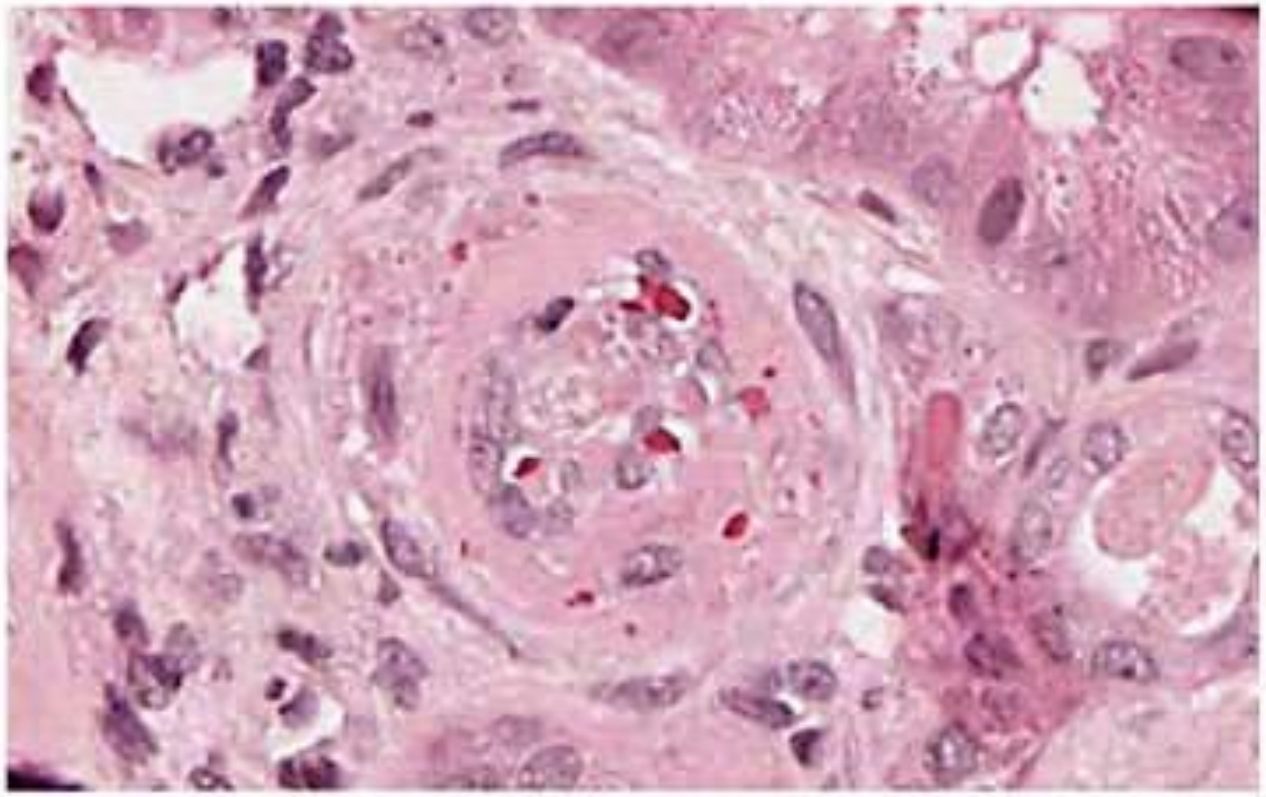
Mesangial hypercellularity



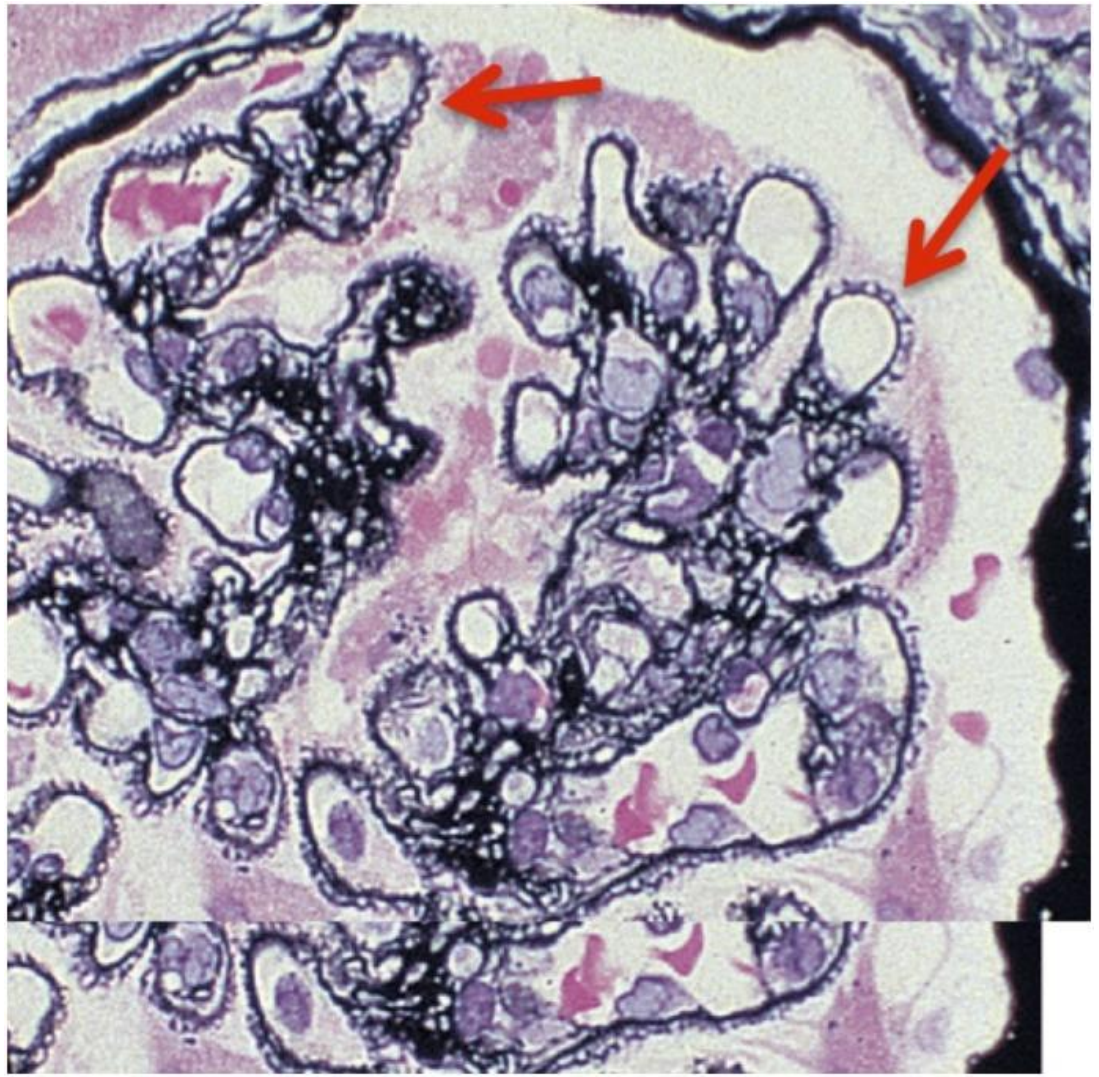
Endocapillary hypercellularity



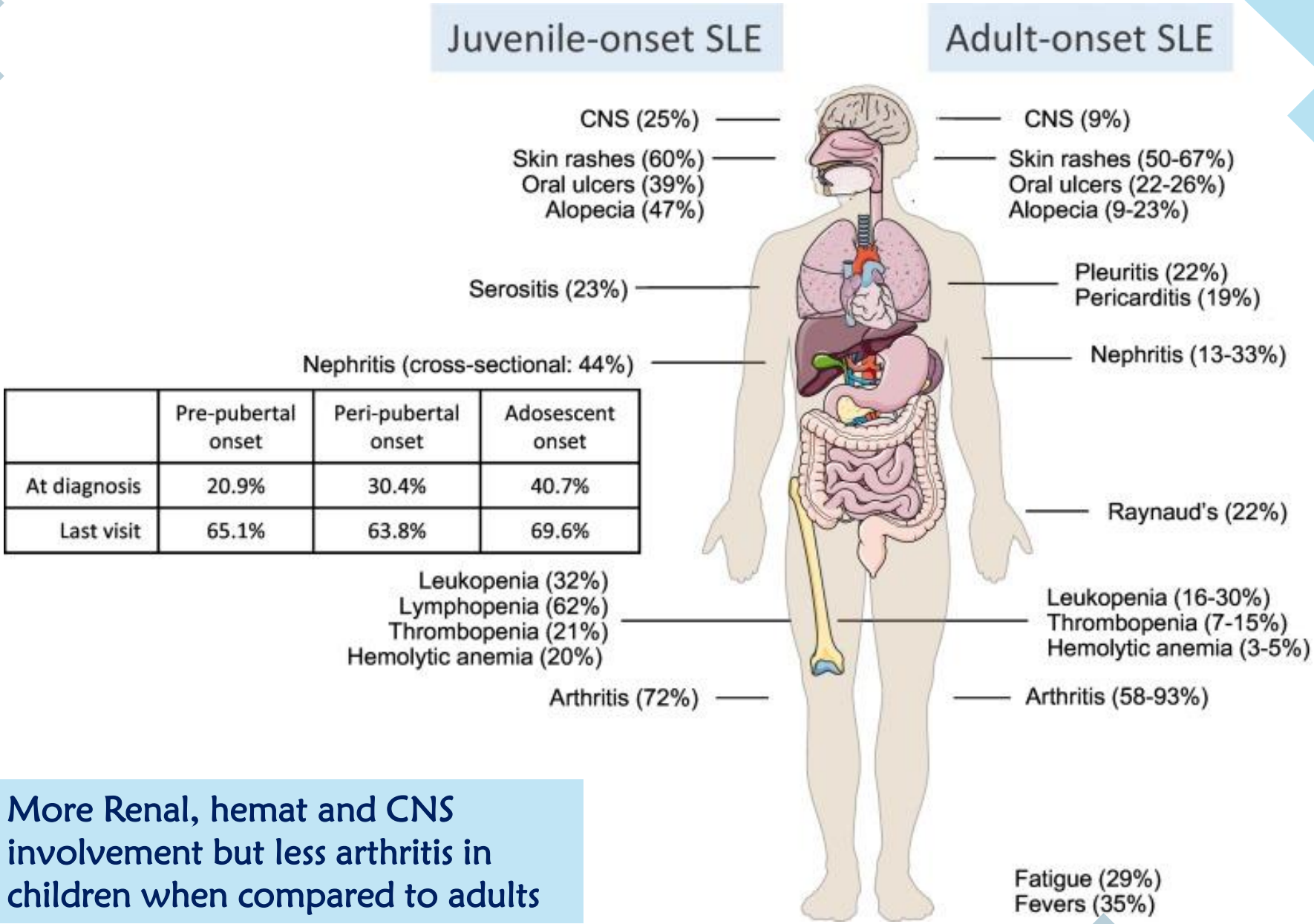
Cellular crescent



TMA in lupus nephritis



Membranous lupus nephritis (Class V)

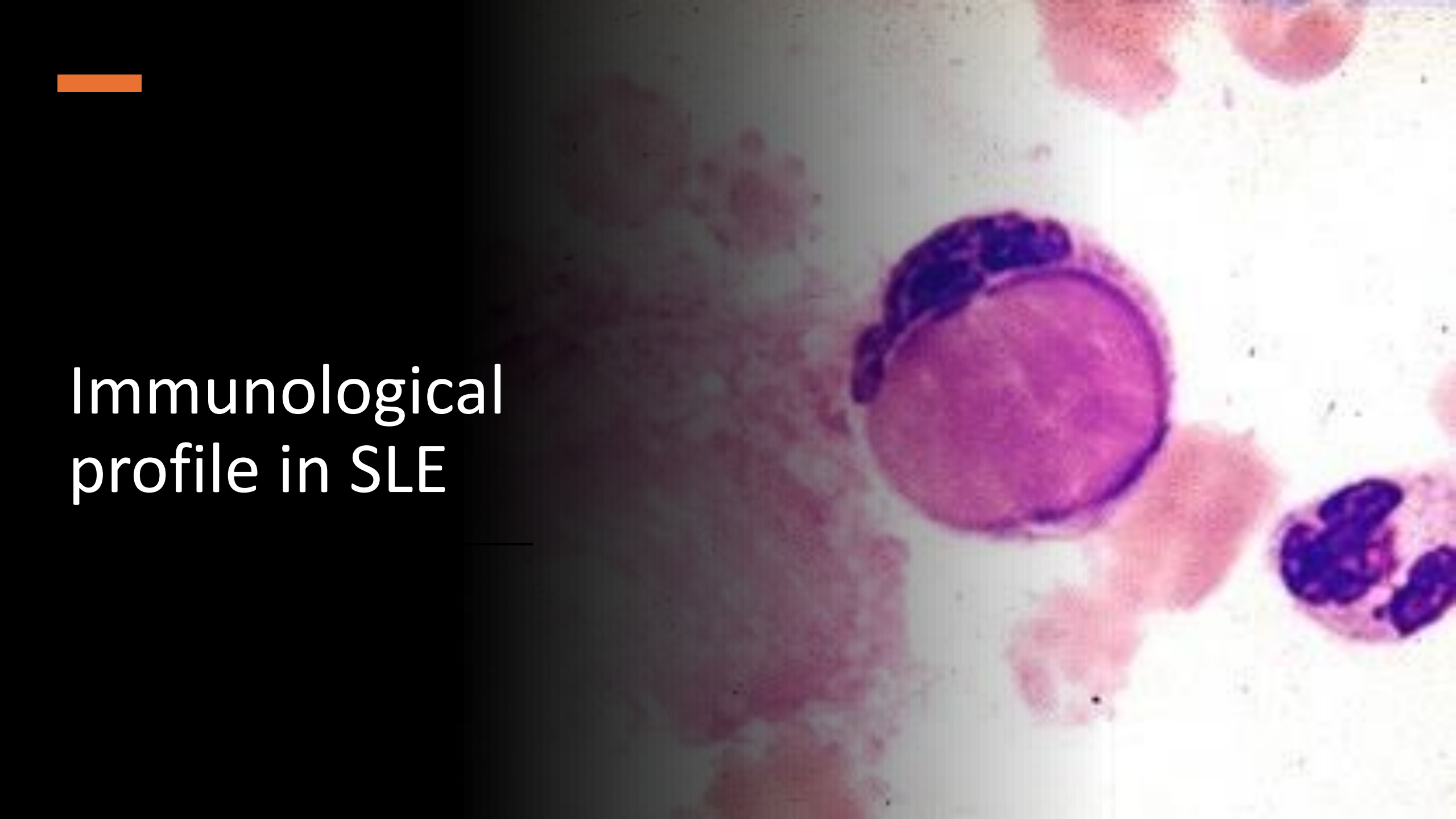


	Pre-pubertal onset	Peri-pubertal onset	Adosescent onset
At diagnosis	20.9%	30.4%	40.7%
Last visit	65.1%	63.8%	69.6%

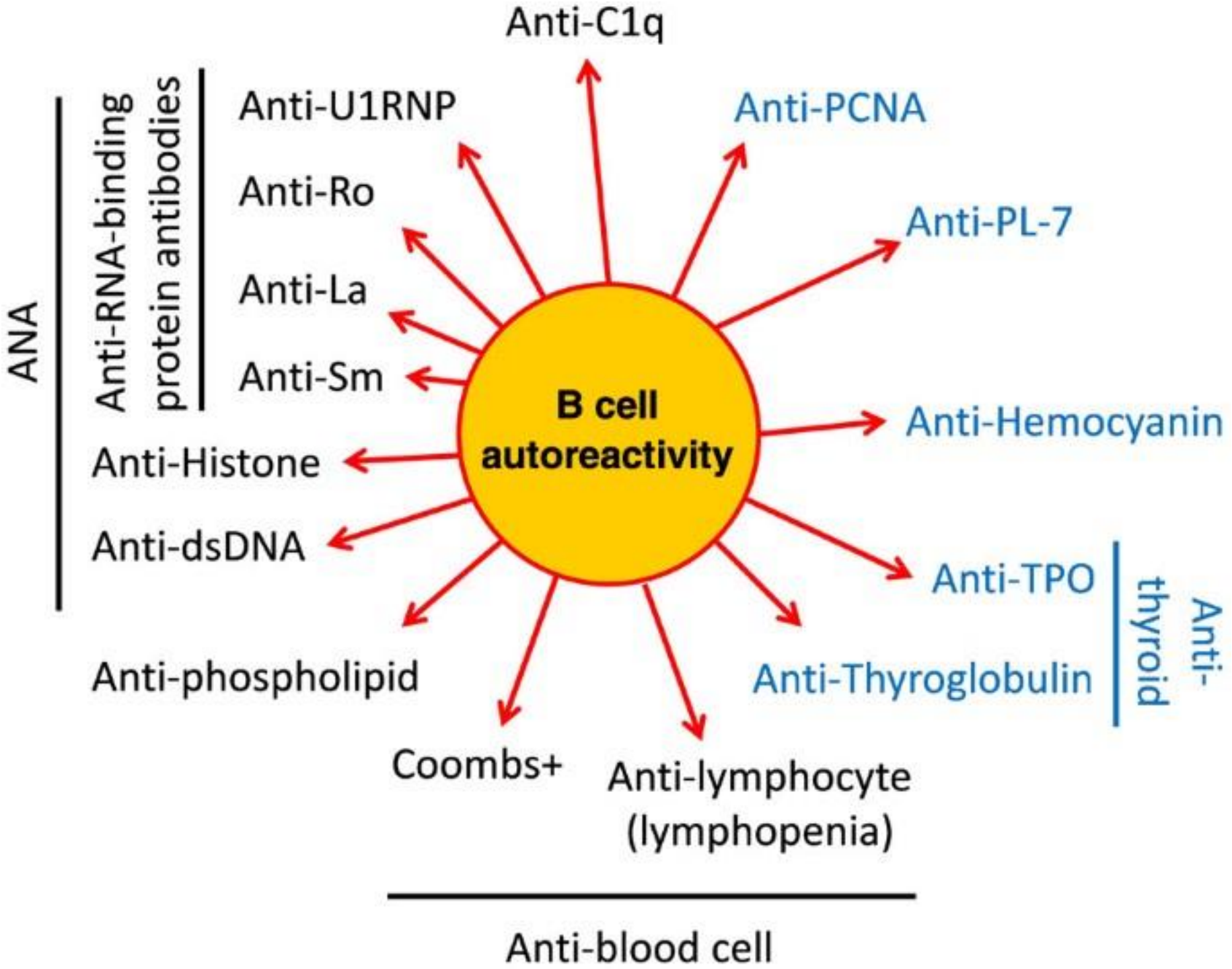
More Renal, hemat and CNS involvement but less arthritis in children when compared to adults

Clin Immunol 2022

Immunological profile in SLE



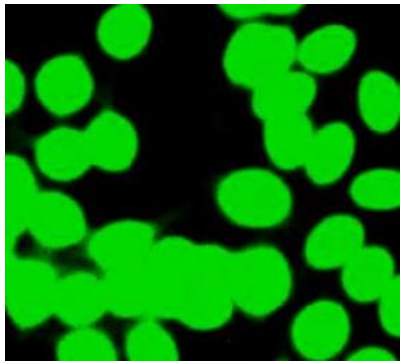
Antibodies in SLE



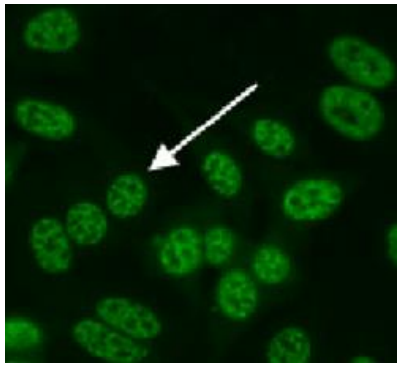
ANA

IF using Hep-2 cell lines; titres >1:80 considered positive

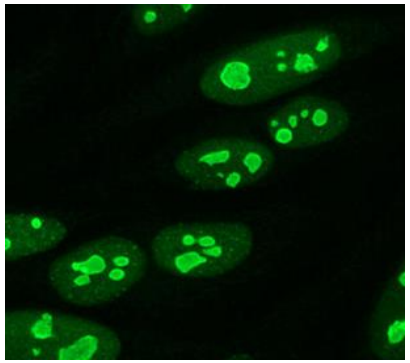
Pattern	Antibodies
Homogenous	Anti-dsDNA Anti-Histone
Speckled	Anti Sm Anti Ro Anti La Anti U1RNP
Nucleolar	Anti Ribosomal P



Homogenous (most common)



Speckled



Nucleolar

ENA profile

Antibody	Sensitivity in SLE	Clinical significance
ANA	>95%	**Not specific** for SLE; but mandatory entry criteria as per 2019 ACR/ EULAR
dsDNA	70-98%	**Specific**, titres correlate with disease **activity**
Anti-Sm	25%	**Very specific** but poor sensitivity
Anti SSA/B (Ro/La)	25-60%	**Neonatal** SLE, ANA neg SLE
Anti-histone	70% (37% for LN)	**Drug-induced** SLE
U1RNP	20-30%	MCTD
Anti-PCNA	5-10%	Arthritis
APLA	20-30%	NP SLE, thromboembolic
Anti-ribosomal	28%	NP SLE
Anti-NR2	44-82%	NP SLE
NMDAR	31%	NP SLE

So what labs to do in a newly diagnosed child?

CBC, ESR, CRP, DCT
Urea, creatinine, Na/K, Ca/P/ALP, AST, ALT, albumin
Thyroid profile
Urinalysis: RBCs, RBC cast, UPCR/24 UP
ANA, dsDNA, ENA profile, APLA, C3, C4
PT/INR, aPTT if planning kidney biopsy
CXR, ECG, ECHO, USG KUB
Kidney biopsy if renal involvement suspected

Defining response to therapy

Criteria	Definition
Complete response (CR)	Proteinuria <0.5 g/1.73m^2/day or <300 mg/m^2 per day Stabilization or improvement (±10–15%) in kidney fn within 6–12 mo of starting therapy
Partial response (PR)	Reduction in proteinuria by at least 50% from baseline Stabilization or improvement (±10–15%) in kidney fn within 6–12 mo of starting therapy
No response (NR)	Failure to achieve PR or CR within 6-12 mo

KDIGO 2024 CPG

Refractory: Worsening kidney fn at 3 mo, lack of PR at 6 mo, lack of CR at 1y, or 2 flares within 2y of induction

Parameter	Proteinuric flare	Nephritic flare
Serum creatinine	Stable (<30% increase over baseline level)	*Mild/moderate*: stable (<30% increase over baseline level) *Severe*: ≥30% increase
Proteinuria	Increase to >2 g/24hr	*Mild*: increase to ≤2 g/24hr *Moderate/severe*: increase to >2 g/24hr
Hematuria	<10 rbc/hpf	*Mild*: ≥10 RBCs/hpf[1] if baseline levels were <10; or, increase by at ≥2 fold if baseline levels were ≥10 *Moderate/Severe*: ≥10 RBCs/hpf; or, increase if previously on partial response
Cellular casts	No change	Reappearance if previously on remission; or, an increase in number of cellular casts if previously on partial response

[1]Red blood cells per high-power field

Defining flares in lupus nephritis

Index	Definition(s)
PGA[1]	· *Mild/moderate*: increase by ≥1.0 compared with the previous visit · *Severe*: increase by ≥1.0 to ≥2.5
SLEDAI	· *Mild/moderate*: increase by >3 · *Severe*: increase by >10
SFI	· *Mild/moderate*: 1) increase of SLEDAI by ≥3 points; and/or 2) new/worse skin, stomatitis, serositis, arthritis, fever; and/or 3) increase in PGA by ≥1.0; and/or 4) treatment intensification: increase in prednisone <0.5 mg/kg or added NSAIDs or hydroxychloroquine · *Severe*: 1) increase of SLEDAI by >12; and/or 2) new/worse CNS involvement, vasculitis, glomerulonephritis, myositis, platelet counts <60,000/mm^3, hemolytic anemia (hemoglobin <70 g/L), requiring doubling of prednisone dose or dose >0.5 mg/kg; and/or 3) need for hospitalization due to SLE; and/or 4) any manifestation requiring prednisone >0.5 mg/kg or new immunosuppressive therapy; and/or 4) increase in PGA to >2.5
BILAG	· *Moderate*: increase from C, D or E to B score in any system · *Severe*: increase to A score in any system
SLAM	· Increase by ≥3
LAI	· Increase by >0.26

[1]PGA, Physician Global Assessment; SLEDAI, SLE Disease Activity Index; SFI, SELENA-SLEDAI Flare Index; NSAI non-steroidal anti-inflammatory drugs; CNS, central nervous system; BILAG=British Isles Lupus Assessment Grou SLAM, SLE Activity Measure; LAI, Lupus Activity Index

SLEDAI 2000

4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.
TOTAL SCORE	_____		⬆ by > 3 points: mild-moderate; ⬆ by > 10 points: severe

BILAG 2004

Record: **ND** **Not Done**
0 **Not present**
1 **Improving**
2 **Same**
3 **Worse**
4 **New**
Yes/No OR Value (where indicated)
***Y/N** **Confirm this is due to SLE activity (Yes/No)**

CONSTITUTIONAL

1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

NEUROPSYCHIATRIC

19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

CARDIORESPIRATORY

44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

A = 12
B = 8
C = 1
D/E = 0

RENAL

78. Systolic blood pressure (mm Hg) value
79. Diastolic blood pressure (mm Hg) value
80. Accelerated hypertension Yes/No
81. Urine dipstick protein (+=1, ++=2, +++=3)
82. Urine albumin-creatinine ratio mg/mmol
83. Urine protein-creatinine ratio mg/mmol
84. 24 hour urine protein (g) value
85. Nephrotic syndrome Yes/No
86. Creatinine (plasma/serum) µmol/l
87. GFR (calculated) ml/min/1.73 m^2
88. Active urinary sediment Yes/No
89. Active nephritis Yes/No

HAEMATOLOGICAL

90. Haemoglobin (g/dl) value
91. Total white cell count (x 10^9/l) value
92. Neutrophils (x 10^9/l) value
93. Lymphocytes (x 10^9/l) value
94. Platelets (x 10^9/l) value
95. TTP
96. Evidence of active haemolysis Yes/No
97. Coombs' test positive (isolated) Yes/No

Change to B in any system = moderate
Change to A in any system = severe

Take home messages

- SLE is a disease with diverse manifestations; assess for activity in each system
- ACR/EULAR 2019 classification criteria currently followed
- Always evaluate for kidney involvement in all patients with SLE & consider biopsy if deranged kidney function, hematuria or proteinuria noted
- Identify the histological subclass, activity & chronicity indices on kidney biopsy
- Watch for flares; scoring systems helpful


WOMEN & CHILDREN'S HOSPITAL
JIPMER WOMEN & CHILDREN HOSPITAL
WOMEN & CHILDREN'S HOSPITAL

Thank you

NPNC 2024

Antenatal Kidney Anomalies

60 minutes

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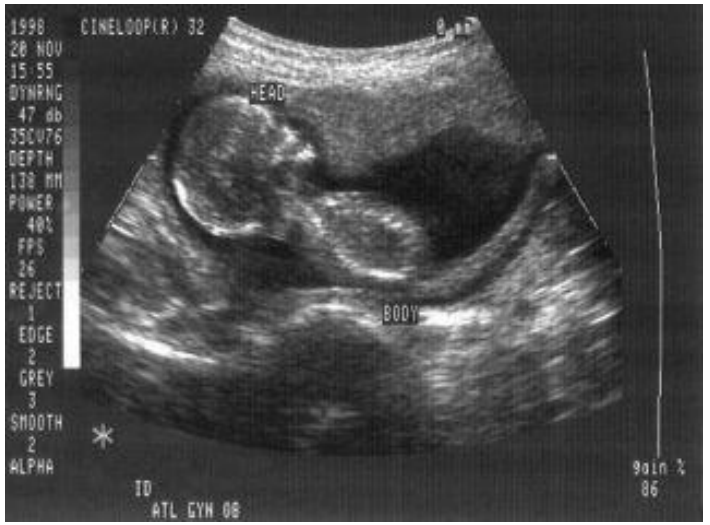


*"**Structure** does not determine **Function** or vice versa, but both are simply different ways of regarding and describing the same thing."*

Jean R. Oliver, *Nephrons and Kidneys*, 1968

Outline

- S**pectrum of fetal renal anomalies** identified by antenatal scan
- Markers of significant underlying renal pathology or poor renal prognosis
- Prenatal evaluation , surgical Indications & interventions
- Appropriate follow up of ANH and immediate post-natal evaluation, management (medical & surgical) & Outcome
- Genetic Counseling in CAKUT and Cystic Kidney diseases

Antenatal Kidney Anomalies - CAKUT

- **Congenital anomalies of the kidneys and urinary tracts (CAKUT)** are embryonic disorders

  Heterogeneous group - Spectrum of defects in the kidneys and outflow tracts

  Structural malformations with/without functional abnormalities

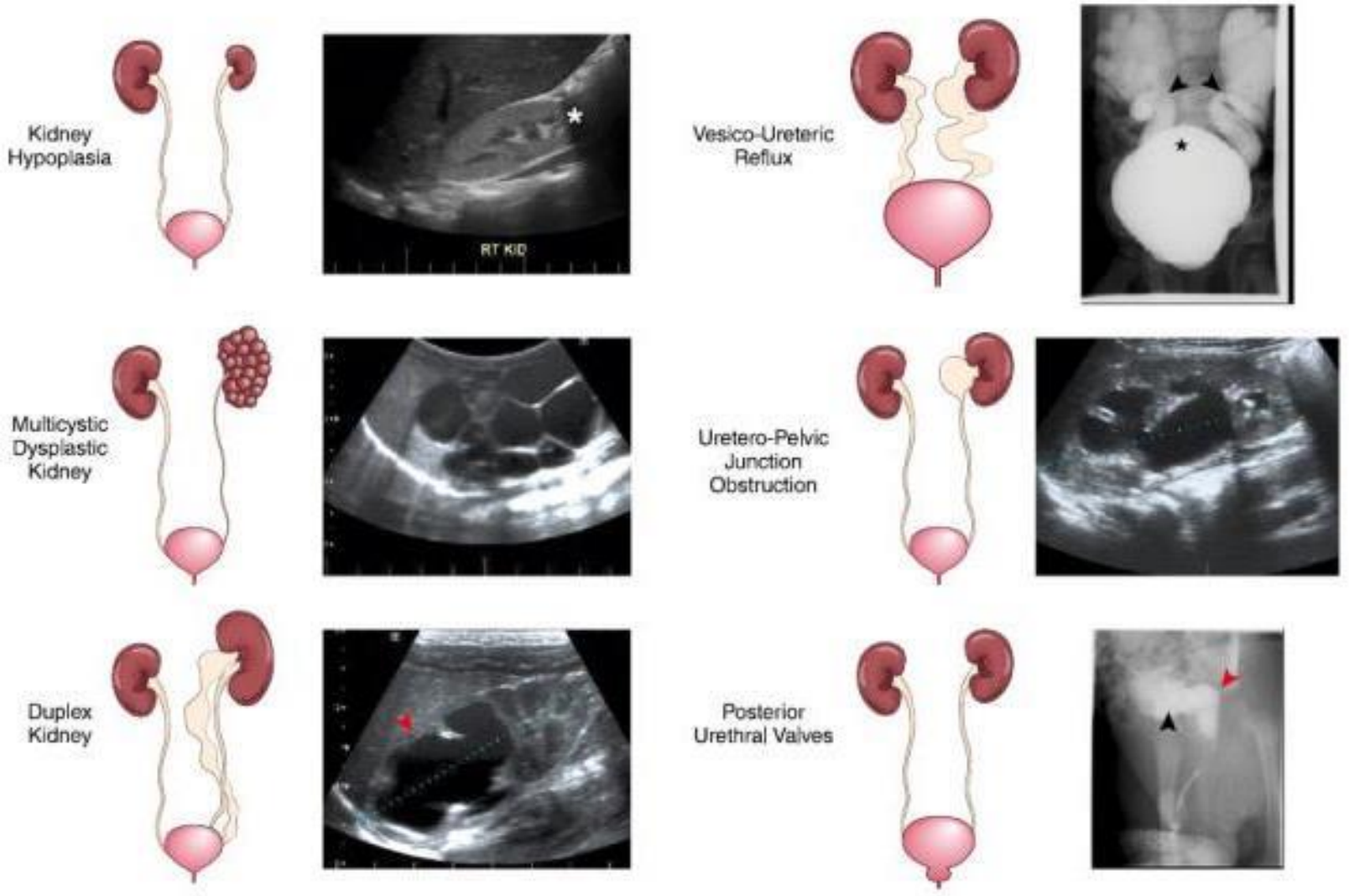
- **Prevalence range between 3 -6 /1000 births**
- Worldwide leading cause of CKD in children
  - 40% to 50% of pediatric ESKD
  - 7% of adult ESKD.
- 20–30% of all congenital malformations detected by routine fetal ultrasound

Sanna-Cherchi, S. et al Pediatr. Nephrol. 2007; 22, 1675–1684
Nicolaou, N. et al. Nat. Rev. Nephrol 2015

Spectrum of CAKUT

Affects renal parenchyma, outflow tract (Ureter, bladder, urethra)

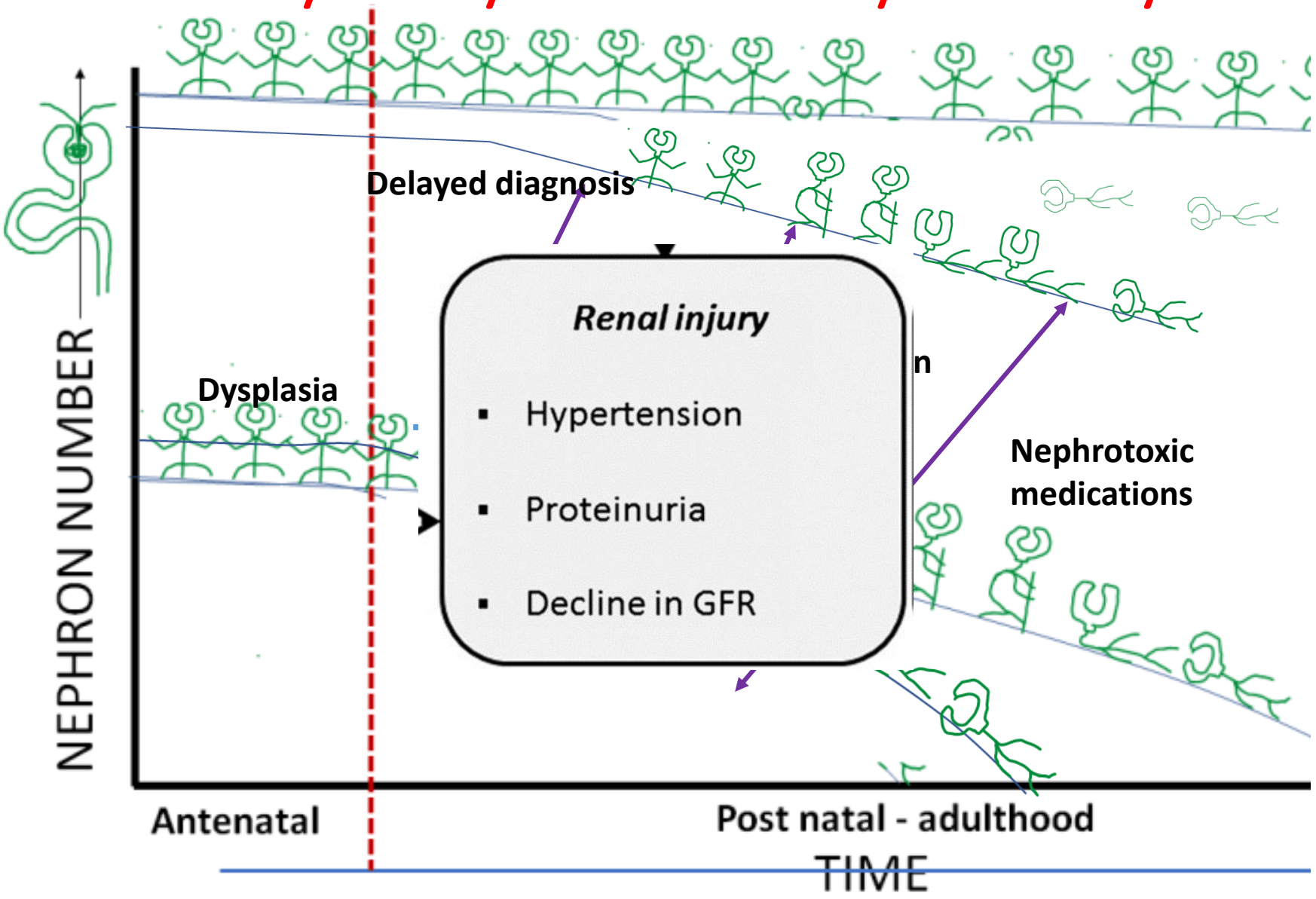
Renal differentiation abnormalities	Renal dysplasia
Renal mass abnormalities	Renal agenesis Renal hypoplasia
Shape and position abnormalities	Supernumerary kidney Ectopic kidney Horseshoe kidney
Upper urinary tract abnormalities	Pelvis and ureter duplication Ureteropelvic junction stenosis Congenital megaureter
Lower urinary tract abnormalities	Ureterovesical junction stenosis Posterior urethral valve Bladder agenesis Bladder exstrophy Neurogenic bladder
Cystic kidney diseases	Isolated kidney cyst Multicystic dysplastic kidney AD polycystic kidney disease AR polycystic kidney disease Spinal cysts – nephronophthisis



Murugapoopathy et al CJASN 2020

OTHERS : Ureterocele, Horseshoe kidney, Megaureters

Why worry about Kidney Anomaly?



SECTION 1

Antenatal diagnosis, evaluation, monitoring and fetal intervention of hydronephrosis

ANH–A morphological finding & NOT an etiology

Affects 1% to 4.5% of all pregnancies
Operator dependent
Mostly benign ,Underlying significant malformation in a subset

Challenge for the clinician

Communication to parents/physician & planning follow up and management

Innocent and self resolving [50 -70 %] Transient or physiologic

Avoid unnecessary worry and investigations

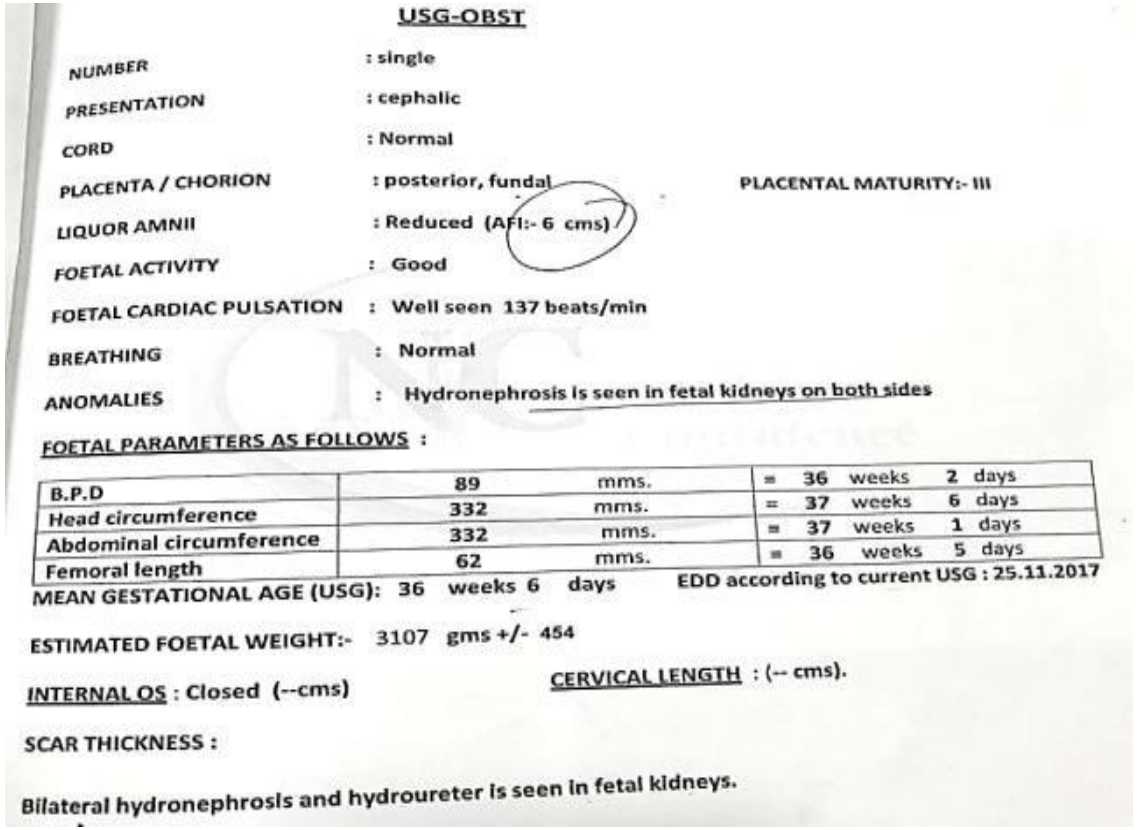
Indication of an underlying significant CAKUT

Ensure timely and appropriate investigations and interventions to diagnose and prevent renal damage

Termination ?

Prenatal Diagnostic Considerations ?

Case 1: Primi Gravida –Fetal Scan at 36 weeks gestation. Please discuss the problems



USG-OBST

NUMBER : single

PRESENTATION : cephalic

CORD : Normal

PLACENTA / CHORION : posterior, fundal PLACENTAL MATURITY:- III

LIQUOR AMNII : Reduced (AFI:- 6 cms)

FOETAL ACTIVITY : Good

FOETAL CARDIAC PULSATION : Well seen 137 beats/min

BREATHING : Normal

ANOMALIES : Hydronephrosis is seen in fetal kidneys on both sides

FOETAL PARAMETERS AS FOLLOWS :

B.P.D	89	mms.	= 36 weeks 2 days
Head circumference	332	mms.	= 37 weeks 6 days
Abdominal circumference	332	mms.	= 37 weeks 1 days
Femoral length	62	mms.	= 36 weeks 5 days

MEAN GESTATIONAL AGE (USG): 36 weeks 6 days EDD according to current USG : 25.11.2017

ESTIMATED FOETAL WEIGHT:- 3107 gms +/- 454

INTERNAL OS : Closed (--cms) CERVICAL LENGTH : (-- cms).

SCAR THICKNESS :

Bilateral hydronephrosis and hydroureter is seen in fetal kidneys.

Define ANH

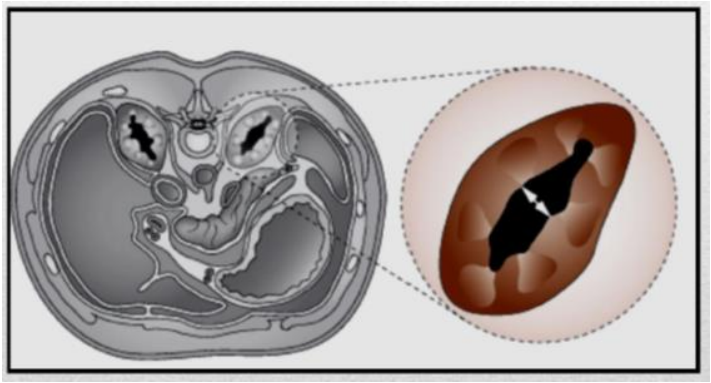
Is the timing of detection important in prognostication ?

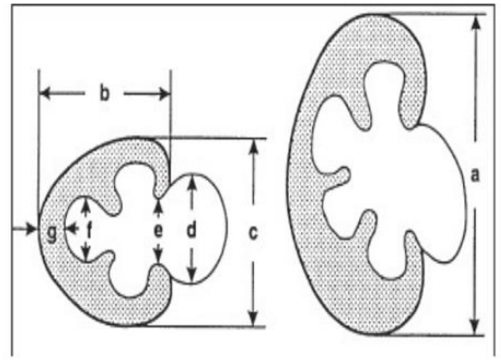
How severe is it in the index case?

Dr. Pio James

Definition of antenatal hydronephrosis

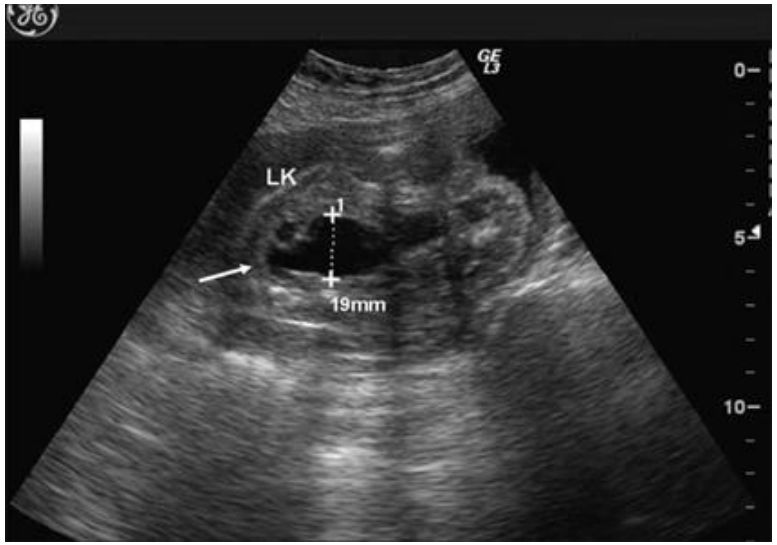
Measurement of the maximum antero-posterior diameter of the renal pelvis in the transverse plane (APD), also referred to as renal pelvic diameter (RPD), is the most generally accepted method to define antenatal hydronephrosis (ANH)





e = APPD

APN Guidelines 2001



APD ≥4 mm in 2nd trimester or if APD ≥7 mm in 3rd trimester signifies ANH

Timing of detection

Hydronephrosis and other renal anomalies is usually detected at 18–20 weeks of gestation; earlier the detection more likely to be significant

APD ≥4 mm in 2nd trimester or if APD ≥7 mm in 3rd trimester signifies ANH

Classification	Renal pelvic anteroposterior diameter, APD	
	Second trimester	Third trimester
Mild	4-6 mm	7-9 mm
Moderate	7-10 mm	10-15 mm
Severe	>10 mm	>15 mm

APD: Anteroposterior diameter

How will you grade ANH by sonography ?

Please discuss APD and SFU grading in assessing the severity of ANH.

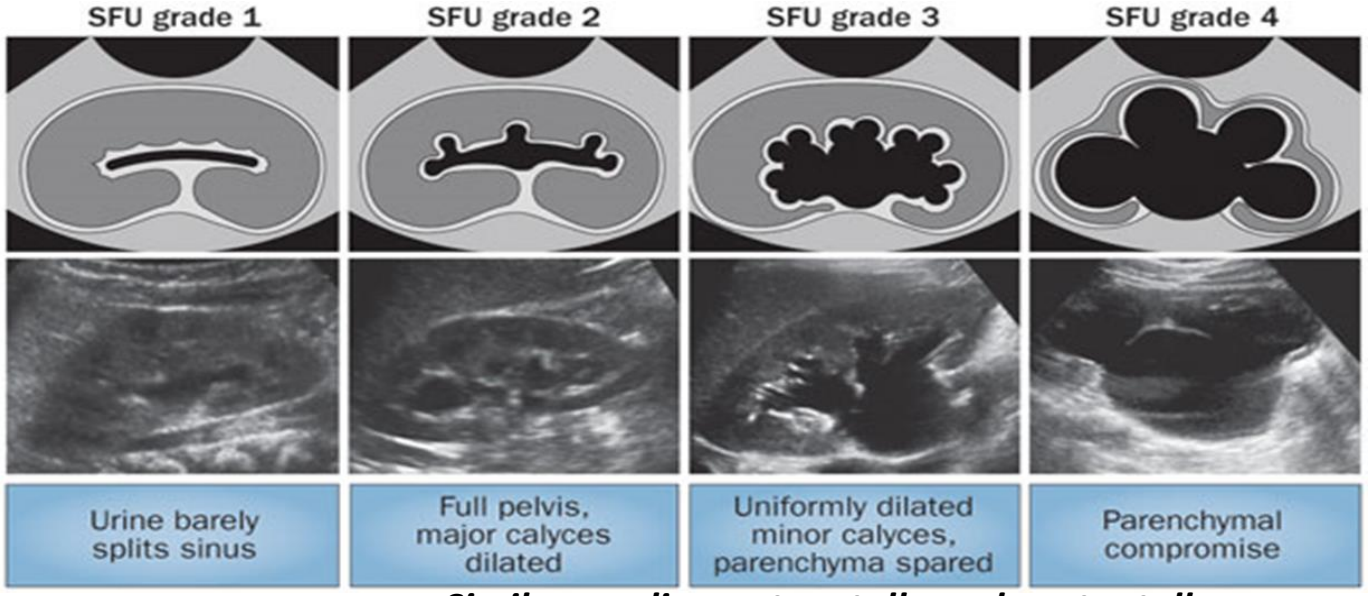
Dr. Beena S.V

AP DIAMETER OF RENAL PELVIS (1986)

Severity of antenatal hydronephrosis	*Second Trimester APD (mm)*	*Third Trimester APD(mm)*
MILD	**4-6**	**7-9**
MODERATE	**7-10**	**10-15**
SEVERE	**> 10**	**> 15**

APD – antero-posterior diameter

SFU GRADING OF HN (1993)



Similar grading antenatally and postnatally

What is UTD Classification System? Is it better than the SFU grading?

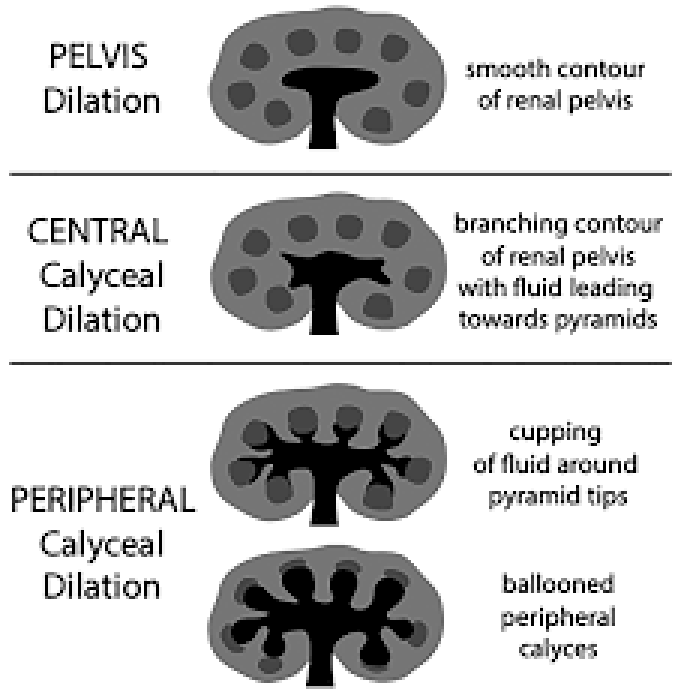
Dr.Beena S.V

Urinary Tract Dilation (UTD) Classification

	Antenatal		Postnatal *(>48h)*		
	UTD A1	UTD A2-3	UTD P1	UTD P2	UTD P3
Anterior Posterior Renal Pelvic Diameter (APRPD)	4 - <7 mm (<28w) 7 - <10 mm (≥28w)	≥ 7 mm (<28w) ≥ 10 mm (≥28w)	10 - <15 mm	≥ 15 mm	≥ 10 mm
		OR	OR	OR	OR
Calyces		Any Dilation	Central Dilation	Peripheral Dilation	Any Dilation
		OR		OR	
Ureter		Any Dilation *(with APRPD ≥ 4mm or calyceal dilation)*		≥ 4 mm *(with APRPD ≥ 10mm or calyceal dilation)*	
		OR			AND
Parenchyma Abnl, Bladdder Abnl, or Oligohydramnios		Yes *(with APRPD ≥ 4mm or calyceal dilation)*			Yes

Parenchyma abnormalities: cortical thinning, hyperechogenicity, or cystic dysplasia; indistinct corticomedullary differentiation

Bladder abnormalities: wall thickening, ureterocele, dilated posterior urethra



What additional information about the kidneys and bladder is required to assess significance of ANH and counsel parents?

[Dr. Pio James]

US parameters		Measurement/findings	Note
Anterior-Posterior Renal Pelvic Diameter (APRPD)		(mm)	Measured on transverse image at the maximal diameter of intrarenal pelvis
Calyceal dilation	Central (major calyces)	Yes/No	
	Peripheral (minor calyces)	Yes/No	
Parenchymal thickness		Normal/Abnormal	Subjective assessment
Parenchymal appearance		Normal/Abnormal	Evaluate echogenicity, corticomedullary differentiation, and for cortical cysts
Ureter		Normal/Abnormal	Dilation of ureter is considered abnormal; however, transient visualization of the ureter is considered normal postnatally
Bladder		Normal/Abnormal	Evaluate wall thickness, for the presence of ureterocele, and for a dilated posterior urethra

Case:2- 22 weeks gestation- Dr . Pio James-Discuss the findings?

KUB

Right kidney

Right kidney measured - 31mm
Right renal pelvis measured -10mm
Corticomedullary differentiation maintained
Mild ureteric dilatation

Left Kidney

Left kidney measured - 28mm
Left renal pelvis measured -9mm
Cortico medullary differentiation maintained
Mild Ureteric dialatation
Bladder appeared normal

Extremities

All the three segments of both upper and lower limbs seen.

Impression

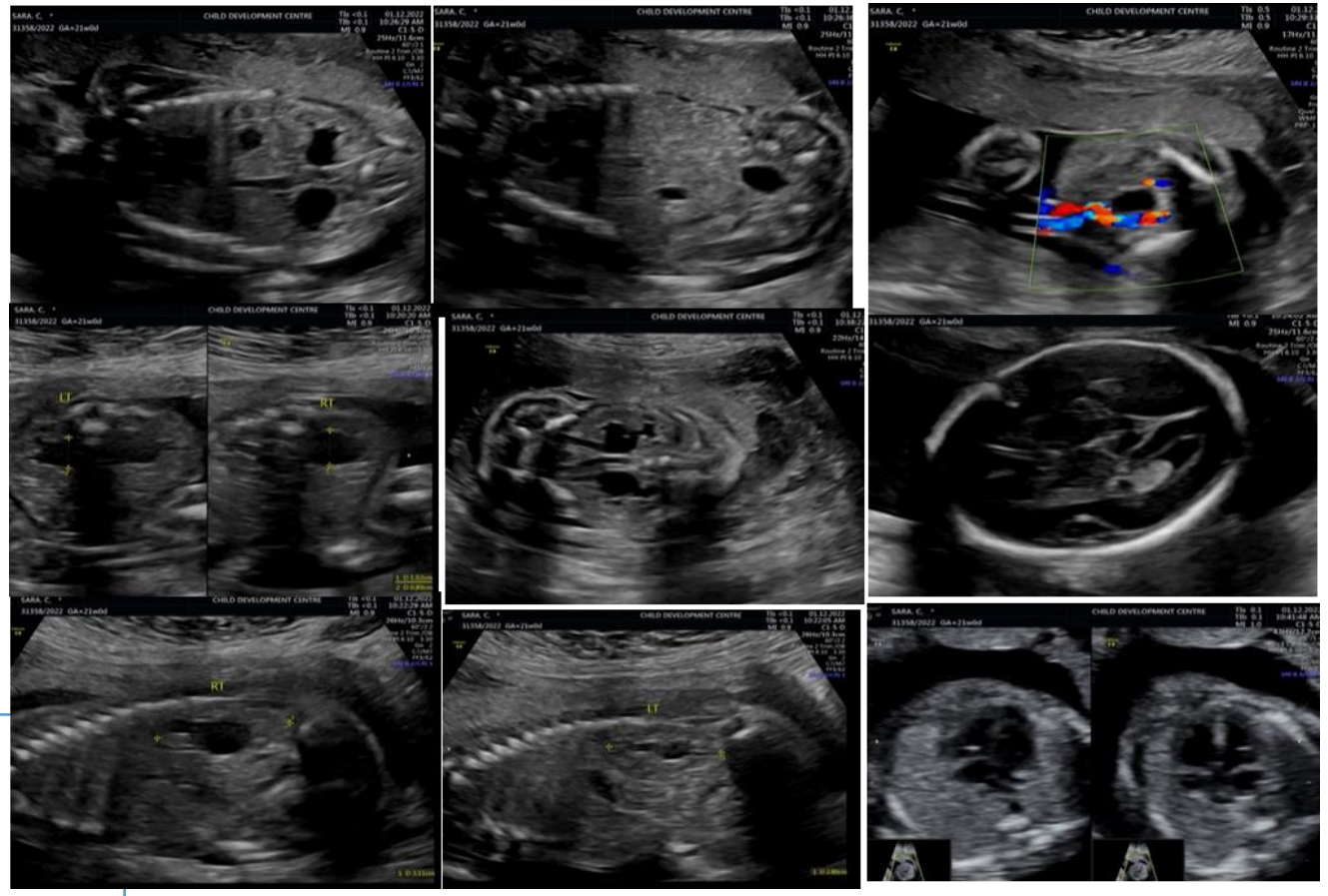
Single intrauterine gestation corresponding to a gestational age of 22 Weeks. Menstrual age 21 Weeks. Corrected EDD 06-04-2023
Placenta - Anterior
Liquor and activity - Normal
Growth - Normal

- **Single umbilical artery**
- **Unilateral Hypoplastic Nasal bone (Right)**
- **Bilateral choroid plexus cyst**
- **Persistent Left superior venacava**

Fetal Echocardiography:
- **Intracardiac echogenic foci in both ventricles**
- **Persistent left superior venacava**

No other obvious structural cardiac defect

- **Bilateral renal pelvicalyceal dilatation with mild bilateral ureteric dilatation (UTD A2-3)**



Could you elaborate on the significance of aneuploidy in CAKUT?
Dr.Sankar

B/L UTDA2-3, Bladder and liquor normal with multiple aneuploidy markers – B/L ANH

Likelihood of aneuploidy in isolated ANH-Low & karyotyping not necessary.

Risk of chromosomal disorders and need for karyotyping.

- Major structural anomaly or with one or more additional soft signs- Risk of aneuploidy high
- Referral to a center with facilities for prenatal diagnosis and counseling.
- Decision regarding invasive testing individualized, based on potential benefits and risks, and should occur at an appropriate time.

Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, Agarwal I. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol. 2013 Mar;23(2):83-97. doi: 10.4103/0971-4065.109403. PMID: 23716913; PMCID: PMC3658301.

Soft Signs on USG ?Please elaborate? (Dr. Pio James)

- Ultrasound features
- Transient
- Nonspecific
- By themselves does not cause any pathology
- Increased Likelihood of fetal chromosomal abnormalities

Second trimester markers

Strong markers

- Ventriculomegaly (>10 mm)
- Unossified nasal bone (UNB)
- Aberrant right subclavian artery (ARSA)
- Increased nuchal fold thickness (NFT) >/= 6 mm

Soft markers

- Echogenic bowel (EB)
- Choroid plexus cyst
- Mild renal pelviectasis (>/=4mm)
- Short femur/ humerus
- Intracardiac echogenic foci in the LV (ICEF)

Is CAKUT a pointer towards genetic abnormalities- monogenic variants /syndromes?

When will you suspect genetic disorders ?

Common chromosomal anomalies associated with CAKUT ?

Dr. Sankar V.H

- **Copy number variants (CNVs)-D**eletions or duplications (16%)both syndromic and non-syndromic forms.
- **De novo microdeletions of chromosome 17q12-** HNF1B gene linked to CAKUT with or without diabetes.
- **PAX2-R**enal coloboma syndrome-Renal hypodysplasia, vesicoureteral reflux, and renal cysts.
- **EYA1-**Mutations in this gene lead to Branchio-Oto-Renal (BOR) syndrome
- **SALL1-**Mutations in this gene lead to Townes-Brocks Syndrome (TBS)

What are the common causes of ANH? When to worry?

Worrying Signs on fetal scan?

Dr. Georgie Mathew

Transient in 40-90%

Pelvi-ureteral junction obstruction 10-30%

Posterior urethral valve 10-20%

Oligohydramnios ?

Amniotic Fluid volume less than 500 ml as indicated by the absence of fluid pockets greater than 2 cm on ultrasound or amniotic fluid index below 5-6.

Worrying signs

- Oligohydramnios
- Severe ANH in 2nd trimester
- Bilateral ANH
- Distended bladder with keyhole sign
- Urinoma
- Ureteral dilatation
- Loss of renal parenchyma/renal dysplasia
- Systemic abnormalities

Hydronephrosis ≠ obstruction

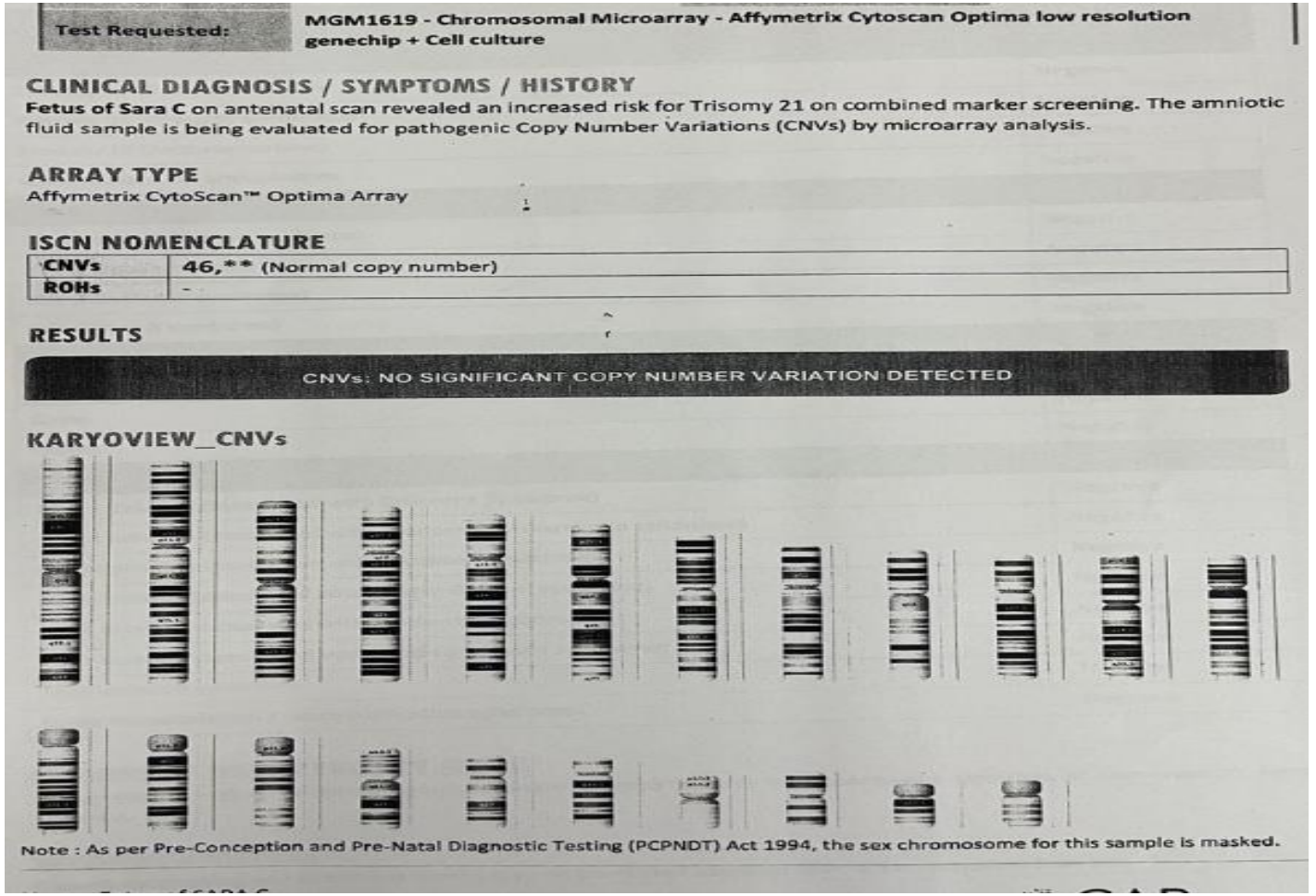
Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, Agarwal I. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol. 2013 Mar;23(2):83-97. doi: 10.4103/0971-4065.109403. PMID: 23716913; PMCID: PMC3658301.

Case:2-

22 weeks gestation with multiple aneuploidy markers

Next step?

Dr .Sankar



Test Requested:	MGM1619 - Chromosomal Microarray - Affymetrix Cytoscan Optima low resolution genechip + Cell culture

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Fetus of Sara C on antenatal scan revealed an increased risk for Trisomy 21 on combined marker screening. The amniotic fluid sample is being evaluated for pathogenic Copy Number Variations (CNVs) by microarray analysis.

ARRAY TYPE

Affymetrix CytoScan™ Optima Array

ISCN NOMENCLATURE

CNVs	46,** (Normal copy number)
ROHs	-

RESULTS

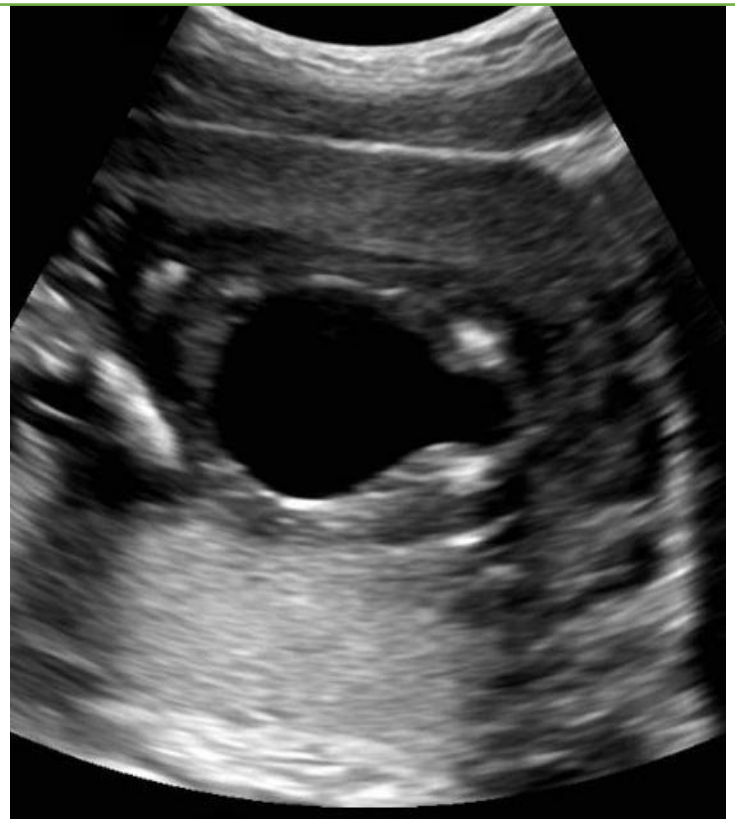
CNVs: NO SIGNIFICANT COPY NUMBER VARIATION DETECTED

KARYOVIEW_CNVs

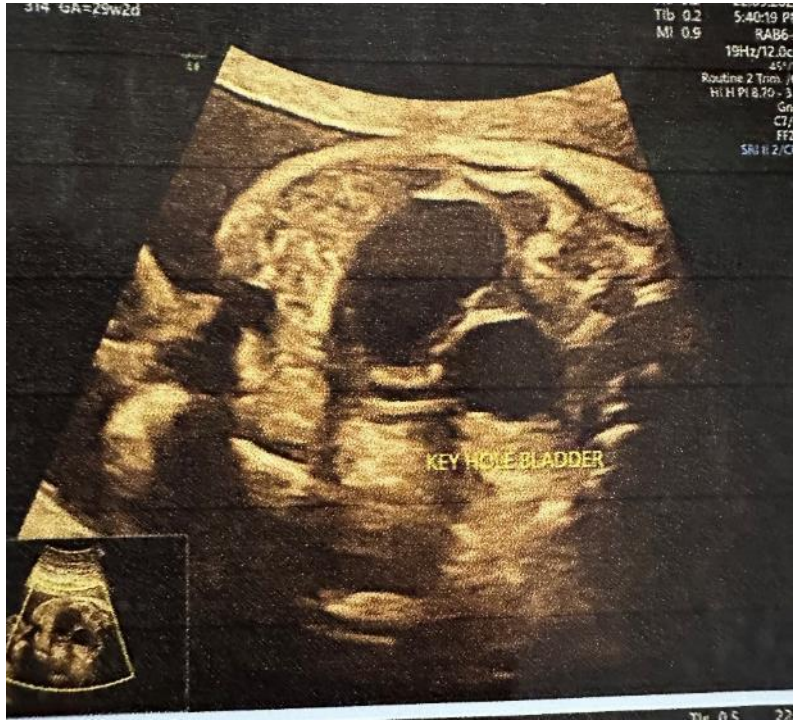
Note : As per Pre-Conception and Pre-Natal Diagnostic Testing (PCPNDT) Act 1994, the sex chromosome for this sample is masked.

Pregnancy Continued

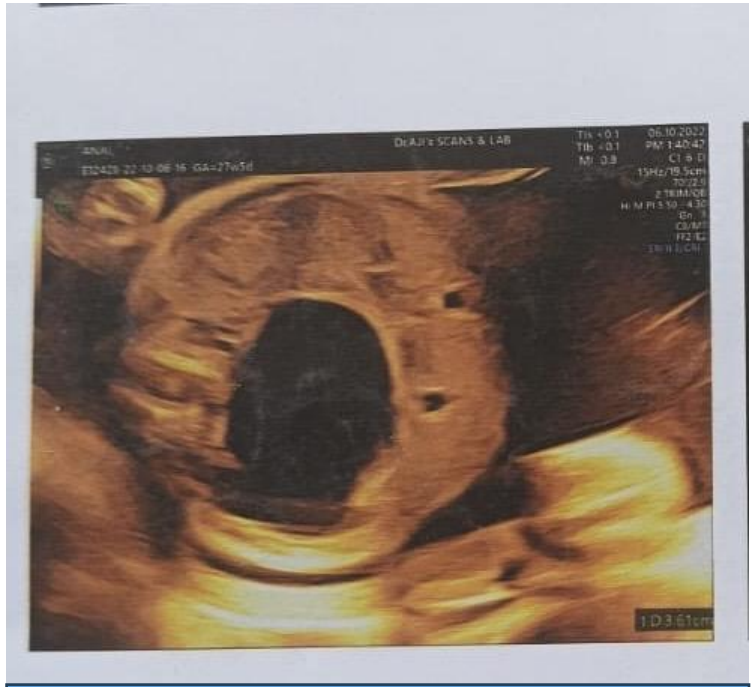
Dr. Pio James
Can you discuss these findings briefly?



PUV



U/L DUPLEX WITH HUN OF ONE MOIETY



PUJO WITH VUJO &URETEROCELE

Case 3: 30-Year Primi Gravida

"Sradha" Fetal Medicine Unit

Department of OBG, SAT Hospital & Child Development Centre
Medical College, Thiruvananthapuram - 695 011
Phone No : 0471 2553540

Patient name	[redacted]	**Age/Sex**	30 Years / Female
Patient ID	24733/2020	**Visit No**	2
Referred by	Dr. O One/ SAT	**Visit Date**	07/12/2020
LMP Date	10/04/2020 LMP EDD: 15/01/2021[34W 3D]		

Counselling:
Thank you for referring [redacted] History and findings were noted.

In todays scan the growth of the fetus is normal with normal liquor and activity. There is Left hydroureteronephrosis, duplex kidney and collecting system and intravesical ureterocele. The association of chromosomal and genetic syndromes is not increased. There is no increased risk of recurrence. Postnatal intervention may be required depending on the presence of vesicoureteric reflux and renal function. Prognosis is generally good

Suggest follow up scans for reassessment every 2 weeks to see evolution of hydroureteronephrosis, development of complication and liquor. The above findings have been explained to the patient in detail.

Suggest:
1. Reassessment after 2 weeks. Appointment fixed in CDC/FMU on 21/12/2020
2. Daily fetal kick count
3. Continue folic acid and iron supplements twice daily
4. Delivery at term. Ceserean section only for obstetric indication.
5. Pediatric surgery/ Urology consultation near term.
6. Postnatal clinical evaluation of the newborn

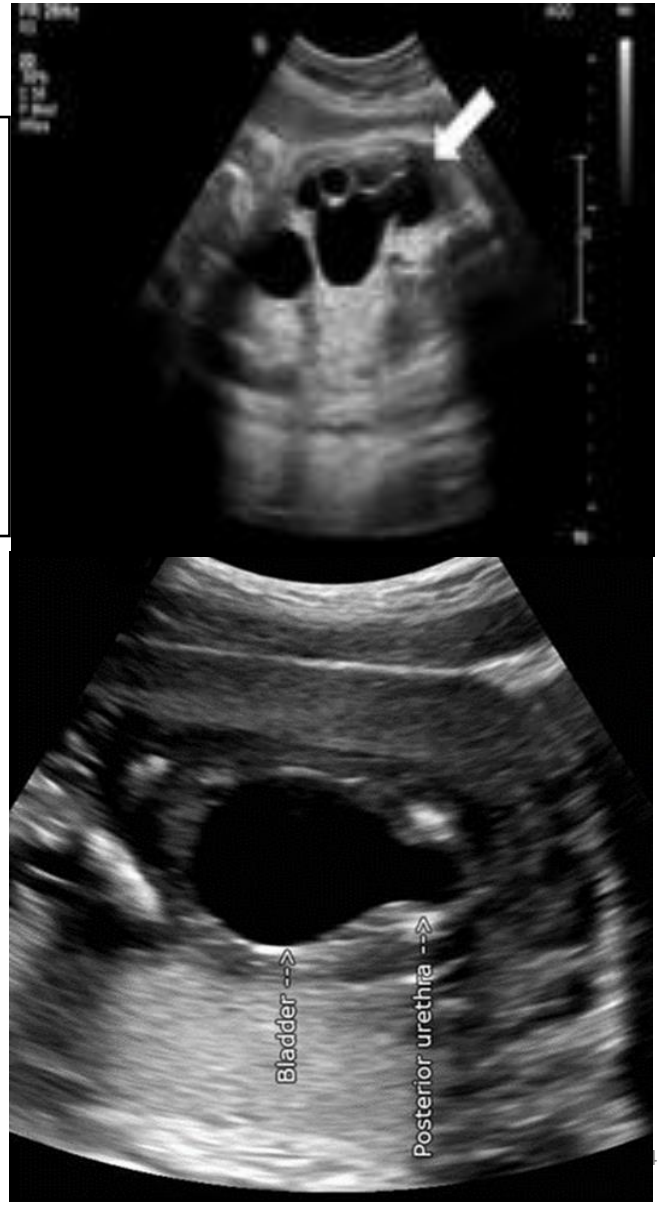
U/L UTD A2-3
Duplex collecting system
Ureterocele
Counseling?

Dr.Pio James

When will you suspect lower urinary tract obstruction?

Dr. Beena S.V

- Bilateral Hydronephroureterosis associated with dilated thick-walled bladder that fails to empty
- Dilated posterior urethra and/ or oligamnios.
- Key Hole Sign



Postnatal pathology / need for surgery

Bilateral hydroureteronephrosis

Dilated posterior urethra

Perinephric urinoma

Progressive calyceal, or ureteric dilatation.

What is the outcome and long-term course? Determinants of Outcome ?
What is “innocent dilatation”? [Dr.Georgie]

- Prognosis & severity of hydronephrosis:

  (% needed surgery or prolonged follow-up):

  RPD > 20 mm, 94%

  RPD 10–15 mm 50%

  RPD was < 10 mm 3%

- Outcome of fetal renal pelvic dilatation

  (Surgery or UTI):

  Mild dilation 0%

  Moderate dilatation 23%

  Severe hydronephrosis 64%

Determinants of Renal outcome

- ✓ Severity of HDN
- ✓ Gestational period of detection
- ✓ Renal parenchymal changes
- ✓ Postnatal diagnosis and treatment

Innocent dilatation:

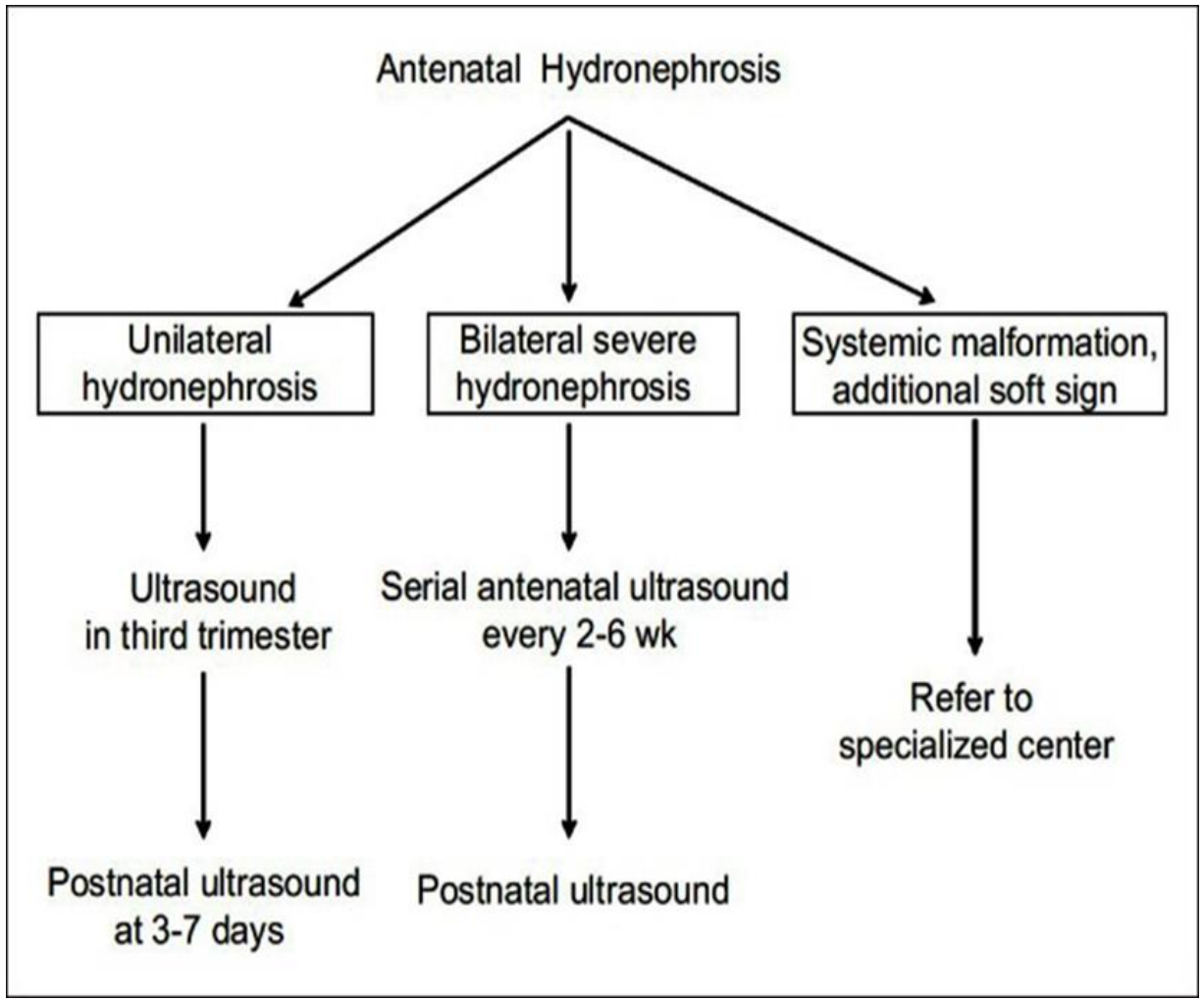
Transient dilatation which resolves postnatally, aetiology being higher urine output in the foetus

Hallmark of “innocent dilatation” :

- Unilateral ANH
- < 10 mm APD (3rd trimester) or SFU grade 1 or 2
- No ureteric dilatation
- No bladder abnormalities

Grignon A, Filion R, Filiatrault D, et al: Radiology 1986 Sep; 160(3): 645-7; Ultrasound Obstet Gynecol. 2005 May;25(5):483-8.

ANH – Protocol for follow up in pregnancy? Dr. Georgie



- Unilateral ANH – at least once in 3rd trimester
- Bilateral – 4 to 6 weekly; based on gestation at detection, severity, oligohydramnios
- Look for associated anomalies-Antenatal transfer to higher centres
- Termination Decision:

  Proceed with pregnancy unless severe oligohydramnios/ major extrarenal life-threatening abnormalities

  Shared decision

Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, Agarwal I. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol. 2013 Mar;23(2):83-97. doi: 10.4103/0971-4065.109403. PMID: 23716913; PMCID: PMC3658301.

What are the markers of poor prognosis on fetal scan? Dr. Pio James

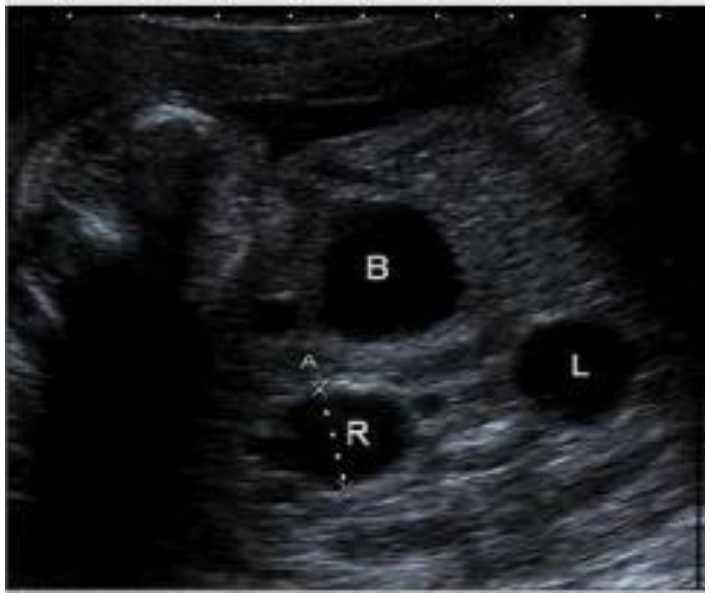
Ultrasound

Renal morphology

- Echogenic parenchyma, Thinning of parenchyma, Cortical cyst
- Abnormally large or small kidneys, loss of CMD

Amniotic fluid volume

- Oligohydramnios – How early it has set in?

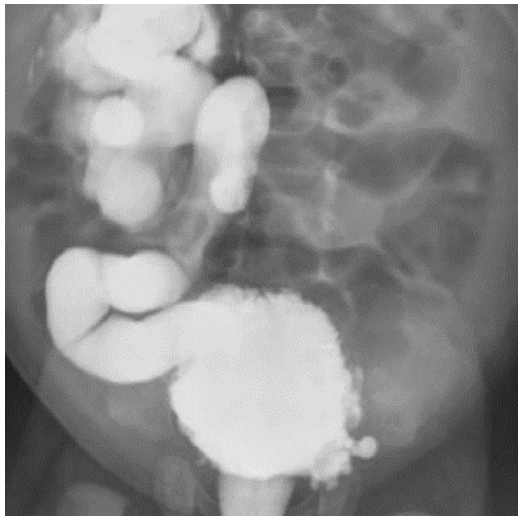


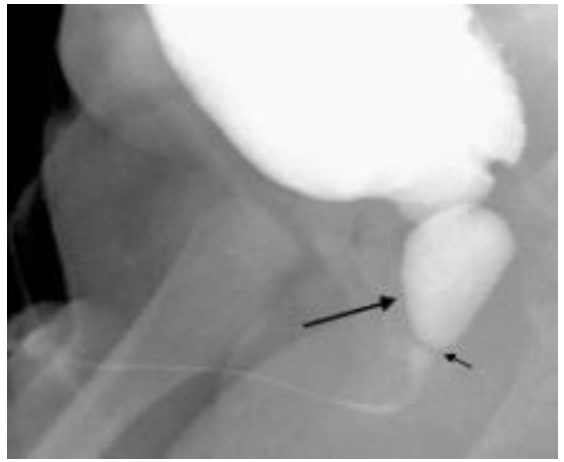
Fetal Urinary electrolytes

- Na - > 100 mEq/L, Cl - > 90 mEq/L
- Ca - > 2 mmol/L, Beta 2 microglogulin - > 2 mmol/L
- Osmolarity - > 210 mEq/L

Baby was born full term ….

- He had dribbling of urine ,palpable bladder and kidneys
- Postnatal scan showed bilateral gross Hydronephroureterosis , thickened trabeculated bladder and dilated posterior urethra.
- Baby was catheterized
- MCU done



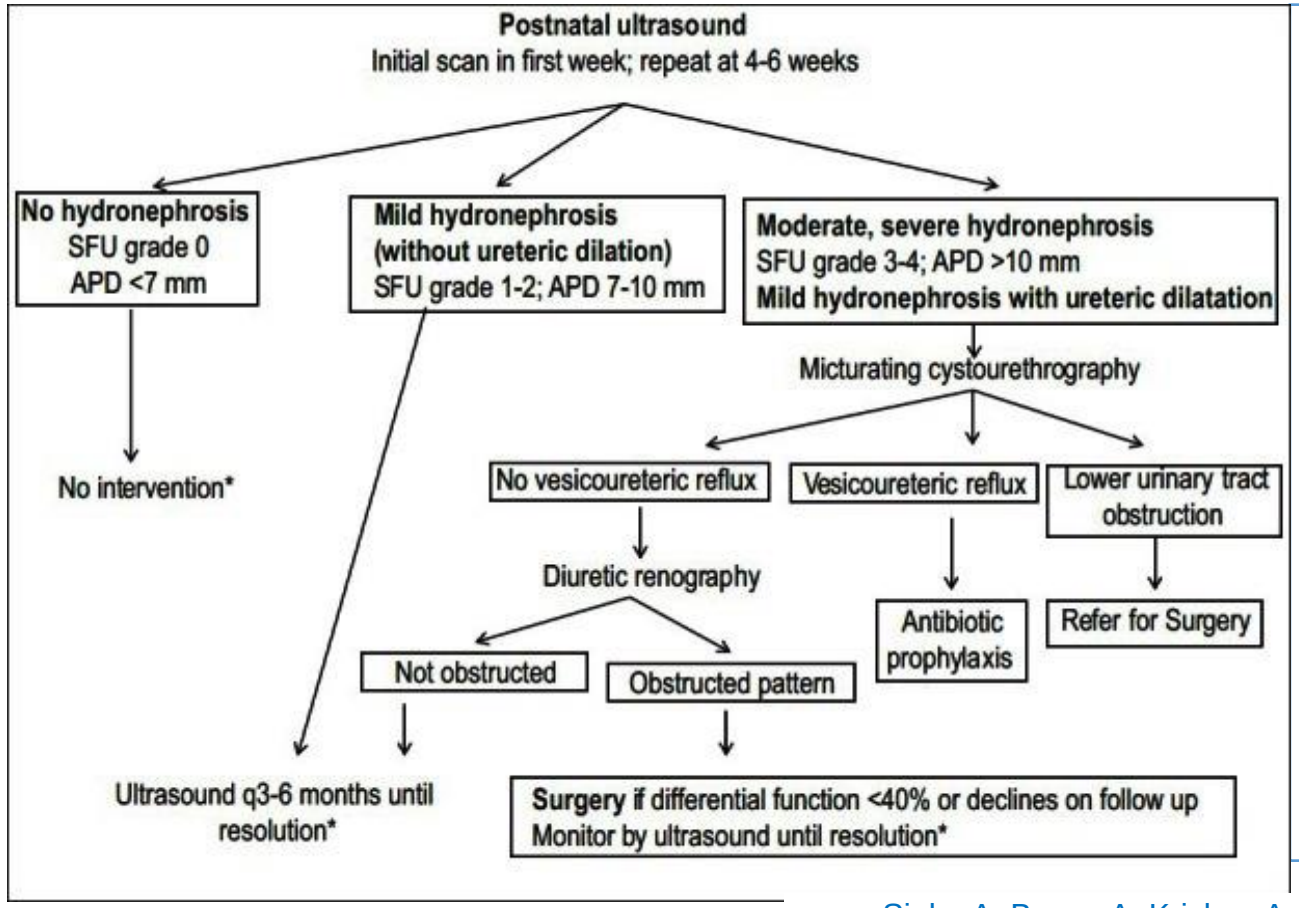


Comment on the MCU ? How will you plan management now ?

[Dr. Beena S.V]

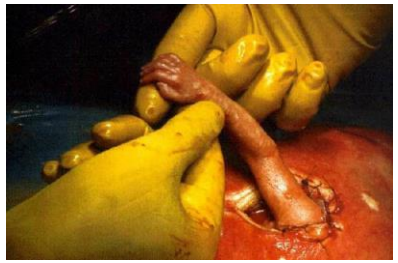
All babies with ANH should have USG in the first week of life (preferably 3-7 days of life)
Severe bilateral ANH, suspected PUV, oligohydramnios – within 24-48 hours of life
MCU – all suspected PUVs – 24-48 hours and possible fulguration

Postnatal work up ? USG – when ? MCU – Timing ? (Dr.Georgie)



- Detailed post natal follow up
- USG/MCU & Renogram
- Surgical intervention may be needed after birth in many
- Parents should be counseled regarding risk of recurrent UTI and progression of kidney disease

Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, Agarwal I. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol. 2013 Mar;23(2):83-97. doi: 10.4103/0971-4065.109403. PMID: 23716913; PMCID: PMC3658301.



Case 4

24 weeks scan in a primi mother showed ANH .Repeat scan shows bilateral severe hydronephrosis and oligohydramnios - suspected PUV.

What are the possible antenatal interventions in this baby with significant bilateral hydronephrosis and oligohydramnios ? Dr. Beena S.V

Indications for antenatal intervention for a genitourinary abnormality

- Severe oligohydramnios
- Suspected favorable renal function
- Absence of life-threatening congenital abnormalities.

Decompression restores amniotic fluid & prevent fetal pulmonary hypoplasia

?? Arrest or reverse renal cystic dysplastic changes

Antenatal management (Dr. Beena S.V)

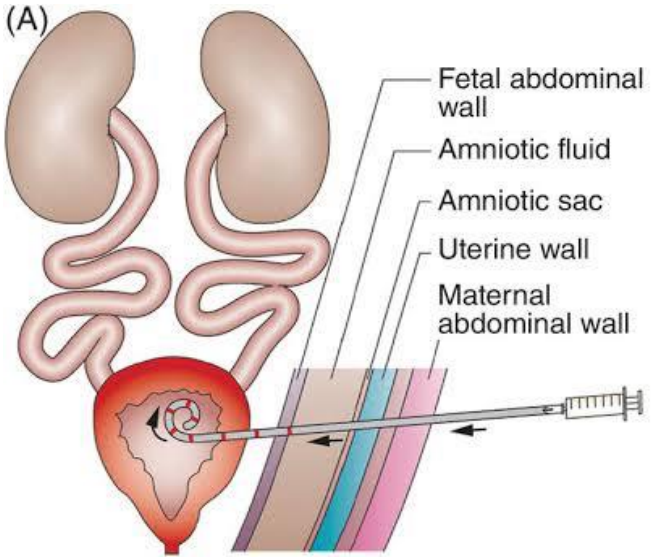
Fetal procedures -

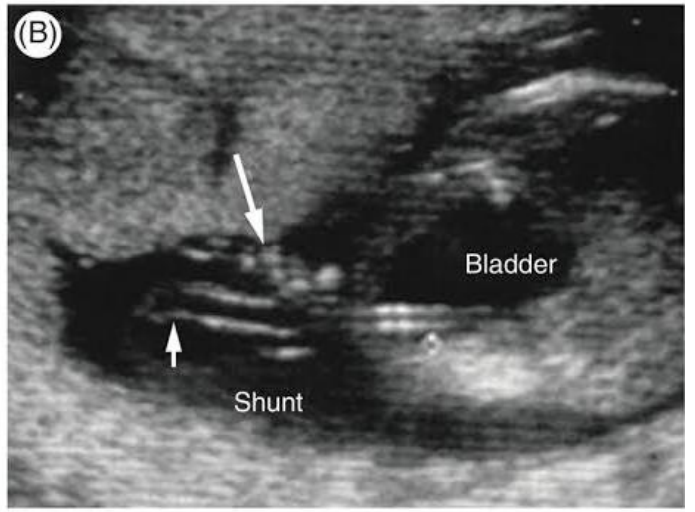
➢To preserve renal function and reduce risk of pulmonary hypoplasia

- ✓ **Vesico-amniotic shunting**
- ✓ **Percutaneous fetal cystoscopy and valve ablation**
- ✓ **Open fetal surgery** are treatment options

➢These highly complicated procedures are only undertaken when *renal function is adequate and there is hope for benefit*

➢This remains an area of debate with concern that the risks in terms of *fetal loss and prematurity* outweigh the potential benefits of limiting the damage that has already been done





Prenatal Evaluation and Treatment for Fetal LUTO

Vesico-amniotic Shunting

Case selection for shunting

- Oligohydramnios – too late for shunting
- Normal amniotic fluid – too early for shunting
- Reducing amniotic fluid on serial scans?

Therapy may not improve renal function

May help better survival

Randomized controlled trials not feasible

Long-term outcomes for shunts

(PUV40%,Urethral atresia20%,Prune belly Syndrome40%)

- Outcome:
  - More than 45% had a GFR of >70ml/min
  - 25 % renal insufficiency
  - 33% on dialysis
  - 33% had a transplant

Haeri S. Fetal Lower Urinary Tract Obstruction (LUTO): a practical review for providers. Matern Health Neonatol Perinatol. 2015 Nov 18;1:26. doi: 10.1186/s40748-015-0026-1. PMID: 27057343

Fetal Cystoscopy -New paradigm

Fetal Cystoscopy in LUTO

- # with oligohydramnios / disordered urinary indices
- # early delivery is not an option

Laser fenestration in-utero

- Two babies with posterior urethral valves
- One fetus with bilateral ureteroceles

Fetal cystoscopy may emerge as a better option but needs more expertise

No evidence exists demonstrating the benefit of antenatal intervention in terms of renal function and only in a select number of cases will it benefit pulmonary function

Case 5

A 27- yr old G2P1, Antenatal USG (2nd trimester) Right HDN – APD28 mm. Left Kidney Normal

Repeat USG in 3rd trimester- R HDN APD 36 mm. Liquor volume Normal

How should we counsel the parents ? (Georgie)

Abdominal wall intact.

KUB

Left Kidney

Left kidneys appeared normal.
Left kidney measured - 33mm Normal
Left renal pelvis - 3.8mm. Normal
Corticomedullary differentiation maintained
Left ureter not dialated

Right Kidney

Size - 55mm
Right renal pelvis measured 28mm (Increased)
Both minor and major calyx dialated
Thinned out cortex
Right ureter not dilated

Bladder appeared normal

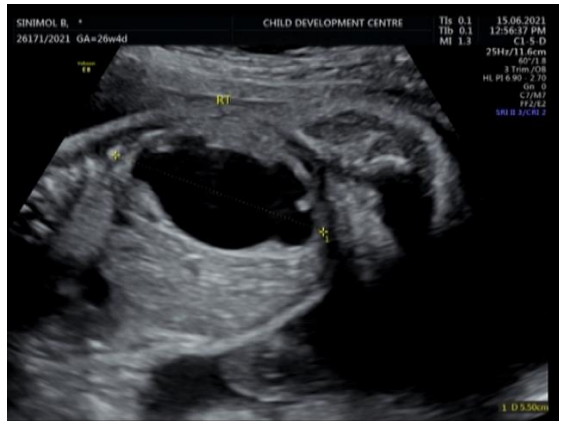
Impression

Single gestation corresponding to a gestational age of 26 Weeks 4 Days
Gestational age assigned as per LMP

Placenta - fundal and posterior
Activity - Normal
Growth - Normal

Hypoechoic Liver
Echogenic small bowel

Right Hydronephrosis
Urinary tract dilatation disorder A2-3 (UTD A2-3)
Suggestive of Peviureteric junction obstruction.



Reassure the family regarding the benign course in majority

- Most unilateral HDN have good long term outcome as long as the other kidney is normal
- Unilateral hydronephrosis of any severity does not need any fetal intervention or early delivery
- Post natal Evaluation will be required

The baby is born full term --

FTND, male child, 3 kg, CIAB. No congenital malformations.

How will you plan the postnatal evaluation ?Indication for MCU ? Timing of USG/Radionuclide Scan / MCU ?

Dr. Beena S.V

USG

- All newborns - postnatal USG within 1st week.
- Within 24-48 hours-Suspected PUVs, Oligohydramnios or severe bilateral hydronephrosis

MCU

- Suspected obstruction/VUR All babies with UTD A2/3
  - PELVIS AP>12 MM
  - DILATED URETER
  - Thickened Bladder,Ureterocele
  - Dilated ureter/duplex kidney
- Any UTD if develops UTI
- Worsening hydronephrosis(increasing pelvic size,calyceal diltn,parenchymal thinning)

Radionuclide scans After 6 weeks -preferably by 3/12-EC /DTPA

Neonatal hydronephrosis is defined as SFU grade ≥ 1 or renal APD ≥ 7 mm.

Postnatal USG on D5- Right APD 34 mm. Left Kidney Normal .Bladder Normal

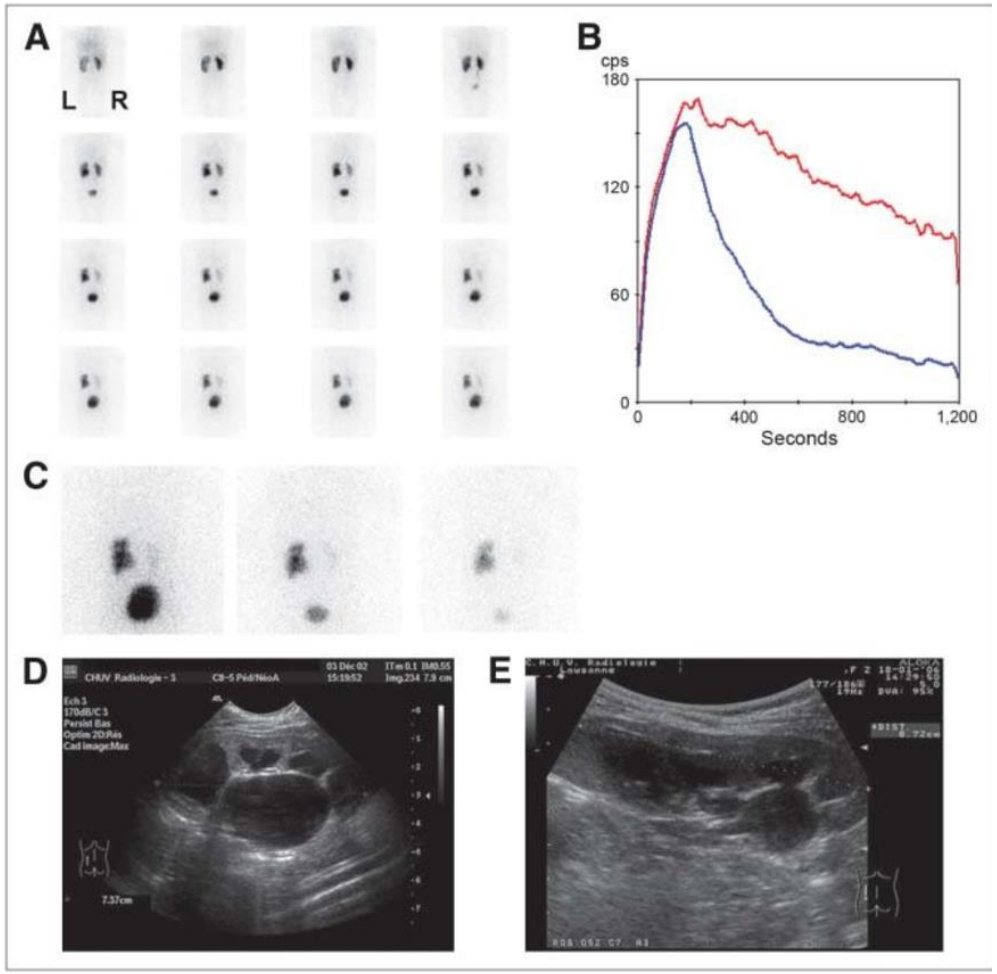
How to manage further ? Antibiotic prophylaxis ? (Dr.Georgie)

ISPN 2023 suggests against using antibiotic prophylaxis for prevention of symptomatic UTI (grade 2 evidence)

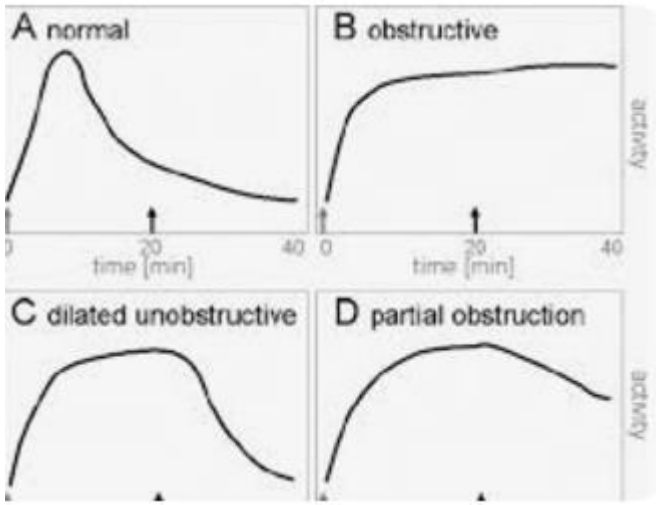
Antibiotic cover for MCU

MCU done; No VUR.

Diuretic renogram is done. Please discuss (Dr.Georgie)

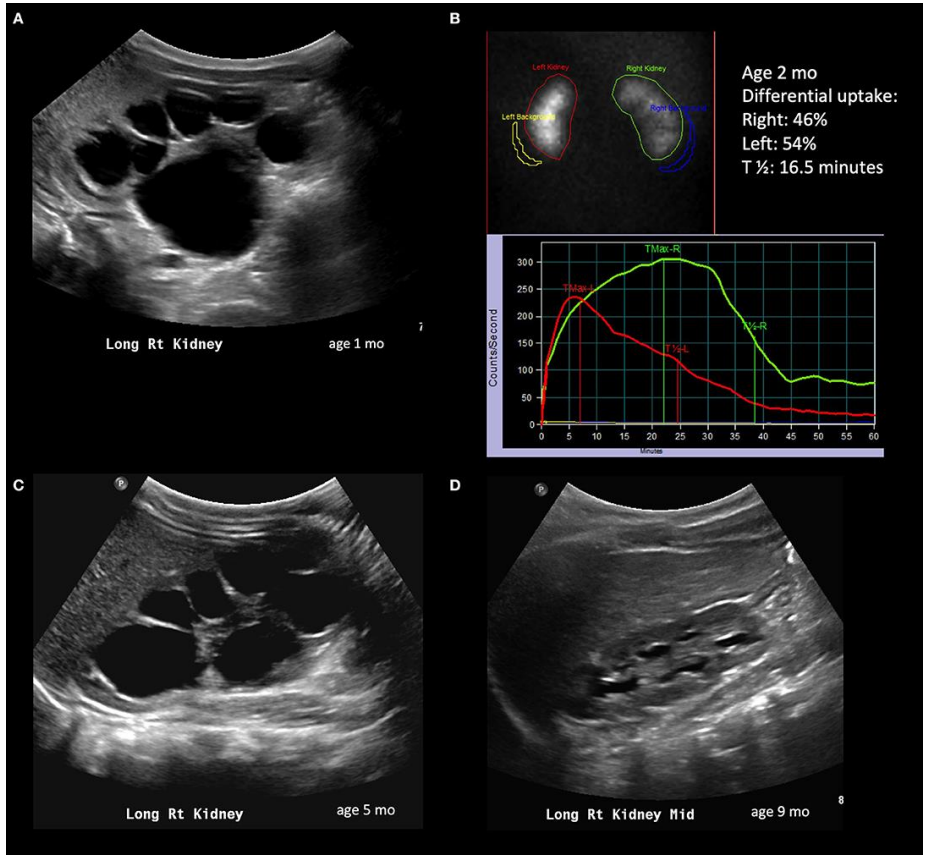


Parameter	Lt Kidney	Rt Kidney
T max (minutes)	16	2.6
T1/2 (minutes)	Not reached	8
Split function (%)	46	54



Left PUJ obstruction with non-draining curve and significant retention of tracer even at 2 hours .
Renal function LK-46%, RK-54%.

Baby was kept on close follow-up. Repeat USG at 2 months showed worsening hydronephrosis with AP diameter of 30mm. There was some cortical thinning also with calyceal dilatation.



What is the plan now? What is the optimum time for surgery in PUJO ?

What are the factors considered in deciding the timing of surgery ? **(Dr. Beena S.V)**

Indications for Pyeloplasty

(Dr. Beena S.V)

Concrete indications

Differential function less than 40% on renogram

Loss of 10% differential function on follow up scan

Increasing Pelvicalyceal dilatation in single kidney

Symptoms : pain, hematuria , mass

APD versus pyeloplasty

More than 20 mm APD, 50% will need pyeloplasty

More than 30 mm APD, 80% will need pyeloplasty

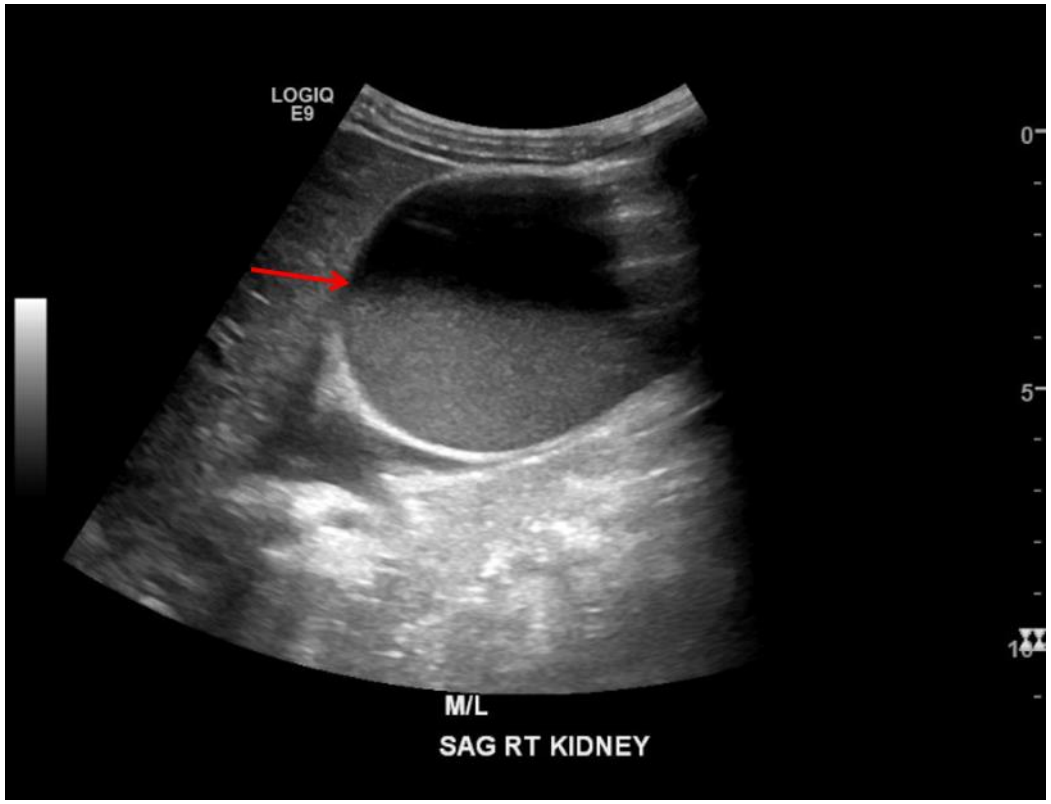
More than 40 mm APD, 100% will need pyeloplasty

1. "Early" pyeloplasty results are excellent
2. But pyeloplasty is (almost) never an emergency
3. Always give time to investigate , observe and ponder before surgery
4. APD > than 30 mm could be considered an indication for surgery rather than lengthy observation.

Percutaneous nephrostomy/RETROGRADE STENTING

- Hydronephrosis with infection
- HN causing pressure effects

BRIDGING PROCEDURE



Will the diagnosis impact on the timing and mode of delivery in ANH ?

[Dr. Georgie]

Diagnosis of ANH should not impact timing and mode of delivery

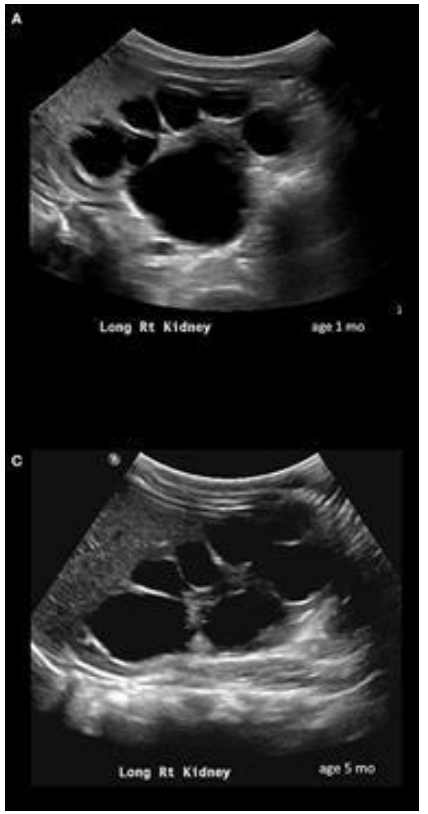
Unless for obstetric indication

Complications of prematurity to be kept in mind

When to perform follow up scans in a case of ANH[Dr. Pio James)

- Normal ultrasound in first week :Repeat scan at 4-6 weeks.
- Persistent HDN in first week : Repeat scan every 3- 6 months up to 2 years & every 6 – 12 months until resolution
- Isolated mild unilateral or bilateral hydronephrosis

(APD < 10 mm or SFU grade 1-2): Sequential ultrasound alone, for resolution or progression of findings



Look for increasing PCS and or ureteric dilatation & cortical thinning

Sinha A, Bagga A, Krishna A, et al. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol. 2013;23(2):83-97. doi:10.4103/0971-4065.109403

- How to counsel a family with abnormal genetic tests?
- How to deal with variants of uncertain significance?
- What is the risk of recurrence in next pregnancy?
- Role of fetal autopsy ?
- Is follow-up required in a future pregnancy?

Dr. Sankar V.H

SECTION 2

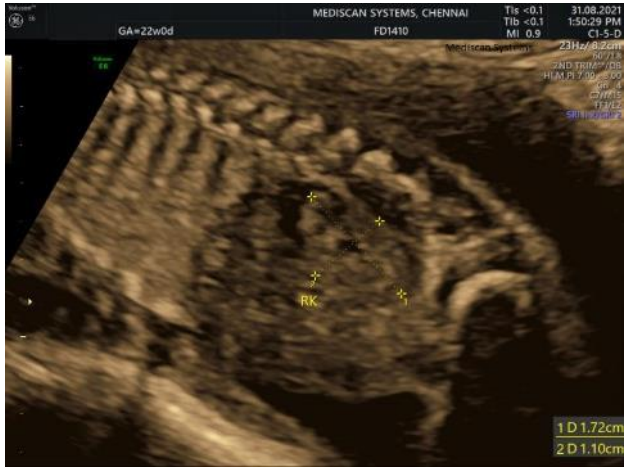
Antenatal diagnosis, evaluation, monitoring and fetal intervention of isolated renal parenchymal abnormalities

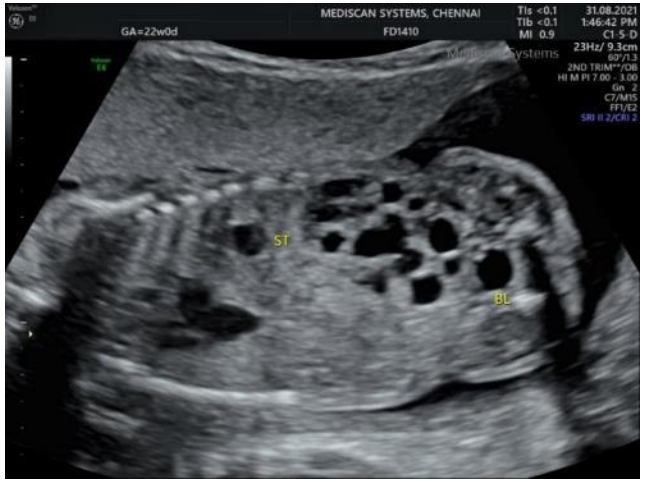
Case 6

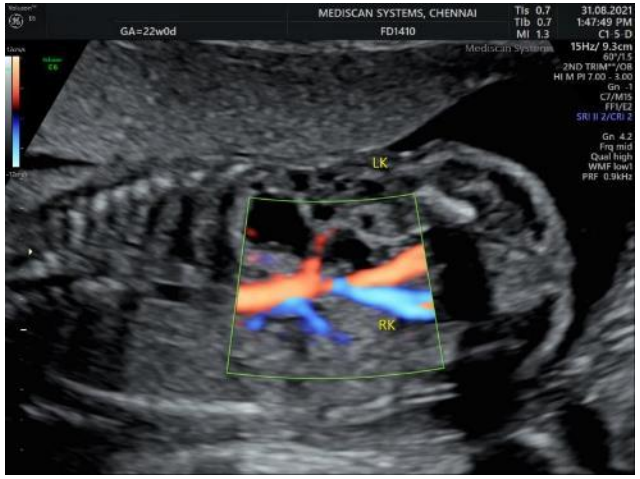
Sonography at 21 weeks in a 26 year old primi

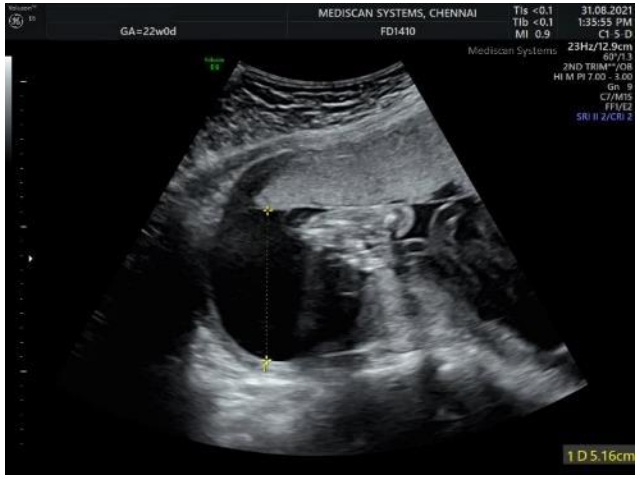
- Right kidney: Normal
- Left kidney: enlarged, echogenic with multiple cysts
- Impression: Left cystic kidney'

No other anomalies detected









What is the probable diagnosis? How will you counsel? [Dr.Pio James]

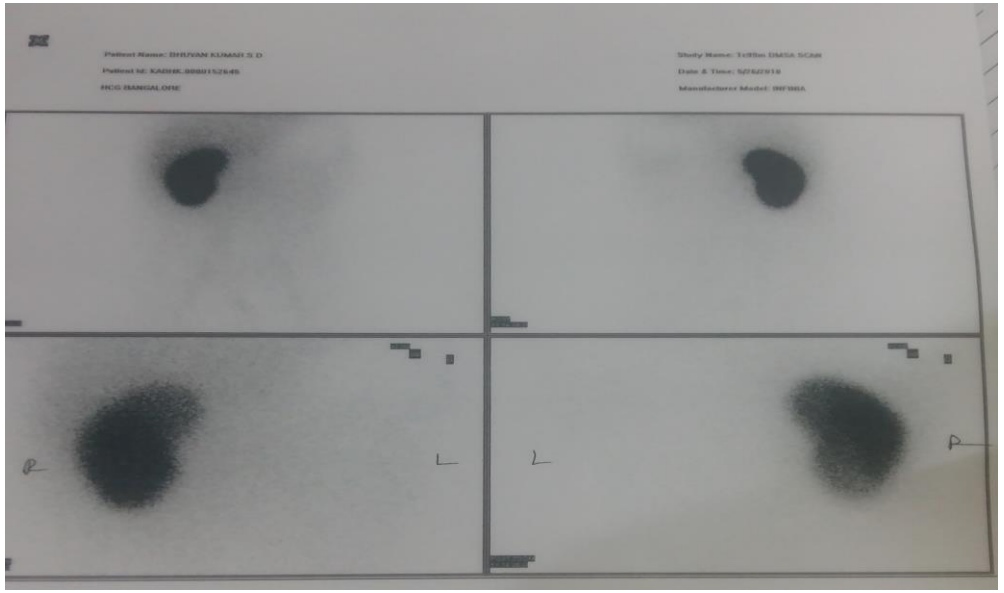
MULTICYSTIC DYSPLASTIC LEFT KIDNEY Right kidney and bladder normal

USG on day 3 of life

R Kidney - 4.2x2.3cm Normal

L Kidney - 5.4 x 2.1cm- completely replaced with multiple cysts, *non-communicating*

DMSA



Further evaluation to confirm diagnosis?
Follow up ? (Dr.Georgie)

Does the child need follow up?

Yes

Requires evaluation for a single kidney workup – kidney function, proteinuria and blood pressure to be closely followed up

DMSA can confirm absent RK if parents are anxious

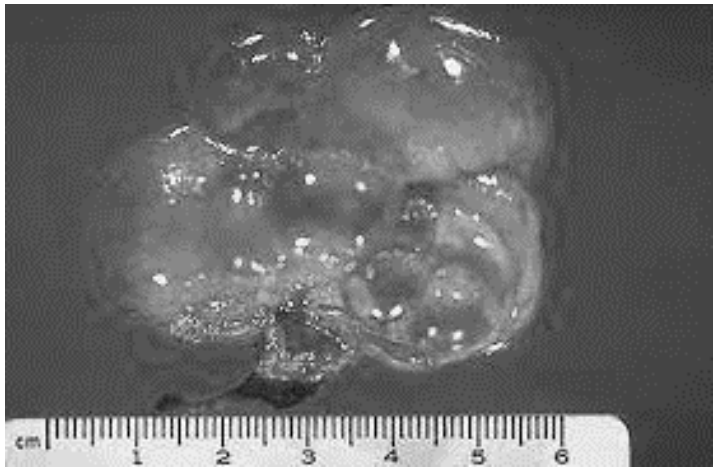
MCU-

One in three may have an anomaly in contralateral kidney

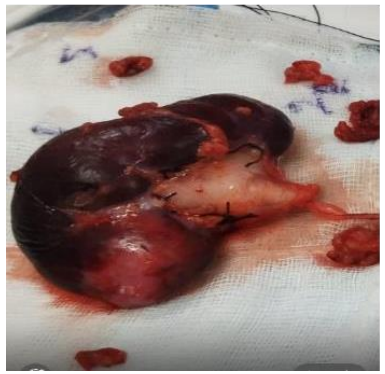
Postnatal Management ? Does this child need Left nephrectomy?

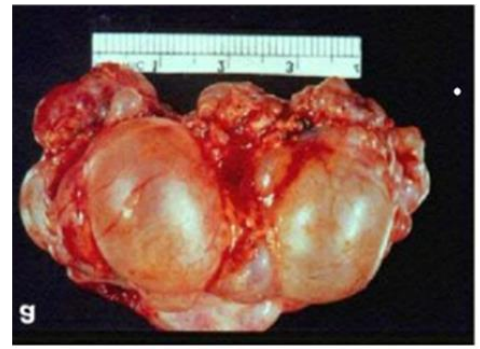
(Dr. Beena S.V)

Management of multi cystic dysplastic kidney



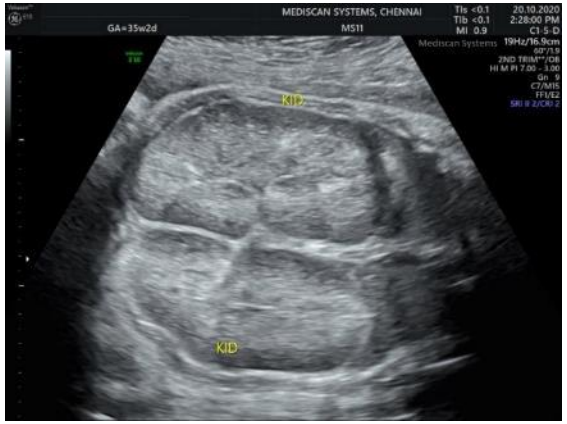
- Persistently enlarged kidney(>5 cm) causing pressure effects
- Associated VUR causing UTI
- ??Hypertension
- Risk of malignancy is negligible
- Single kidney report hypertension in 27-47% of patients, proteinuria in 23-47% of patients, and renal insufficiency in 3-13% of patients

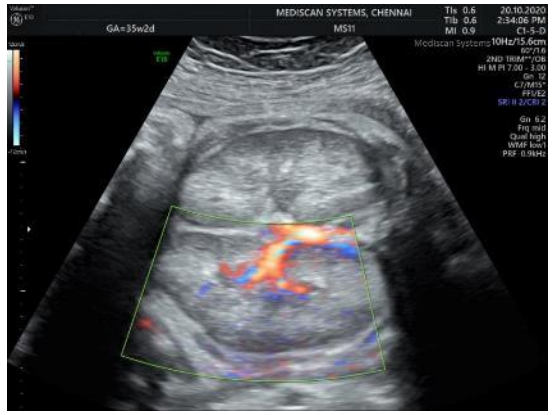


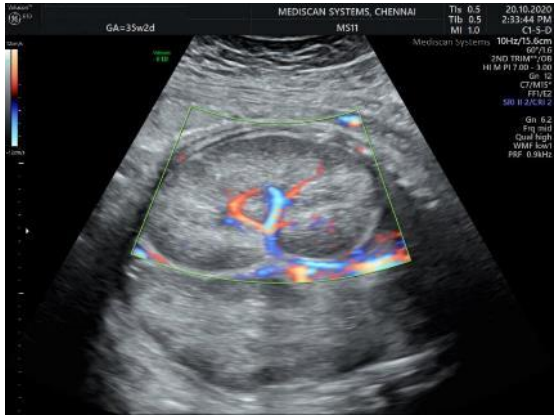


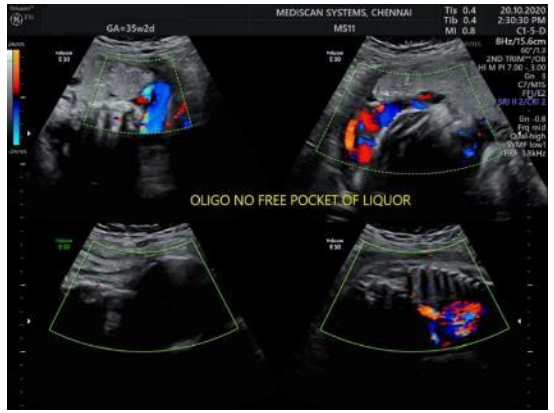
Case 7

Primi gravida -second trimester pregnancy-Fetal scan









Bilateral, symmetrically enlarged, echogenic kidneys filling the fetal abdomen. Liver normal Severe oligamnios
All other organs normal

Discuss the findings. What is the possible diagnosis?

Counseling? (Dr. Pio James).

Possibility of Polycystic Kidney disease ARPKD

Both the parents were normal on evaluation and there was no family history of renal diseases on the maternal or paternal side

Perinatal presentation with sonologically enlarged echogenic kidneys, oligohydramnios / anhydramnios Associated with pulmonary hypoplasia ,severe renal failure at birth and high mortality.

Refer for genetic evaluation &Pediatric Nephrology opinion

23/12/2024

The couple was referred for genetic Evaluation & Counseling

Is family history important?
What are the various genetic causes of cystic diseases seen in the antenatal scenario?
What are the salient points in Counseling this couple?

[Dr. Sankar V.H]

- "Prenatal Genetic Diagnosis Prenatal ultrasound (US) detection of ARPKD often is not early enough for pregnancy termination." Woodford et al, J Pediatr 2014

ARPKD- Is it an indication for termination of pregnancy? Dr. Sankar

- Counsel the parents regarding the long term outcome. Genetically proven situations option can be given regarding termination as the long term outcome is dismal with severe respiratory distress and renal insufficiency at birth

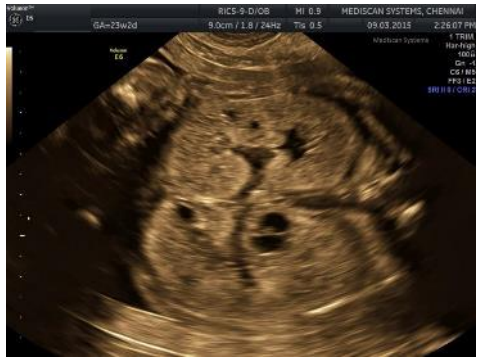
Molecular genetic testing on tissue obtained by chorionic villus sampling or amniocentesis can be used to identify pathogenic variants in the PKHD1 gene.

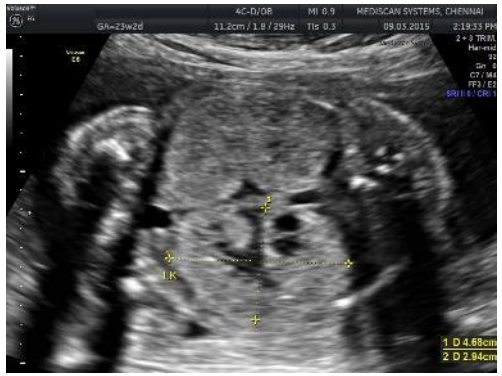
Genotype may have some association with phenotype and that individuals with truncating variants are more likely to have poor outcomes than those with missense variants.

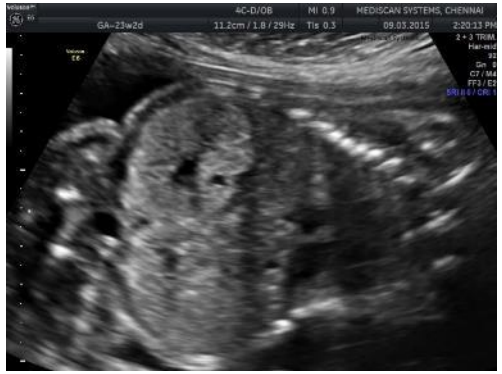
The presence of single pathogenic variant in PKHD1 gene confirms the diagnosis of ARPKD

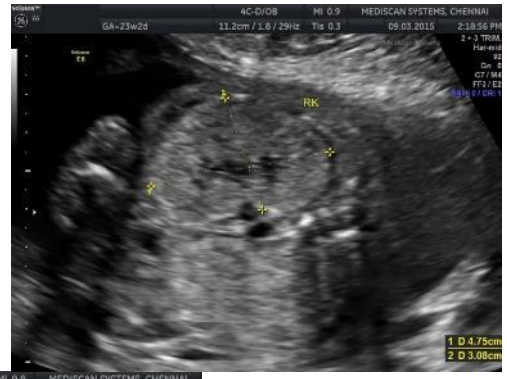
Genetic Counseling stressing the 25% risk of disease and 50% risk of being a carrier to each off spring is mandatory. Prenatal mutation detection possible in70-80% if abnormal gene already known.

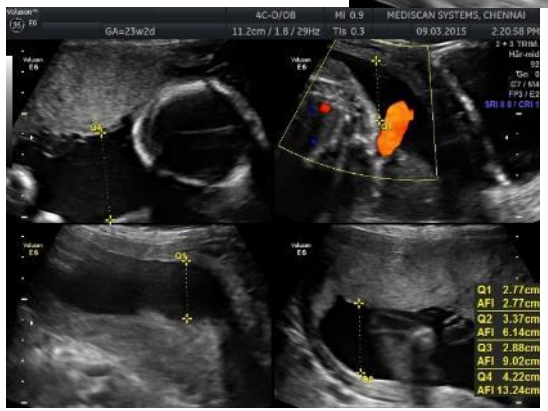
Case 8 Primi gravida -second trimester pregnancy-Fetal scan
Discuss the findings –Dr.Pio James

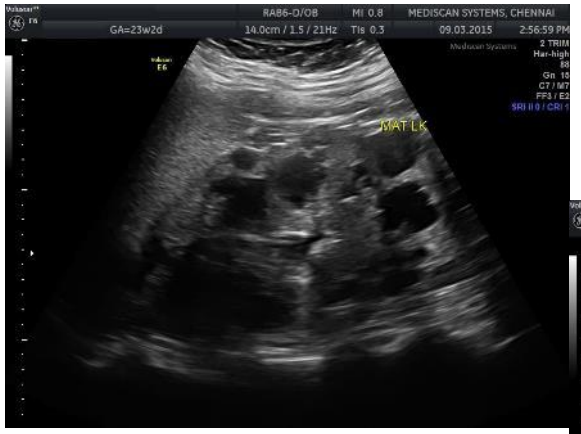




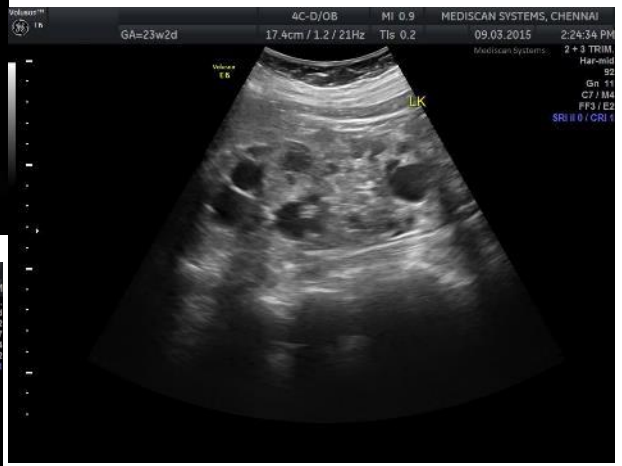


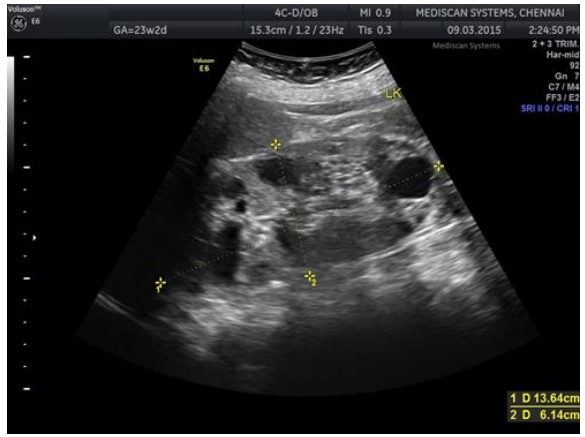






Maternal kidneys





Counseling?
Termination?

What are the possibilities ? Will you suggest termination?
Dr. Georgie

Possible differentials

ADPKD

Nephronophthisis(ADTKD), *HNF1B*, etc

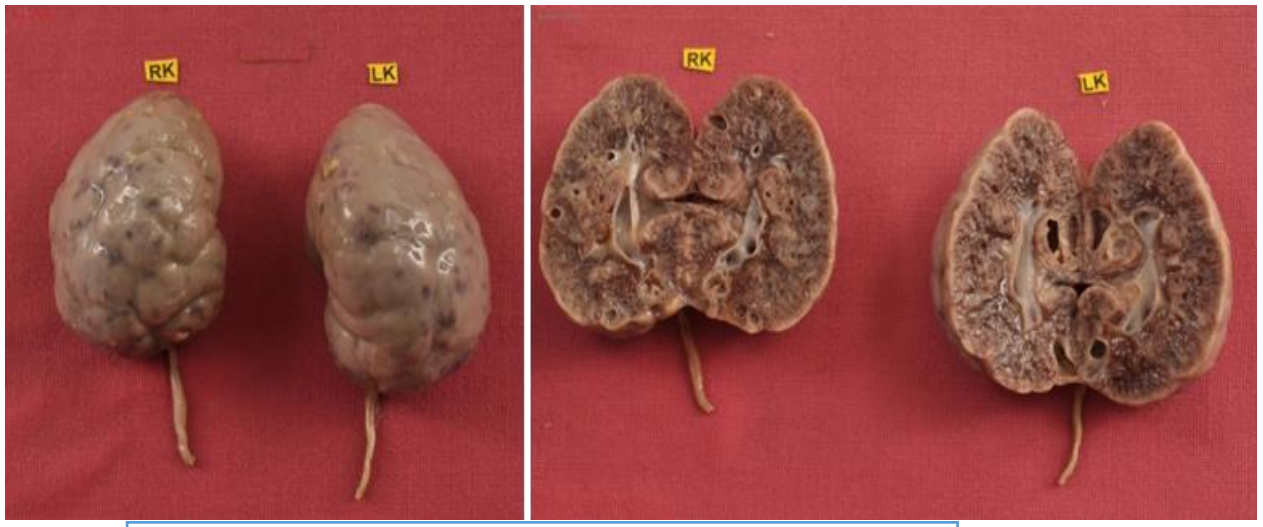
Other standard indications of terminations may apply

Potential of severe disease needs discussion with parents and the team with expertise

Case 9

MALE FETUS 35 -36 WEEKS GA
BILATERAL AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE
BILATERAL SEVERELY HYPOPLASTIC URETERS BLADDER
HYPOPLASTIC ADRENALS.
HPE:- NON CONTRIBUTORY

Case 10



MALE FETUS OF 24-25 WEEKS GA
MASSIVELY ENLARGED CYSTIC KIDNEYS
SEVERELY HYPOPLASTIC URETERS
KIDNEYS - BILATERAL POLYCYSTIC KIDNEY DISEASE.

Couple was referred for genetic Evaluation Is family history important?

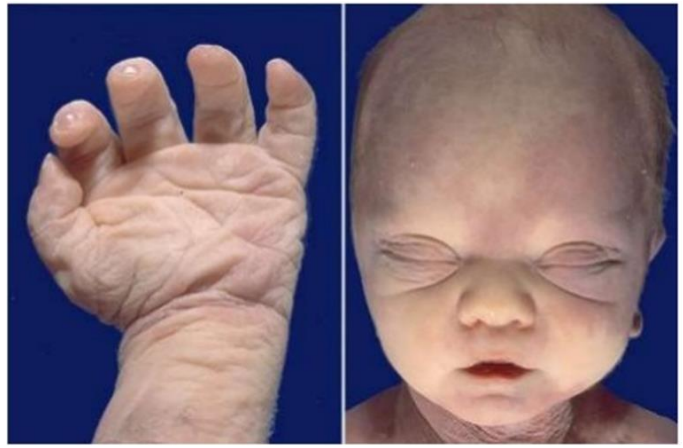
- What are the various monogenic cystic diseases and Inheritance patterns?
- VUS Significance?
- What steps to prevent recurrence in next pregnancy? (Dr.Sankar)

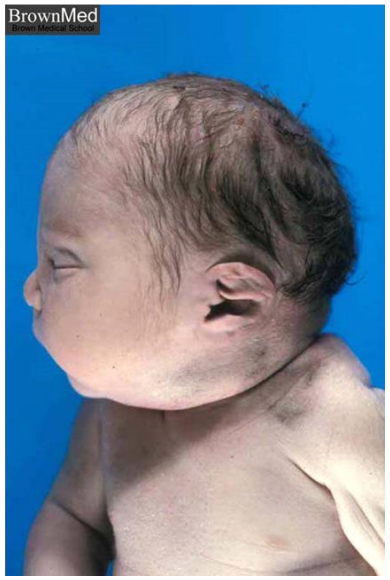
How will you assess baby's with PCKD after delivery ?

Dr. Georgie

Physical Examination with attention to the presence of

- Palpable kidneys
- Palpable bladder
- Deficient abdominal wall
- External Genitalia- Cryptorchidism
- Spine
- Lower limbs –CTEV





Extra renal anomalies

Potters sequence

Abnormal Urinary stream

Postnatal management (Dr.Georgie)

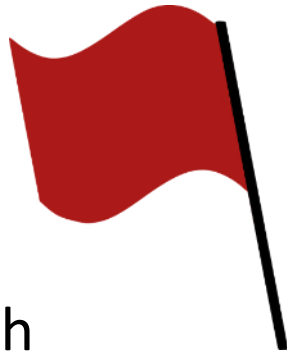
General supportive care in the critical early postnatal period to reduce Renal injury

- Fluid balance
- Infection control
- Minimizing nephrotoxic drugs
- Manage Metabolic issues

Watch out for pulmonary hypoplasia and its consequences (Potters sequence)

Red Flags -high risk of neonatal mortality

Severe Oligohydramnios
Prematurity
LBW
Sepsis
Severe renal dysfunction at birth



What is outcome of ARPKD? Can we intervene?

Depends on the time of presentation of disease. Mortality in Neonatal presentation- 30-40%. No fetal or neonatal intervention improves the ultimate outcome.

Case 11

- 34 weeks of gestation : antenatal scan showed right kidney ‘not visible 'in its normal position; left kidney normal ; amniotic fluid normal
- Post natal scan showed right kidney not visible, left kidney 4.5 cms in length with no hydronephrosis, normal parenchymal echogenicity; rest normal

Does the child require any further evaluation and follow up?

What are the factors to be assessed on follow up?

(Dr. Georgie)

What imaging investigation to confirm diagnosis? Further Evaluation & Follow up ?
Factors to be assessed on follow up. Dr.Georgie

Requires evaluation for a single kidney workup – renal function, proteinuria and hypertension to be closely followed up

DMSA can confirm absent RK if parents are anxious

MCU may show abnormalities in 1/3rd

DMSA: shows good uptake in the right renal fossa, without any scars.

No other uptake in the fields examined

General principles during follow up of MCDK/Single kidney

Dr.Georgie

Watch for compensatory hypertrophy (usually 1.5 to 2 SD of normal size for age) and **parenchymal integrity**

Monitor for markers of renal injury – *Proteinuria , blood pressure , eGFR (Schwartz formula)*

24 hour Ambulatory blood pressure monitoring is useful

Prevent UTI/ Treat UTI promptly

Avoid nephrotoxic medications

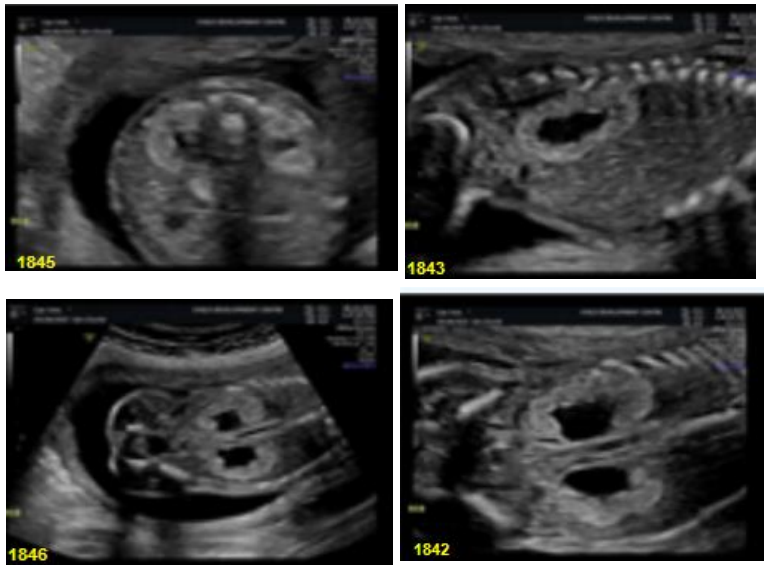
Good bladder/bowel habits

Maintain hydration and electrolytes; growth ; prevent obesity ? Contact sports

Case 12:
31-Year Primi second trimester fetal Scan

KUB
Bilateral Echogenic kidneys
Left kidney:
Shape - Normal
Size : Renal lenght 25.9mm (Normal)
Pelvicalyceal dilatation present
Renal pelvis measured - 10.7mm
Poor Corticomedullary differentiation
Renal artery was imaged in colour Doppler
No ureteric dilatation
Right kidney:
Shape - Normal
Size : Renal lenght 23.8mm (Normal)
Pelvicalyceal dilatation present
Renal pelvis measured - 8.5mm
Poor Corticomedullary differentiation
Renal artery was imaged in colour Doppler
No ureteric dilatation
Normal sized bladder with filling and emptying observed

Extremities
All three segments of both upper and lower limbs seen



Placenta - Anterior
Liquor and activity- Normal
Growth - Normal

Doppler:
Mean uterine artery PI - 0.62 (3%tile)
Umbilical A PI - 1.15 (45%tile)

- Intracranial structures appeared normal

- Bilateral Echogenic kidneys
- Urinary tract dialation disorder (UTD A2-3)
- Normal Bladder and Liquor

How to Counsel the family?

Prognosis? Further work up ?

Dr. Pio James

Impression
Single gestation corresponding to a gestational age of 21 Weeks 3 Days
Gestational age assigned as per LMP

Counselling:

Todays scan findings were explained to the couple in detailed. There is bilateral echogenic kidneys with bilateral moderate renal pelviectasis. The kidney size, bladdder and liquor appeared normal for the period of gestation. Etiology could be a normal variant or associated with chromosomal or genetic etiology. We suggest genetic testing and follow up reassessment every 4 weeks for bladder, liquor and kidneys and for evolving anomalies. We may not be able to predict the long term renal function.

Suggest:

1. Chromosomal microarray + DNA store
2. In the unfortunate event of fetal/perinatal demise, we would suggest that the fetus and placenta can be sent in 10% formalin (9 parts of tap water and 1 part of formalin) for detailed autopsy and HPE. This will help us in confirming the diagnosis as well as to rule out other anomalies that may not be evident on ultrasound. Information thus gained would help them prior to their subsequent pregnancies.
3. Reassessment after 2 weeks

Bilateral echogenic kidneys---- Further Evaluation

Dr. Sankar –Please discuss

Note - Maternal Cell Contamination test result: 'Negative'.

*** OMIM Gene List:**

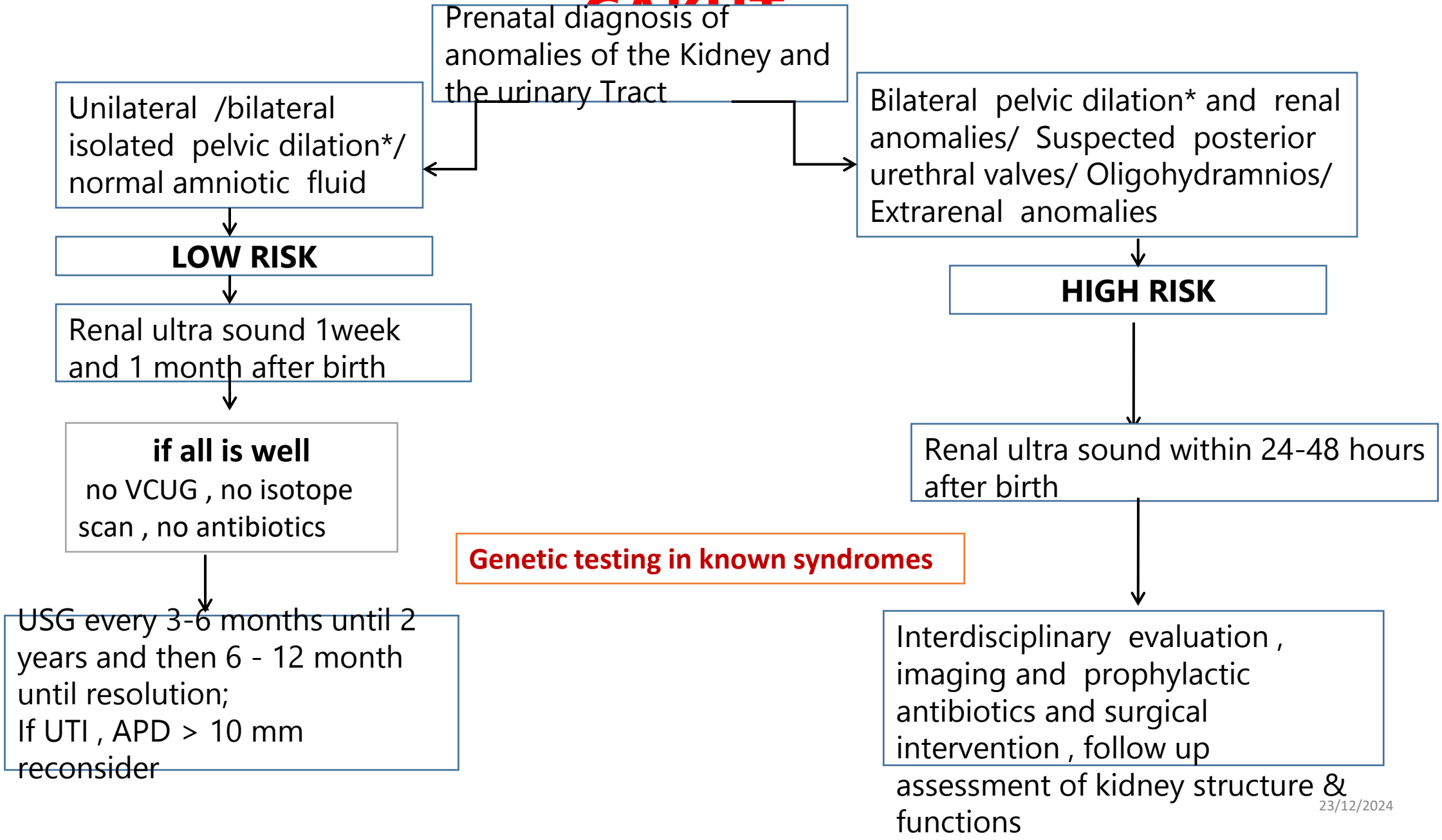
Molecular Karyotype	CN State	Type	Size (Kb)	Primary Genes (OMIM)
17q12(36327837_38072742)x1	1.0	CN Loss	1744906	*TBC1D3G, TBC1D3H, TBC1D3F, ZNHIT3, MYO19, PIGW, GGNBP2, DHRS11, MRM1, LHX1, AATF, ACACA, TADA2A, DUSP14, SYNRG, DDX52,* ***HNF1B****, TBC1D3D, TBC1D3C*

Test result of most common anomalies

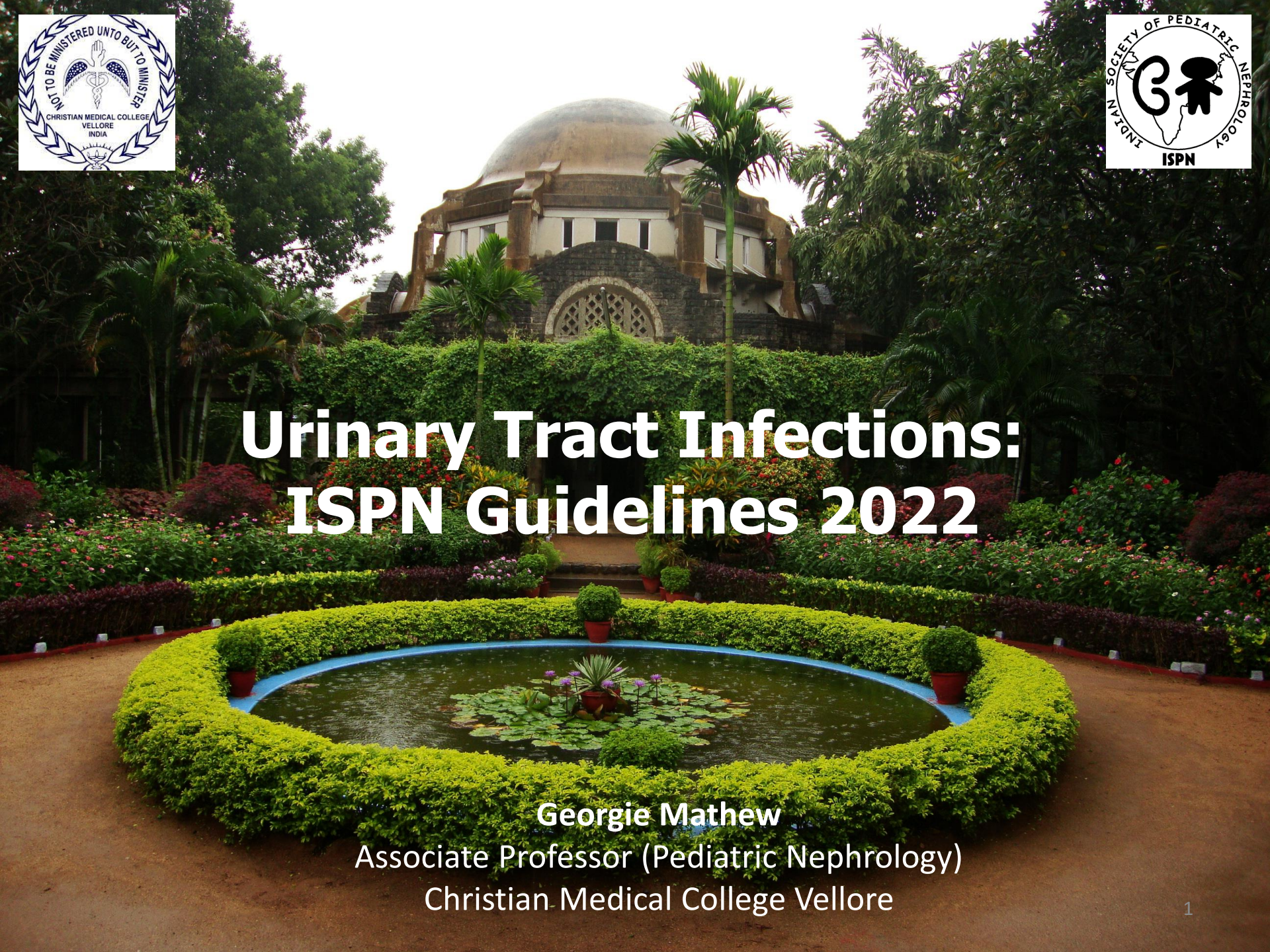
CONTENTS	RESULT
Autosomal Aneuploidies	
Trisomy 21 (Down syndrome)	Negative
Trisomy 18 (Edwards syndrome)	Negative
Trisomy 13 (Patau syndrome)	Negative
Other autosomal aneuploidies	Negative
Sex Chromosome Aneuploidies	
Monosomy X (Turner syndrome)	Negative

Final Decision : Terminated the pregnancy after medical board

Risk Stratification and evaluation in Fetal CAKUT



Thank You



Urinary Tract Infections: ISPN Guidelines 2022

Georgie Mathew
Associate Professor (Pediatric Nephrology)
Christian Medical College Vellore

Overview

Diagnosis & therapy of UTI

Imaging after UTI

Recurrent UTI, bladder bowel dysfunction

Vesicoureteric reflux

Antibiotics prophylaxis

Other interventions

Guideline Development Process: 2020-22

Appoint Work Groups, Evidence Review Team (ERT)

- Discuss process, methods
- Refine topics/questions

Assign topics to systematic review or narrative review

- Performed new or updated existing reviews
- Adapted IOM systematic review standards

Create evidence profile

GRADE (Grading of Recommendations, Assessment, Development and Evaluations)

- Rate **quality of evidence** for each outcome and its **'certainty'**
- **Generate recommendations**

Apply AGREE (Appraisal of Guidelines, Research and Evaluation) checklist

Recommendations vs. Clinical practice points

Recommendations

- Systematic review conducted
- Ample evidence available
- Evidence shows clear preference of one action over other
- Guidance is actionable
- Statements supported with
  - Quality of evidence
  - Balance of benefit and harm
  - Values & preferences
  - Feasibility, equity, acceptability
  - Resource

Clinical practice points

- No systematic review conducted
- Insufficient evidence
- Evidence inconclusive
- Guidance as table/figures/algorithm

Adapted from KDIGO 2020

Workgroups

Group coordinators

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Madhuri Kanitkar
Arpana Iyengar
Manish Kumar
Sudha Ekambaram
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Kumud Mehta
Kishore Phadke
Uma Ali

Symptoms of UTI

7% of girls and 2% of boys (more, if uncircumcised) develop at least one UTI by 7 years of age

Vary by age

<2 months: Non-specific

Sepsis, vomiting, lethargy, poor feeding, jaundice

2–24 months

Fever (>100.4°C) without a focus: 5% due to UTI

>2 year old: Symptoms referable to urinary tract

Urinary frequency, urgency, hesitancy

Dysuria

Suprapubic, abdominal or flank pain or tenderness

Dirty urine, malodorous urine

RIVUR trial 2008, NICE guidelines 2018

When to suspect a UTI?

Young child with unexplained fever for >3 days

Symptoms referable to urinary tract

<2-months-old with irritability, lethargy, poor feeding

Not if..

Fever with localizing symptoms: coryza, diarrhea

Non-specific abdominal pain

Older child with failure to thrive

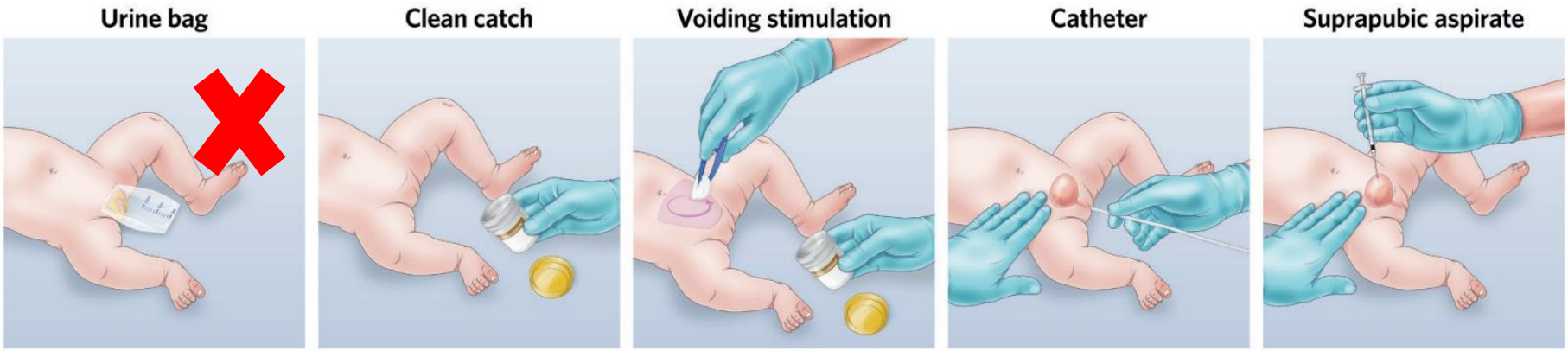
Nocturnal enuresis

Nephrotic syndrome

Chronic kidney disease

Method of urine collection

Precontinent children



"Quick wee" technique

Clinical practice point

If toilet-trained: **Suggest** using clean-catch specimen

Not-toiled trained, stable child: Attempt clean-catch initially

If unsuccessful, catheterize or take suprapubic aspirate (SPA)

Not-toiled trained, sick infant: Prefer catheterization or SPA

Urine can be stored at 4°C for up to 24-hr

Role of Screening tests

TEST	SENSITIVITY, %	SPECIFICITY, %
Leukocyte esterase positive	83	78
Nitrite test positive	53	98
Leukocyte esterase/ Nitrite positive	**93**	72
Microscopy, WBC	73	81
Microscopy, Bacteria	81	83
LE, Nitrite, Microscopy positive	**99.8**	70

AAP Clinical Practice Guidelines, Pediatrics 2016

Microscopy for bacteria and Gram stain has excellent accuracy
Leukocyte esterase can replace microscopy for WBC
Dipstick may be negative in 10%; cannot replace urine culture

Williams, Lancet 2010

Recommendation

Suggest using urine dipstick (leukocyte esterase + nitrite combination) as a screening test

Wherever feasible, urine microscopy (for bacteriuria and pyuria, in a freshly voided sample), should be used to screen for UTI (2⊕⊕⊕◯)

Diagnosis of UTI

Recommendations

Suggest basing diagnosis of UTI on the significant growth of a single bacterial species in presence of symptoms

UTI is **suggested** by the growth of single uropathogenic bacteria $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4-5}$ (CFU/ml) by suprapubic aspiration, catheterization, and clean-catch, respectively

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Asymptomatic bacteriuria

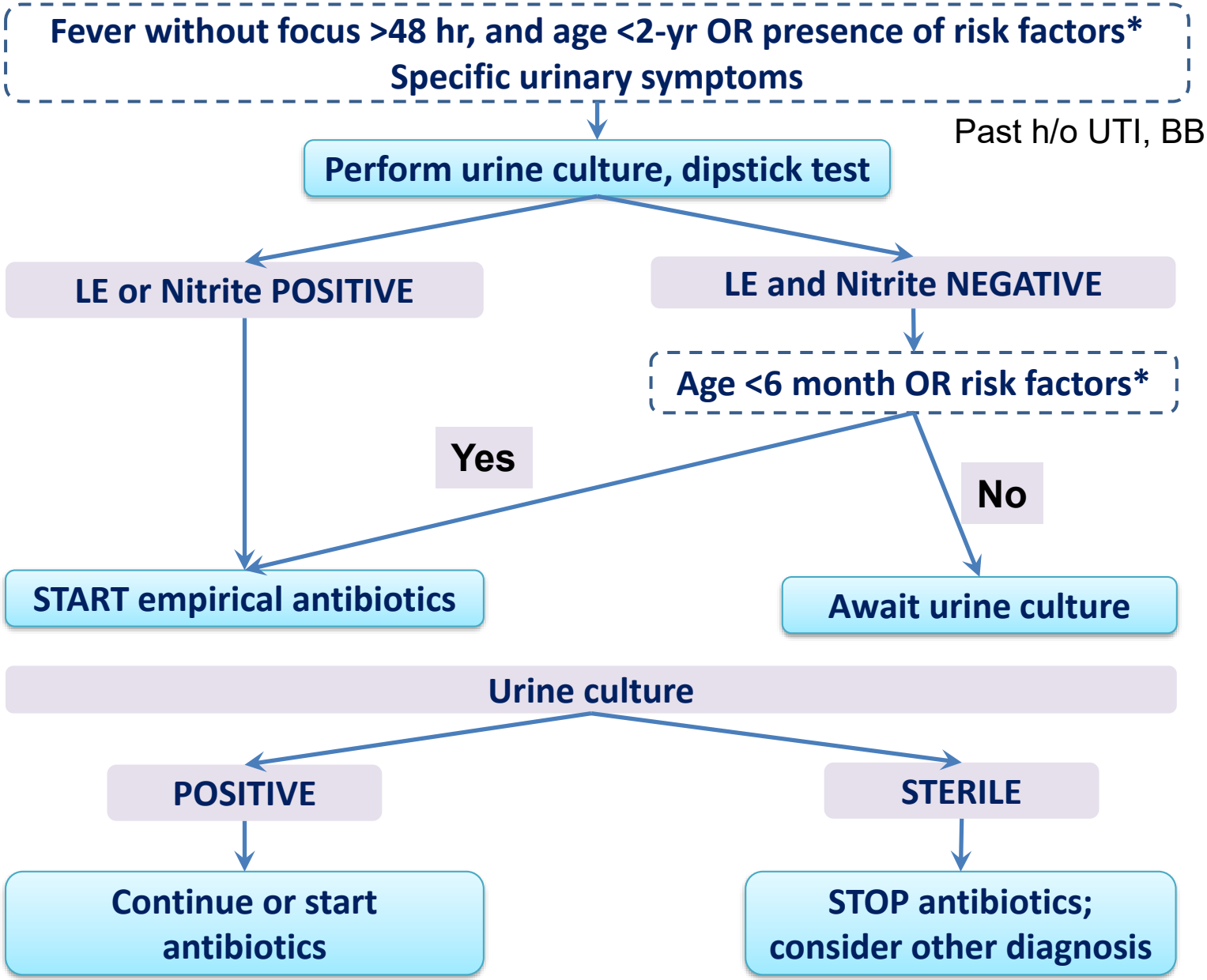
Clinical practice point

Suggest NOT to perform routine culture or repeat urine culture after treatment if there is clinical response

Suggest NOT to treat asymptomatic bacteriuria

Approach to diagnosis of UTI

2022



Treatment of UTI

2022

Recommendations

Recommend using oral antibiotics for acute pyelonephritis, EXCEPT in:

- Infants aged <1 month
- Children with bacteremia/sepsis
- Children unable to ingest (1⊕⊕⊕◯)

Suggest IV antibiotic for initial 3-4 days or until defervescence, followed by oral antibiotic therapy

Suggest using 3rd generation cephalosporins or amoxicillin-clavulanic acid as empirical antibiotic in febrile UTI (2⊕◯◯◯)

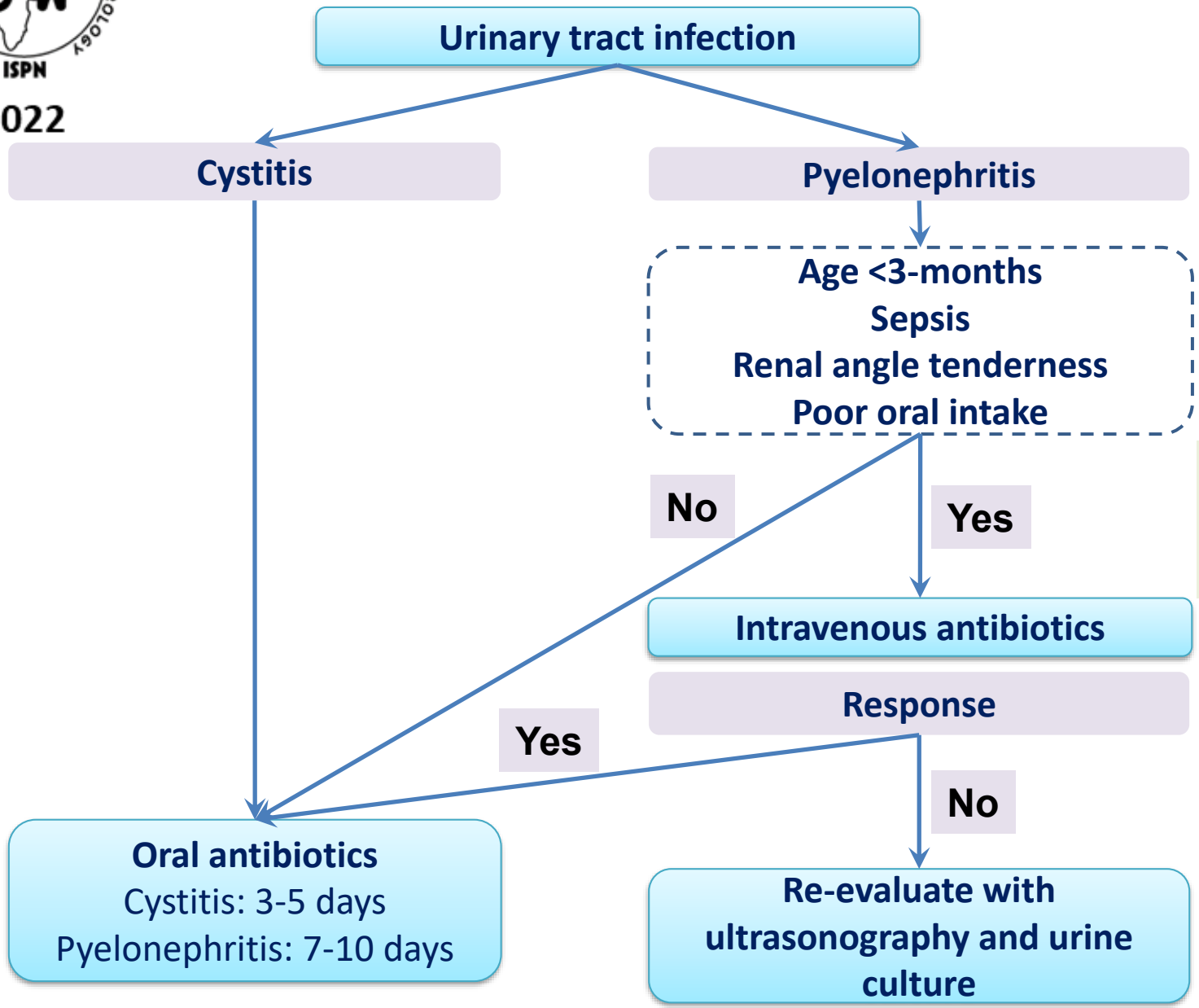
Suggest short course (3-5 days) of oral antibiotic for lower UTI (1⊕⊕⊕◯)

Clinical practice points

Suggest initial intravenous antibiotic to treat acute pyelonephritis in children aged 1-3 month

Suggest 7-10 days of antibiotic treatment for acute pyelonephritis in children aged >6 months

Approach to management of UTI



Common mistakes !

Diagnosing UTI

- ✘ On leukocyturia alone
- ✘ In asymptomatic patient
- ✘ With low colony counts
- ✘ With mixed growth on culture

- ✘ Performing urine culture after stopping treatment
- ✘ Not evaluating for bladder–bowel dysfunction

BBD & Recurrent UTI

Bladder bowel dysfunction (BBD): combined bladder and bowel dysfunction in the absence of neurological abnormality.

Int Children Continence Soc 2017

Bladder	Bowel
Urgency Wetting of pants Holding maneuvers **Hesitancy** **Frequency**	**Constipation** <3 stools/wk Hard stools blocking toilet Painful defecation

Independent predictor of UTI; delays resolution of VUR; therapy results in downgrading of VUR

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Clinical practice point

Suggest all children with UTI should be evaluated for BBD

Suggest antibiotic prophylaxis be given to all children with recurrent febrile UTI and BBD, irrespective of the grade of VUR

Ultrasongraphy after UTI

ISPN 2022

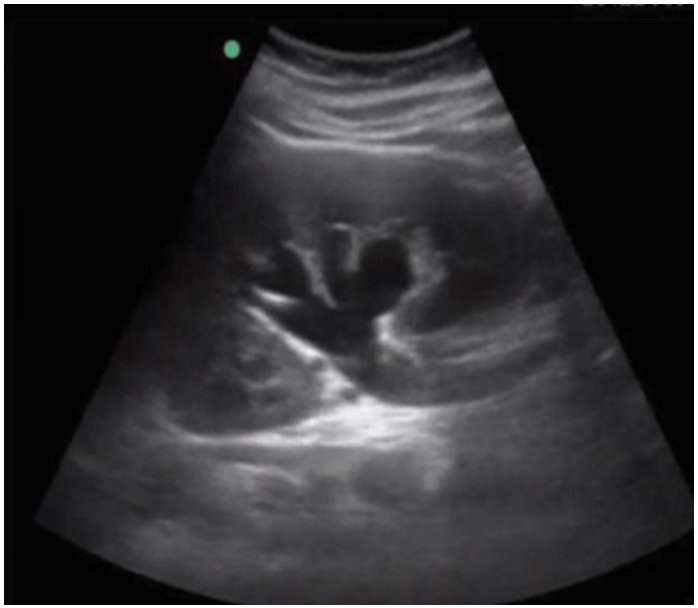
Clinical practice point

Perform ultrasonography of the urinary tract in all children *after* an episode of UTI

Repeat after 4-6 weeks, or **perform during UTI** if urosepsis, non-response, renal dysfunction

Findings that suggest VUR

- Renal hypoplasia
- Abnormal echogenicity
- Hydronephrosis
- Ureteric dilatation
- Uroepithelial thickening
- Bladder abnormality



Dimercaptosuccinic acid (DMSA) scan

Early DMSA (within 2-weeks of UTI)

Abnormal in presence of pyelonephritis

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Recommendation

Do not perform acute-phase DMSA scan in children with febrile UTI (2⊕◯◯◯)

Late DMSA (4-6 months after UTI)

More relevant, since it detects damage!

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Clinical practice point

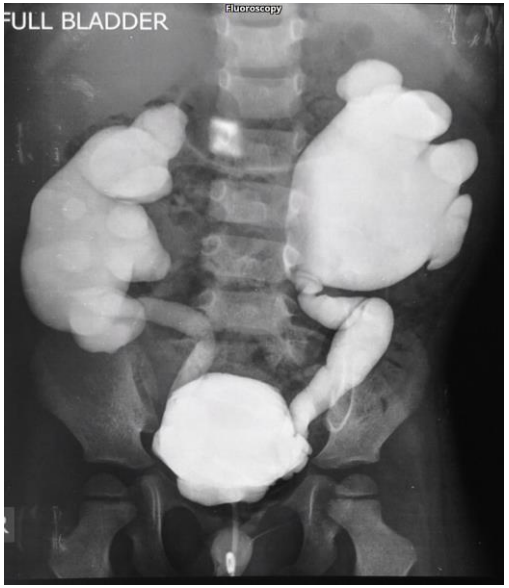
Suggest performing a late-phase DMSA scan to assess kidney scarring in children with recurrent UTI or high-grade VUR

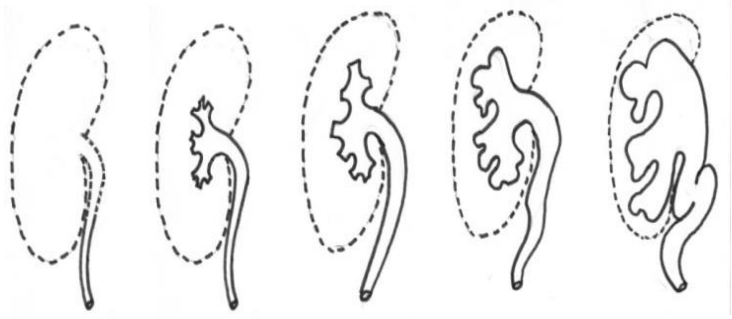
Micturating cystourethrography

Gold standard for diagnosis of VUR

Provides clear anatomy of urinary tract

Invasive; risks of infection; radiation exposure





Grade I Grade II Grade III Grade IV Grade V

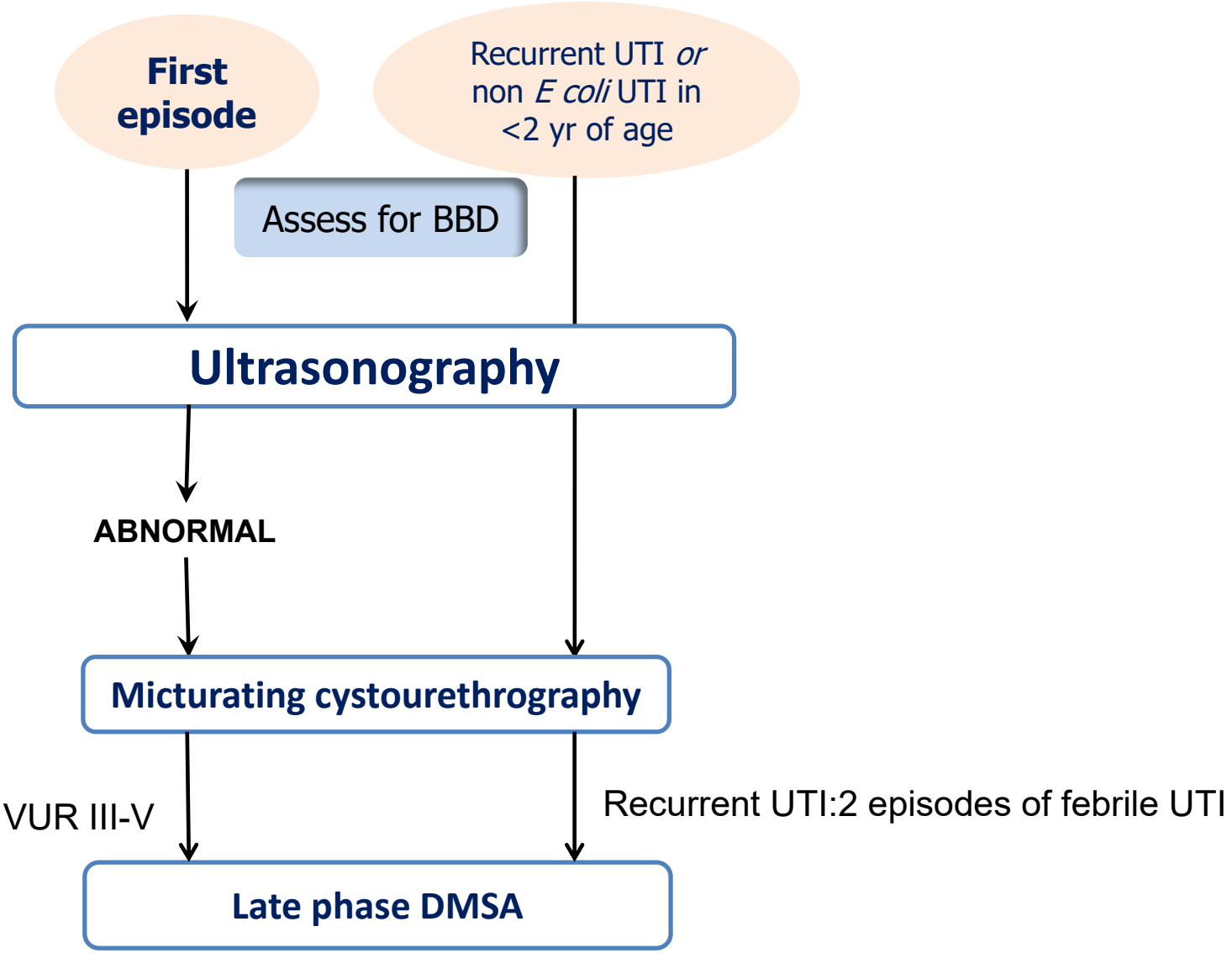
Clinical practice point

Suggest performing MCU in children with one of the following:
(a) children <2 yr with non-E.coli UTI

(b) abnormal ultrasound scan

(c) Recurrent UTI

Approach to imaging after UTI



BBD bladder bowel dysfunction

Antibiotic Prophylaxis

Normal urinary tract

Recommendation

Recommend against using prophylaxis for prevention of UTI in children with normal urinary tract (1⊕⊕⊕◯)

Vesicoureteric reflux

Considerations

Prophylaxis in high grade VUR is marginally beneficial

Renal scarring not prevented by prophylaxis in VUR

Odds of multidrug resistance 6 times more on prophylaxis

Antibiotic Prophylaxis in high grade VUR

Recommendation

Suggest prophylaxis for prevention of febrile UTI only in children with high-grade VUR (2⊕⊕◯◯)

Suggest using co-trimoxazole or nitrofurantoin as first-line antibiotic for prophylaxis in >6 months of age (2⊕⊕◯◯)

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2022

Clinical practice points

Consider using prophylaxis in low-grade VUR in infants & recurrent febrile UTI

Suggest discontinuation of prophylaxis in older than 2 years if:

(i) toilet trained, (ii) no BBD, and (iii) no febrile UTI in the last 1-yr

Management of VUR

Recommendations

Suggest antibiotic prophylaxis as the first line of management in patients with high grade VUR (2⊕⊕⊕◯)

Suggest surgical reimplantation be considered in patients with high grade VUR and recurrent febrile UTI while on prophylaxis (2⊕⊕⊕◯)

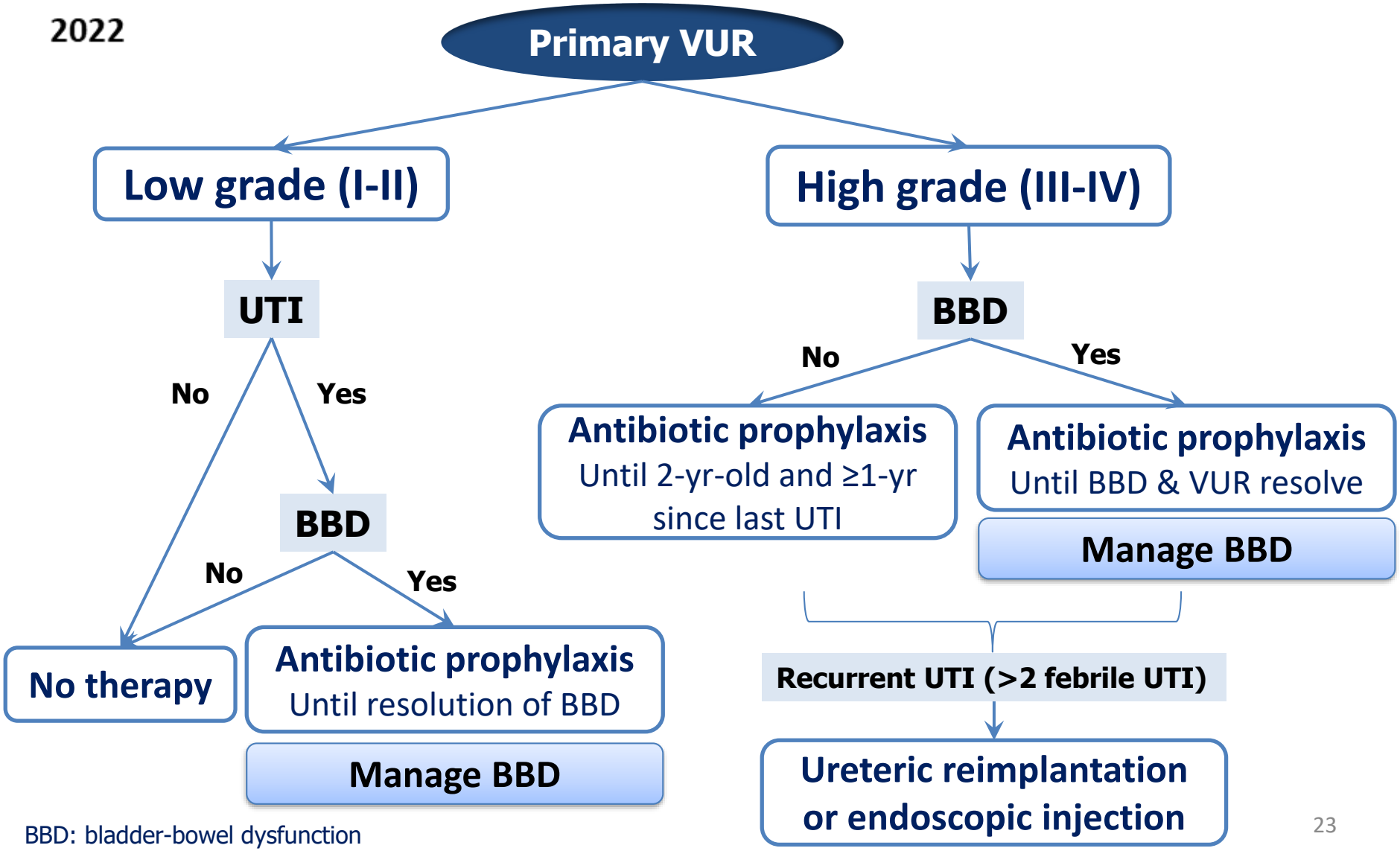
Clinical practice points

Suggest open reimplantation be preferred over endoscopic treatment

Suggest surgical intervention as an alternative for high grade VUR, beyond first year of life, if so preferred by parents

No consensus on the type of surgery (open/robotic/laproscopic)

Approach to management of VUR



BBD: bladder-bowel dysfunction

Prevention of UTI

Cranberry

Large pro-anthocyanidin polymer that inhibits bacterial adherence

No better than antibiotic prophylaxis in preventing UTI

Large quantity of active ingredient required (36-72 g/day)

Non-uniform availability

ISPN 2022

Recommendation

Suggest using cranberry products to prevent UTI in children with recurrent UTI and normal urinary tract (2⊕⊕◯◯)

Circumcision

ISPN 2022

Recommendation

Suggest circumcision be offered to prevent UTI in boys at risk of recurrence (2⊕⊕⊕◯)

Key Points

Evidence-based guidelines with methodological rigor

Most infections can be treated using oral antibiotics

Imaging evaluation following UTI is more selective, less aggressive

High emphasis on BBD, which is associated with recurrence

Antibiotic prophylaxis is recommended for patients with recurrent UTI, BBD, high grades of VUR

Antibiotic prophylaxis is as good as surgery for VUR

Concern of antimicrobial resistance with use of prophylaxis

Indications for surgery are limited

Acknowledgments

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Evolving Trends in Pediatric Kidney Care

Prasad Devarajan MD FAAP FASN
Director of Nephrology and Hypertension
Cincinnati Children's Hospital Medical Center
SAT ISN SCR Update, 2024

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Few Evolving Trends in Pediatric Kidney Care

- Omics: Genomics, Proteomics, Big Data, Bioinformatics
- Increasing use of Genetics in pediatric kidney care
- Increasing use of Electronic Health Records
- Personalized, Predictive, and Targeted approaches
- Artificial Bioengineered Kidneys
- Expectation for value: decrease cost and increase quality
- Expectation for optimal patient and family satisfaction
- **Artificial Intelligence to support all aspects of kidney care**

Definition of Artificial Intelligence (AI)

- *The science and engineering of making intelligent machines* (John McCarthy, 1956)

- *The theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and language translation* (Oxford Dictionary, 2022)

AI in Medicine

- *Physical AI:* Instrumentation that directly assist in patient care, e.g., robotics in surgery, advanced neural prosthetics, digital pathology, digital radiology

- *Virtual AI:* Computer algorithms derived from machine learning or natural learning processing to analyze large quantities of data (big data) to discover patterns that aid in medical decision-making

Mistry & Koyner, ACKD 2021, 28:74-82

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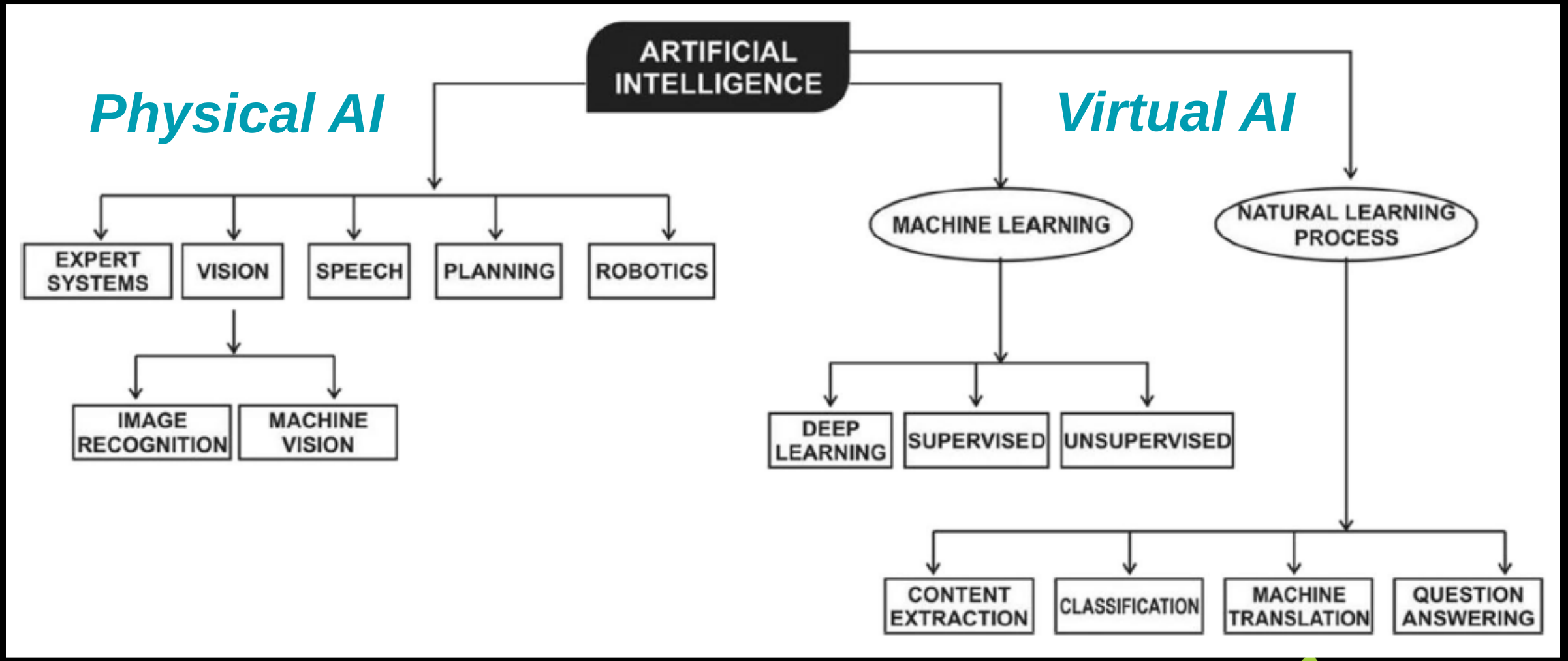
AI in Medicine



Raina R, Pediatr Nephrol 2024, 39:2309-24

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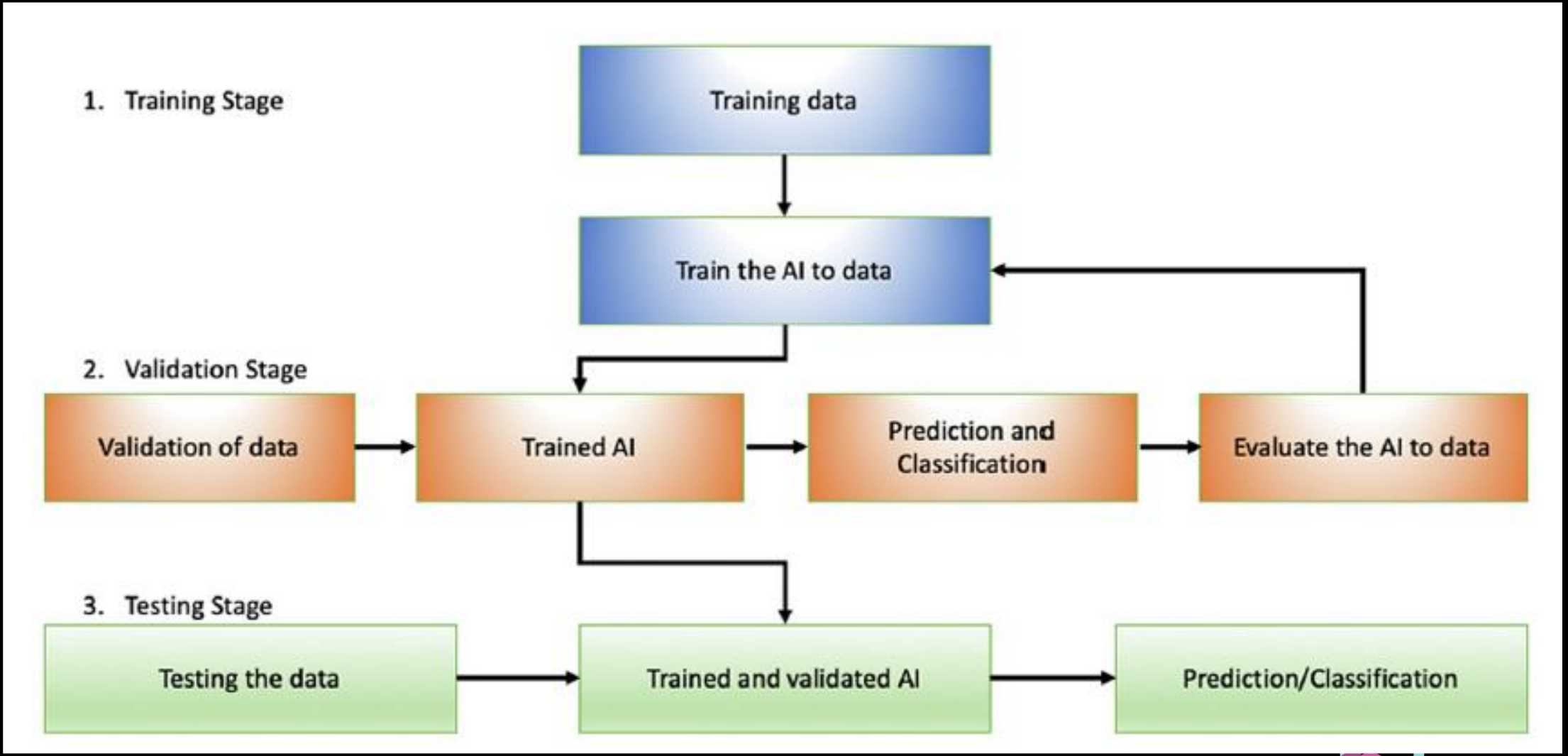
AI Data Training: Three Independent Stages



Filler G, AKDH 2022, 30:17-24

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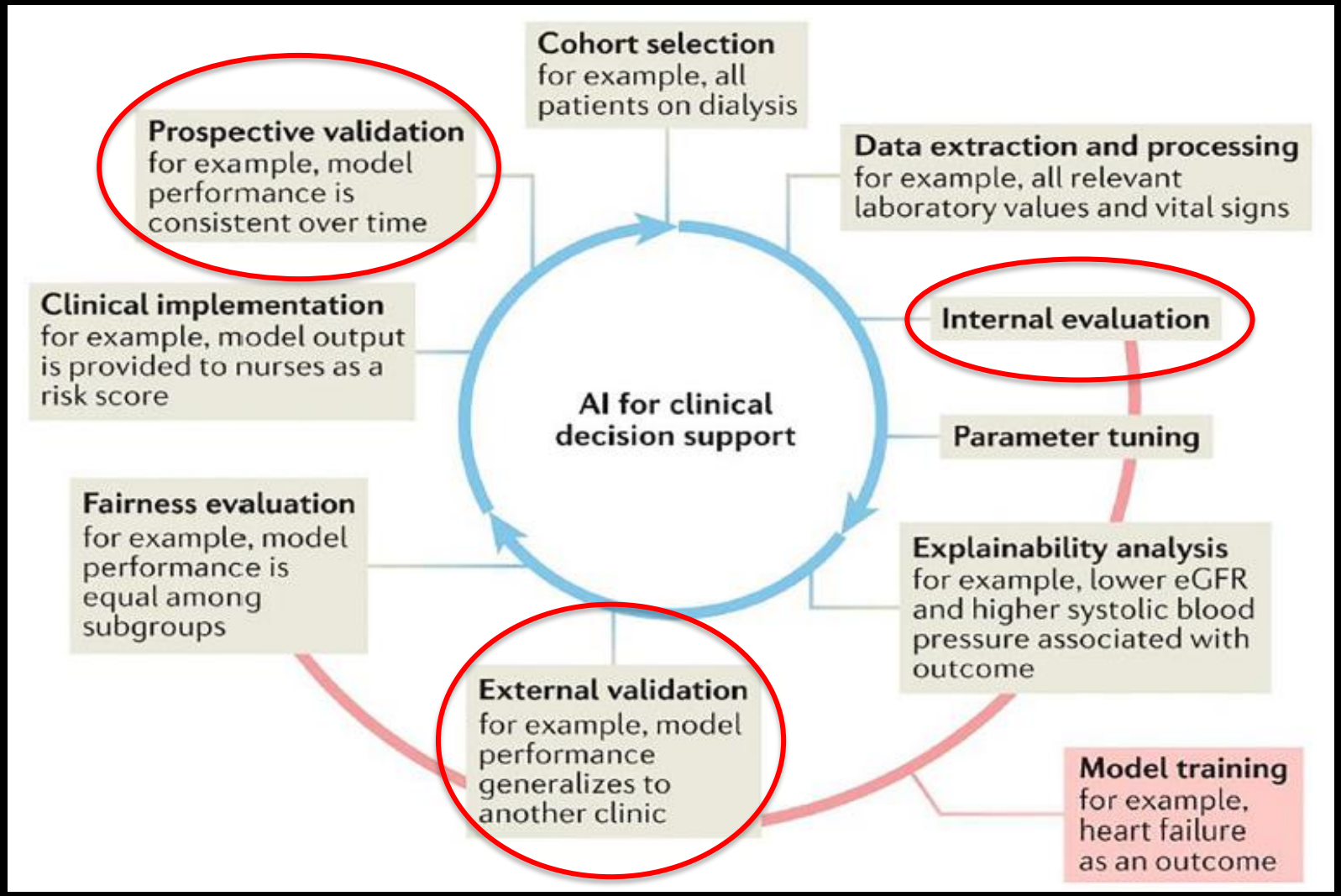
AI Data Training: Three Independent Stages



Loftus TJ, Nat Rev Nephrol 2022, 18:452-65

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Examples of AI in Adult Nephrology: Risk Prediction

Domain	Patient Data	Sample Size	AI Method	Findings	Reference
AKI	Demographics, diagnoses, procedures, test results, orders, vital signs, health factors	703,782 ICU patients	Deep Learning	Predicted 56% of AKI episodes and 90% of AKI requiring dialysis 48 hours in advance (AUC 0.92)	Tomasev et al, Nature 2019; 572:116-119

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CRRT Mortality	Demographics, mechanical ventilation, comorbidities, vital signs, test results	1,571 CRRT patients	Machine Learning	Better at predicting mortality (AUC 0.78) versus SOFA (AUC 0.67) or APACHE (AUC 0.61)	Kang et al, Crit Care 2020; 24:42

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Kidney failure in CKD	Demographics, chronic conditions, diagnoses, procedures, medications, medical costs	550,000 CKD patients	Machine Learning	Accurate prediction of kidney failure within 6 months (AUC 0.93)	Segal et al, BMC Nephrol 2020; 21:12882

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Diabetic Kidney Disease	Tests, profiles, medications, diagnoses, medical examinations, nutrition consultations	64,059 T2DM patients	Deep Learning	Accurate prediction of progression within 6 months (AUC 0.74)	Makino et al, Sci Rep 2019; 9:11862

Examples of AI in Pediatric Nephrology: Risk Prediction

Domain	Patient Data	Sample Size	AI Method	Findings	Reference
AKI in PICU	Test results, medications, vital signs, ventilator status	16,863 PICU patients	Machine Learning	Predicted Stage 2/3 AKI with a lead time of 30 hours (AUC 0.89)	Dong et al, Crit Care 2021; 25:288

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AKI in PICU	Demographics, diagnoses, test results, medications, procedures	1,395 AKI patients	Machine Learning	Predicted Major Adverse Kidney Events: death, dialysis, kidney dysfunction (AUC 0.81 for MAKE30 and 0.85 for MAKE90)	Deng et al, Sci Rep 2022; 12:8956

Examples of AI in Pediatric Nephrology: Risk Prediction

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AKI after surgery	Demographics, vital signs, test results, preop conditions, surgery types	3,386 post-op patients	Deep Learning	Predicted post-operative AKI (AUC 0.91)	Zeng et al, J Am Med Inform 2022; 30:94-102

Examples of AI in Pediatric Nephrology: Risk Prediction

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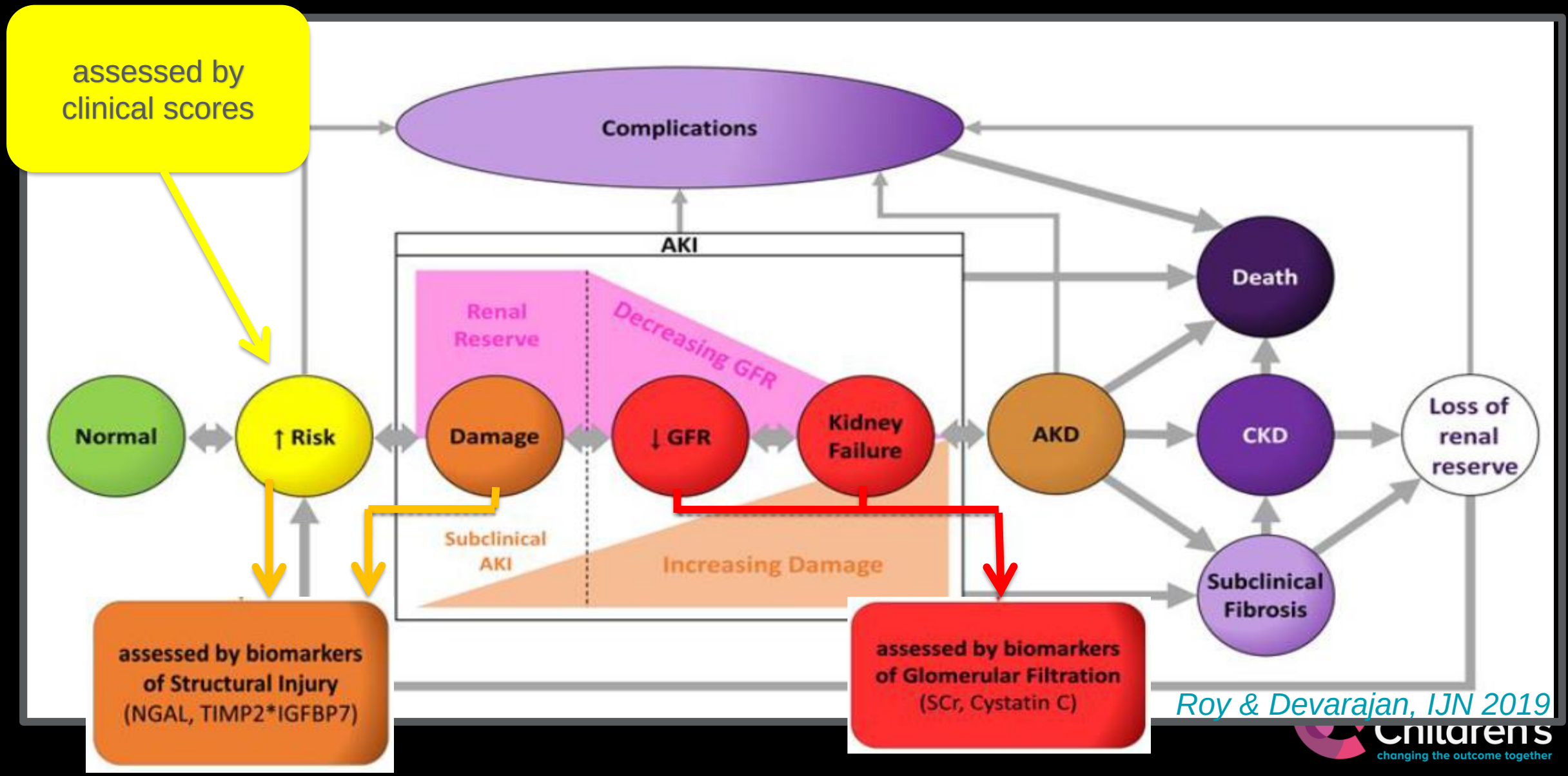
AKI after cardiac surgery	Oxygen delivery, complexity of surgery, medications, inotrope requirement, demographics	396 post-op patients	Machine Learning	Oxygen delivery value of 350 ml/min/m^2, younger age, bypass time, inotrope need showed strong association with AKI	Hayward et al, JTCVS 2023; 165:1505-1516

AI in AKI Risk Prediction: Our Approach



Roy & Devarajan, IJN 2019

AI in AKI Risk Prediction: Our Approach

Hospital Patients at Risk

- **Critically Ill**
  - sepsis, major surgery/trauma, ventilator, hypotension, blood loss, burns
- **Cardiac Surgery**
  - prolonged cardiopulmonary bypass, complex surgery
- **Fluid Overload**
- **Multiple Nephrotoxin Exposure**
  - contrast, antibiotics
- **Transplant**
  - bone marrow & solid organ (including kidney)

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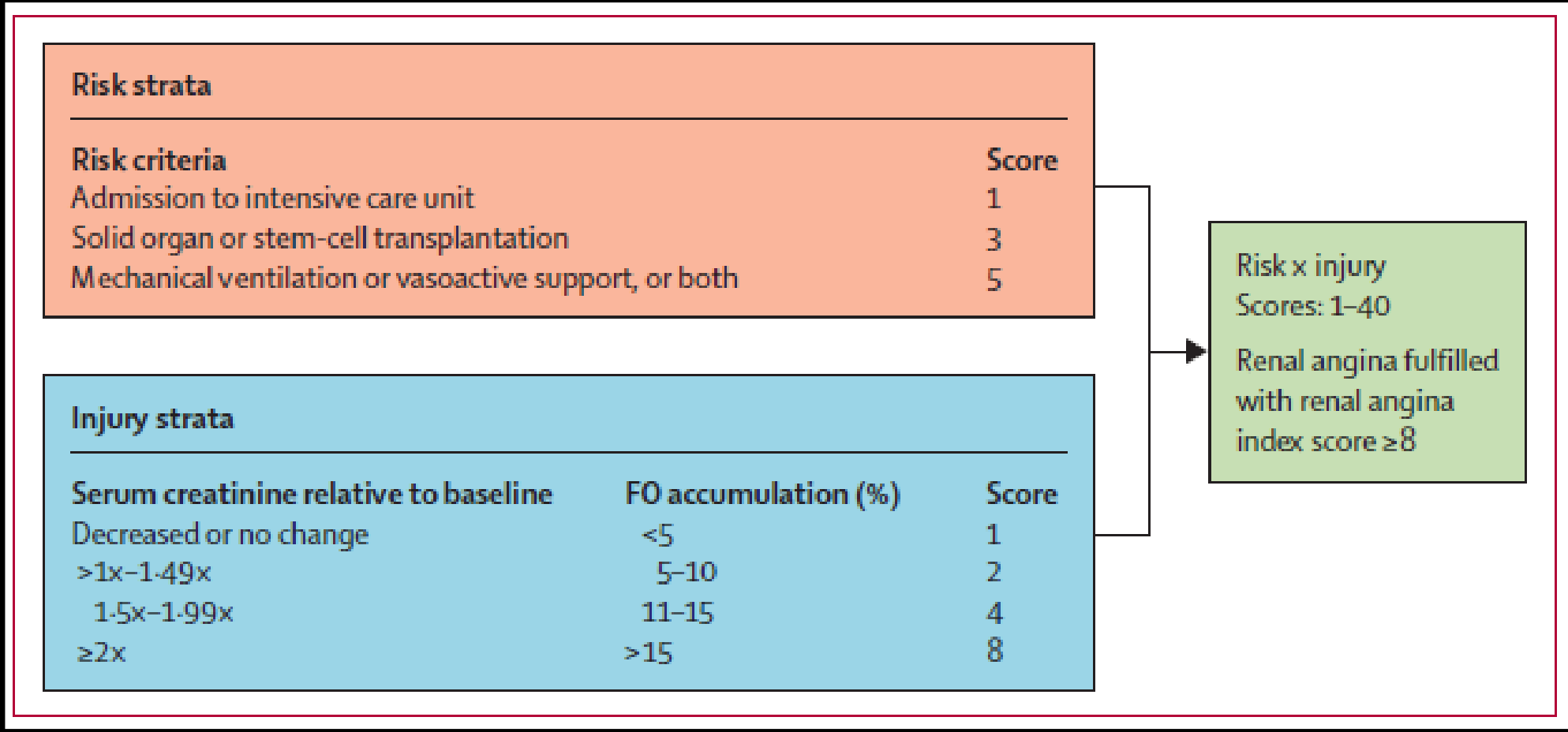
AI-Derived Clinical Scores for AKI in our PICU – Renal Angina Index

Based on clinical settings that are known to cause AKI in your setting that will <u>automatically trigger biomarker measurement</u>



Risk strata

Risk criteria	Score
Admission to intensive care unit	1
Solid organ or stem-cell transplantation	3
Mechanical ventilation or vasoactive support, or both	5

Injury strata

Serum creatinine relative to baseline	FO accumulation (%)	Score
Decreased or no change	<5	1
>1x–1·49x	5–10	2
1·5x–1·99x	11–15	4
≥2x	>15	8

Risk x injury
Scores: 1–40

Renal angina fulfilled with renal angina index score ≥8

Incorporating Biomarkers Into Renal Angina Index

Nephrol Dial Transplant (2016) 31: 586–594
doi: 10.1093/ndt/gfv457
Advance Access publication 2 February 2016

ndt
Nephrology Dialysis Transplantation

Original Article

Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: a prospective cohort study

Shina Menon[1], Stuart L. Goldstein[1], Theresa Mottes[1], Lin Fei[2,3], Ahmad Kaddourah[1], Tara Terrell[1], Patricia Arnold[1], Michael R. Bennett[1] and Rajit K. Basu[1,4]

Incorporating NGAL Into Renal Angina Index

Terms	Sensitivity	Specificity	AUC-ROC (95% CI)
Day_0 RAI	80 (52–97)	72 (64–78)	0.80 (0.58, 1.00)
Day_0 RAI+ NGAL	86 (42–99)	85 (77–90)	0.97 (0.93, 1.00)
Day_0 RAI+ KIM-1	43 (10–82)	95 (90–98)	0.77 (0.53, 1.00)
Day_0 RAI+ L-FABP[c]	86 (57–98)	56 (58–64)	0.82 (0.69, 0.95)
Day_0 RAI+ IL-18[c]	57 (29–82)	97 (92–99)	0.79 (0.65, 0.92)

Menon et al, NDT 2016; 31:586

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How We Routinely Use NGAL in AI-Derived RAI+ patients

NGAL Result	Action
Normal	Kidney damage is ruled out. Continue routine clinical care. Safely use fluids, diuretics, and potentially nephrotoxic interventions

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Slightly Elevated	Be vigilant for kidney damage; repeat NGAL testing in 24 hours.

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Moderately Elevated *or* Trending Up	Predicts current or future kidney damage. Follow NGAL levels, initiate KDIGO bundle, adjust fluid therapy, adjust potential nephrotoxic interventions, early Nephrology consult.

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Severely Elevated *or* Rapidly Trending	Predicts severe kidney damage. Follow NGAL levels, stop nephrotoxic medications and contrast agents. Initiate Nephrology consult and early consideration for kidney replacement therapy.

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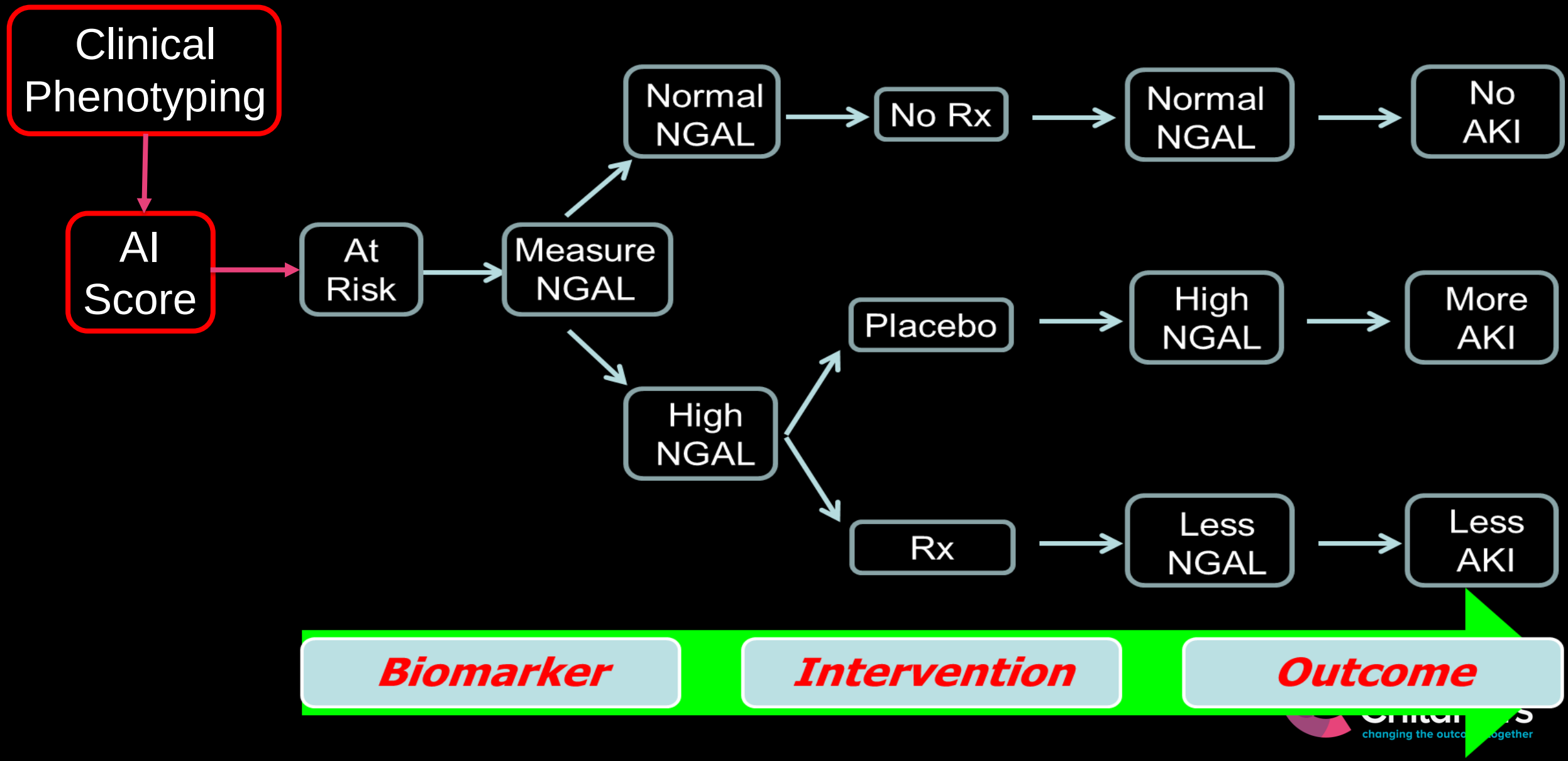
Severely Elevated *or* Rapidly Trending	Predicts severe kidney damage. Follow NGAL levels, stop nephrotoxic medications and contrast agents. Initiate Nephrology consult and early consideration for kidney replacement therapy.
NGAL level is Trending Down	Predicts recovery from kidney damage. Stop dialysis. Stop other kidney support medications. Follow NGAL levels. Allow the kidneys to recover.

How We Routinely Use AKI Biomarkers



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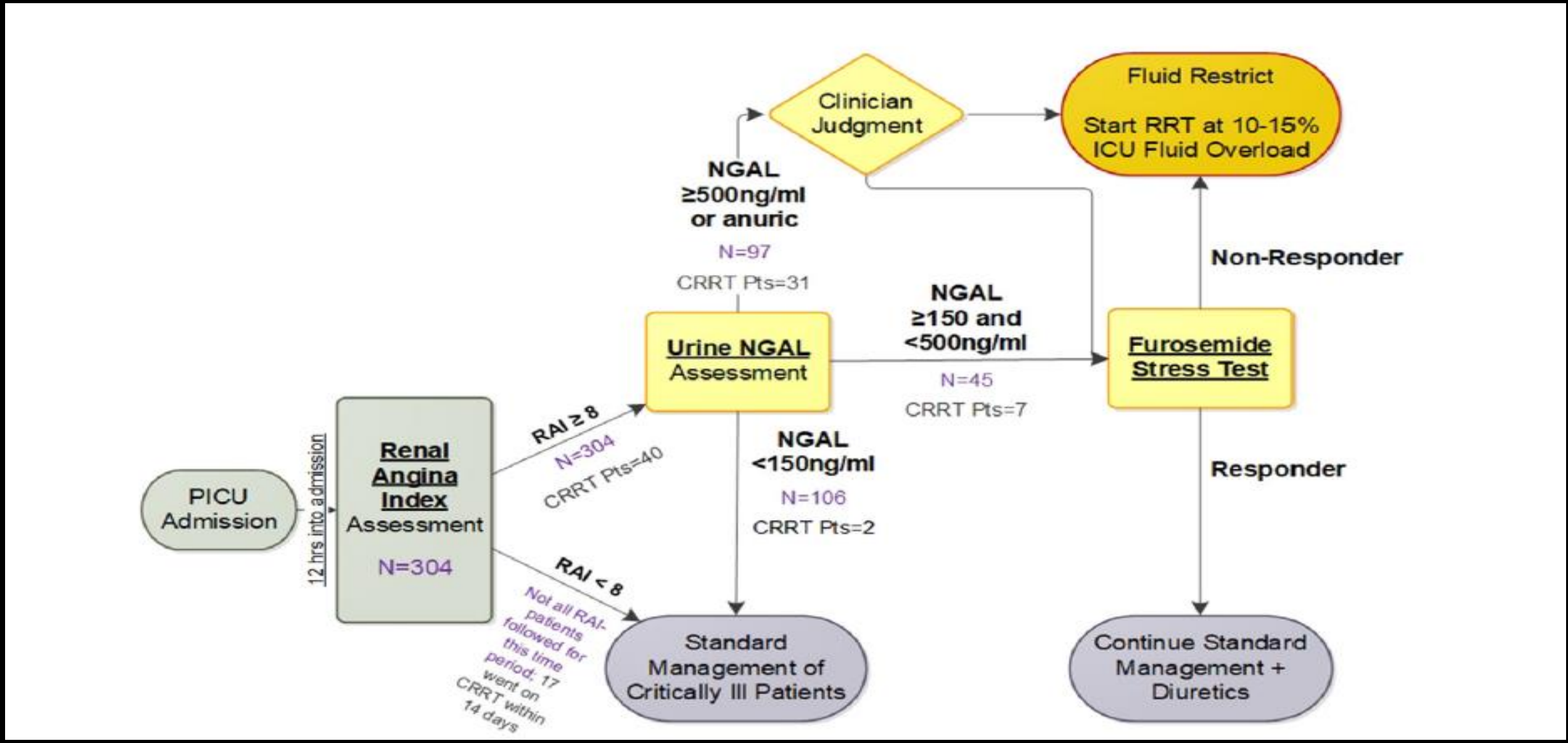


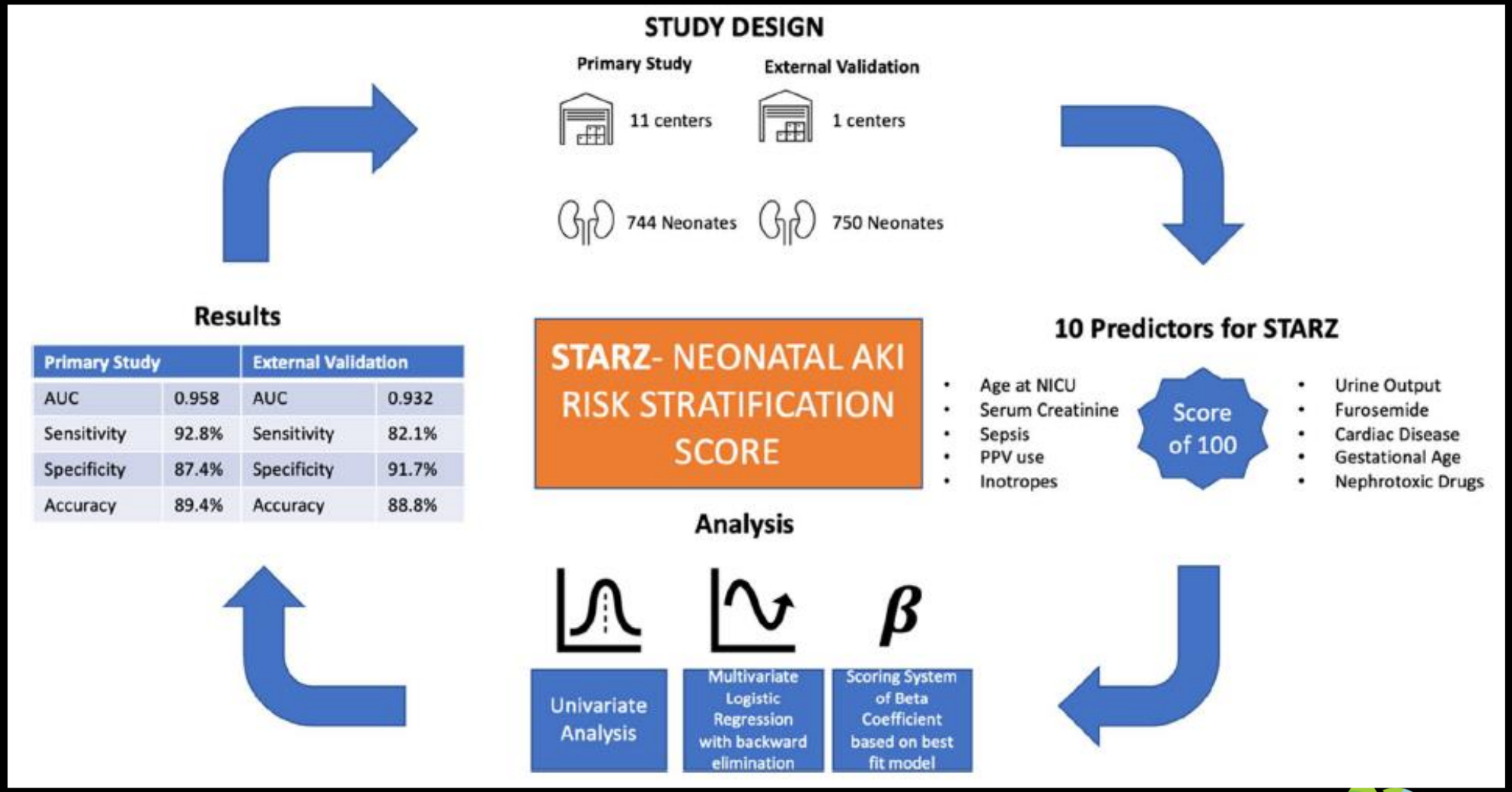
Kidney Int Rep (2023) ■, ■–■; https://doi.org/10.1016/j.ekir.2023.09.019

Table 2. Compairsons between the pre-TF2 and TF2 cohorts

All patients who received CRRT ($N = 178$)				
Variable		**Pre-TF2 ($n = 71$)**	**Post-TF2 ($n = 107$)**	***P*-value**
Pre-CRRT patient demographics and fluid status				
Patient age (yrs)	Median [IQR]	8.1 [2.0, 15.1]	10.3 [2.3, 17.0]	0.37
Patient PICU admission weight (kg)	Median [IQR]	26.5 [13.3, 49.0]	30.7 [13.2, 59.0]	0.21
CRRT duration among CRRT survivors (d)	Median [IQR]	5.8 [2.9, 12.2]	4.0 [1.9, 9.7]	0.06
		Pre-TF2 ($n = 33$)	Post-TF2 ($n = 70$)	
PICU LOS after CRRT D/C among PICU survivors (d)	Median [IQR]	8.6 [4.5, 13]	2.6 [0.7, 8.6]	0.002
Total PICU length of stay among PICU survivors (d)	Median [IQR]	24 [12, 39]	13 [6, 26]	0.02
Patients who received CRRT within 14 days of PICU admission ($N = 151$)				

Estimate $12,500 hospital cost savings per CRRT patient

AI in Neonatal AKI: Score Derivation



Raina R, Pediatr Nephrol 2024, 39:2309-24

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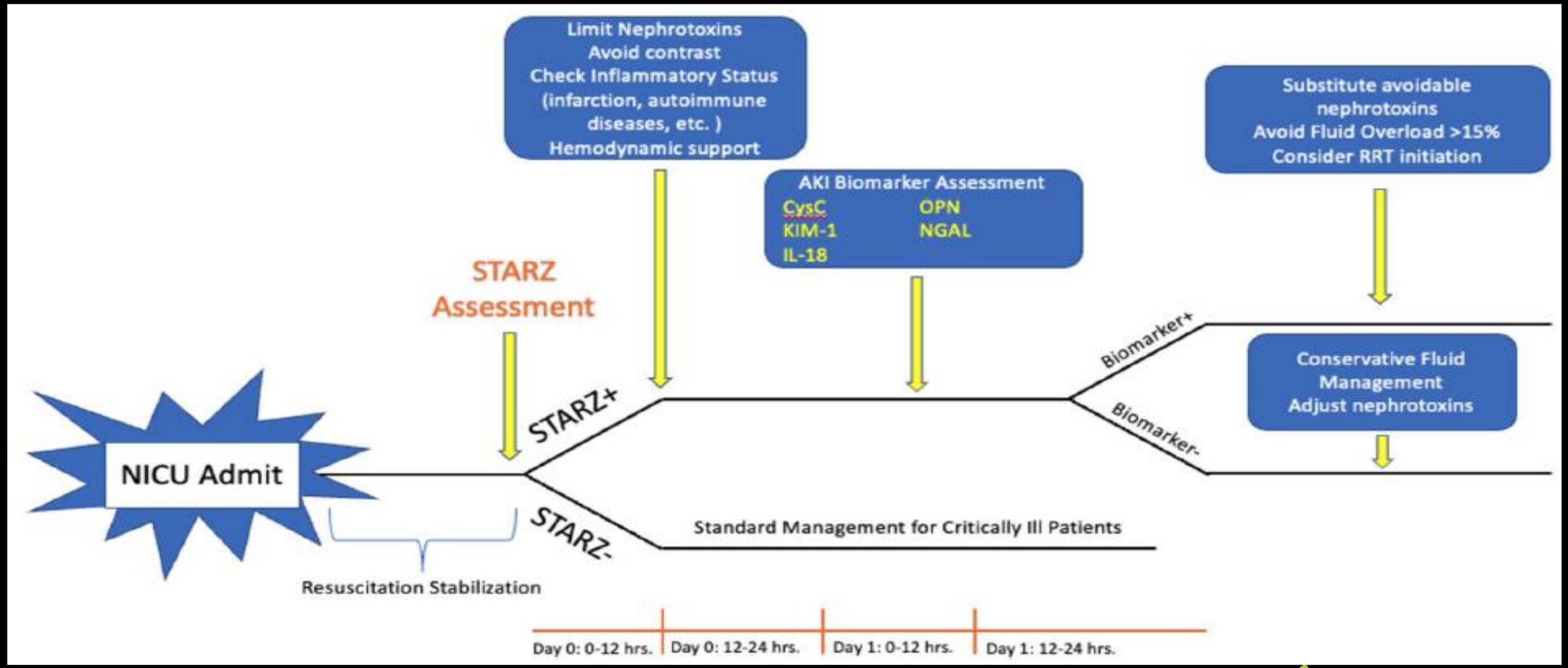
AI in Neonatal AKI: Score Implementation



Raina R, Pediatr Nephrol 2024, 39:2309-24

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Few Evolving Trends in Pediatric Kidney Care

- Omics: Genomics, Proteomics, Big Data, Bioinformatics
- Increasing use of Genetics in pediatric kidney care
- Increasing use of Electronic Health Records
- Personalized, Predictive, and Targeted approaches
- Artificial Bioengineered Kidneys
- Expectation for value: decrease cost and increase quality
- Expectation for optimal patient and family satisfaction
- **Artificial Intelligence to support all aspects of kidney care**

Thank you for your attention!

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Genetics in kidney disease To decide, decipher and beyond

Dr Christy Cathreen Thomas

Assistant Professor, Pediatric Nephrology

Government Medical College, Thiruvananthapuram

Introduction

There is no doubt that accessibility to genetic testing has considerably changes the pediatric nephrology practice

- They help in resolving diagnostic challenges/confirm diagnosis
- They guide therapy (to treat or not to treat)

Relatively new arena

It has added its own challenges

GENETIC TESTING

Genetic testing is defined as the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites with the aim of detecting heritable disease

cytogenetic, molecular cytogenetic, biochemical, and DNA-based tests

Role of genetics

Diagnosis-Therapeutic advantage

Preventive therapies

Pharmacological decision making/Pharmacogenomics

Understanding the pathophysiology-therapeutic research

Gene therapy

“Think genetic” –to what extent?

When should I opt for genetics?

Diseases with a known genetic cause or contribution

Which test should I opt ?

Types of genetic change anticipated

Even if I see some changes in the genetic testing, how will I know it is significant ?

Case 1

3 month old boy was brought to pediatric nephrology clinic for evaluation of cystic kidneys

He had antenatal history of large echogenic kidneys

Now having large sized kidneys with small cysts mainly cortical, no hydronephrosis, liver & spleen normal

Parents USG normal, born of nonconsanguinous marriage

Renal function, serum electr
acid and magnesium are norma

PRIMARY CILIOPATHY vs CAKUT

HNF1B/ ARPKD/ Infantile NPHP/ denovo ADPKD

Case 2

10 year old girl presented with hypokalemic paralysis and detected to have

Polyuria and polydipsia

Blood-NAGMA, persistent hypokalemia, hyperchloremia, hypophosphatemia and normal RFT and blood counts

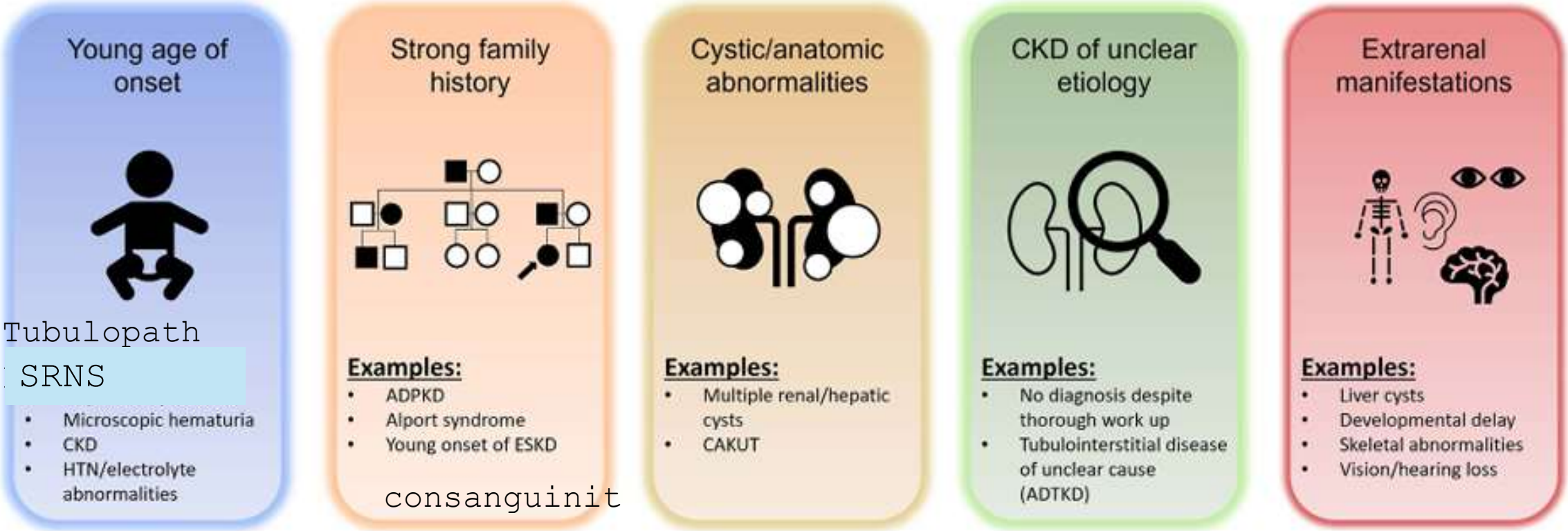
Urine-Hypercalciuria, nephrocalcinosis, phosphate wasting, high beta2 microglobulin excretion, no glucosuria

Ultrasonography- normal sized kidneys with medullary nephrocalcinosi

Ophthalmology a
normal

RTA- Distal RTA with proximal dysfunction or
Proximal RTA with hypercalciuria

When should we opt for genetics in pediatric Nephrology?



Tubulopath

SRNS

consanguinity

High yield

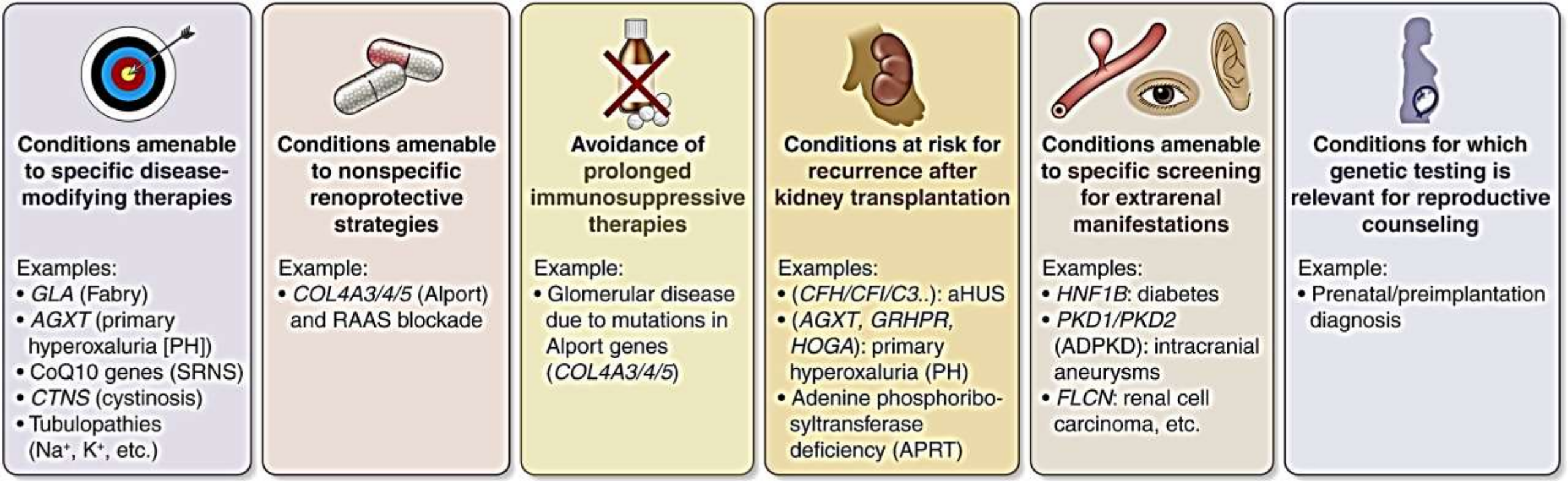
Cystic kidney disease -23.9%-49.6%

Primary glomerulopathy 7.2%-16.9%

Tubulointerstitial disease -

Aron et al. Am J Kidney Dis 2024

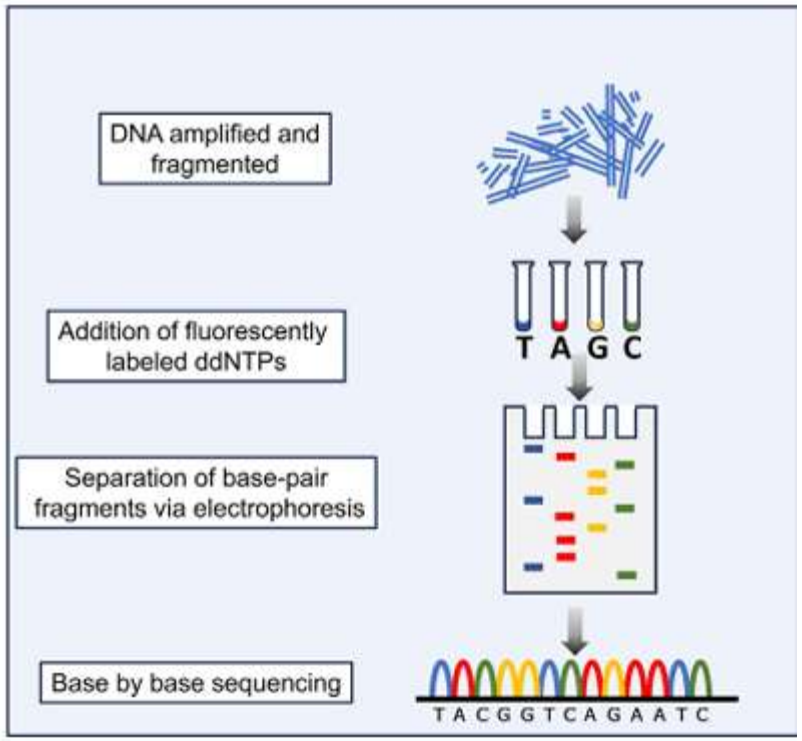
Actionable gens in nephrology



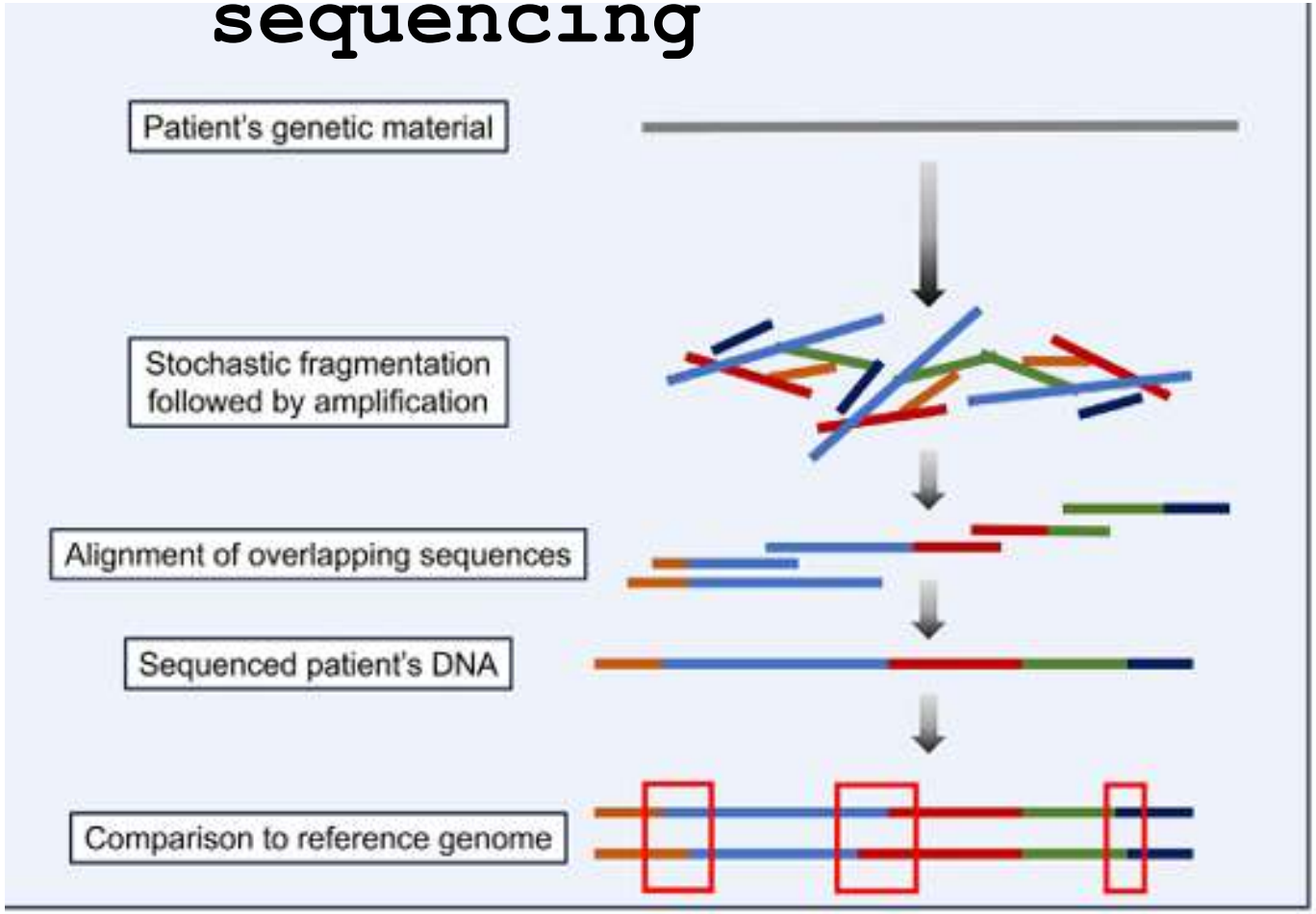
Kidney International (2022) 101, 1126–1141

TESTING METHODS

Sanger sequencing



Next generation sequencing



Micro array/MLPA

Test to choose – The options

Test name	Region tested	Advantage	Disadvantage
Sanger Sequencing	Small regions SNV/small deletion/insertion	Gold std /Known variant in family/Easy interpretation	Only for small regions & data Not for comprehensive tests
Targeted panels	Limited no of genes	Easy interpretation	Limited asseessment
Clinical exome sequencing	Clinically relevant genes	Focused evaluation	Filters out data exons were relevance is not known
Whole exome sequencing	Exons + flanking introns	Broad discovery & diagnosis Comprehensive data, Noval	More VUS, more data
Whole genome sequencing	Exons +noncoding region	Rare disease/ novel/non coding variants	Data interpretation, cost
MLPA	Small genomic	Customisable	Known target/ not for

REPORT

Mutation/polymorph… → VARIANT

Case 1

***HNF1B* (-)** (ENST00000617811.5)	Exon 5	c.1091C>A **(p.Ser364Ter)**	Heterozygous

Case 2

Gene (Transcript)	Location	Variant	Zygosity
***ATP6V1B1* (+)** (ENST00000234396.10)	Intron 11	c.1144-1G>T **(3' Splice site)**	Homozygous

Digital DNA sequence –composite of multiple individual DNA

Helps in mapping and aligning

GRCh38-maintained by Genome reference consortium

Reference	C	T	A	T	G	C	A	A	G	C	A	G	T	T
Patient Sequence 1	C	C	A	T	G	T	A	A	G	T	G	G	T	T
Patient Sequence 2	T	C	A	T	G	T	C	A	G	C	A	A	C	T
Patient Sequence 3	C	C	G	T	G	T	A	A	G	C	A	G	T	T
Patient Sequence 4	C	C	A	T	G	T	A	A	G	C	A	G	T	T
Patient Sequence 5	C	C	A	T	G	T	A	A	G	C	A	G	T	T
Patient Sequence 6	T	C	A	T	G	T	C	A	G	C	A	A	C	T
Patient Sequence 7	T	C	A	T	G	T	C	A	G	C	A	A	C	C
Patient Sequence 8	T	C	A	G	G	T	C	A	A	C	A	A	C	T

Variant calling and gene annotation

RefSeq/Ensembl Genome Browserlimited ma

GRCh38- Representation of the Indian/South Asian genome is poor

is mainly European and African

How different are we from each other ?
Genetic Variability

Average two people are different 0.1% of their genome

3-4 million differences out of 3 billion base pairs

Single nucleotide change
Small insertion/deletions
Copy number variations
Structural variants
Microsatellites or small tandem repeats

IMPACT

Neutral
Beneficial variant
Harmful variant

REPORT

Mutation/polymorph… → VARIANT

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Variant classification

VARIANT CLASSIFICATION OF IS THE MOST IMPORTANT STEP FOR THE CLINICIANS

The **2015 ACMG and AMP** (Association for Molecular Pathology

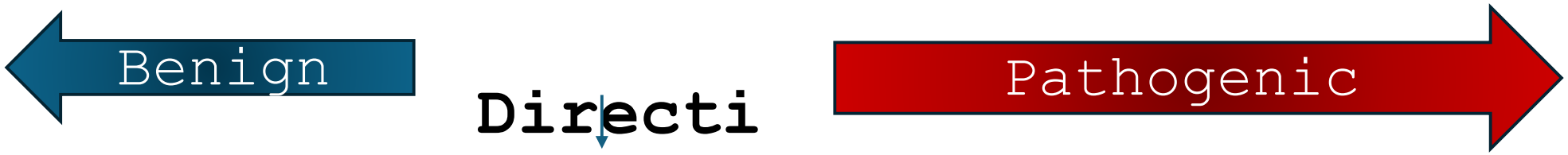
guidelines described specific rules and evidence used

for variant classification and interpretation

> *"Variant analysis is at present imperfect and the variant category reported does not imply 100% certainty"*

Richards et al. Genet Med. 2015

Is this variant significant ?



Direction

Variant classification based on evidence codes in different domain

ACMG/AMP 5 tier Classification

Pathogenic (P)
Likely pathogenic (LP)
Variant of uncertain significance (VUS)
Likely Benign
Benign

Positive result

- **P** or **LP** variant in an AD, mitochondrial, or X-linked disorder
-a homozygous or compound heterozygous P or LP variants in an AR condition

Richards et al. Genet Med. 2015

Harrison et al. Curr Protoc Hum Genet. 2019

EVIDENCES

Richards et al. Genet Med. 2015

Population frequency data	• Allele frequency data 5% or>0.05 , Absence in healthy • PM2 threshold < 0.01% or 0.0001 • Exome Sequencing Project,1000 Genomes Project, ExAC or gnomeAD
Variant type & location	• Null variant where LOF known mechanism • Missense variant, region intolerant to change
Case-level data	• Phenotype, Segregation analysis, Denovo variant • Previously reported
Functional analysis	• Invitro/in vivo experiments/functional assays of protein /nucleic acids
Computation & prediction data	• Bioinformatic Algorithms Polyphen/SIFT/Mutation Taster/CADD score

Evidence codes

	Benign Criteria		Pathogenic Criteria			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**VeryStrong**
	−18.7	−2.08	2.08	4.33	18.7	350.0
Population Frequency Data	*BA1 ^{G,S} BS1 ^{G}			PM2^{G}		
Variant Type and Location		BP1 BP3 BP7	PP2^{G}	PM1^{G} PM4 PM5	PS1	PVS1^{G,S}
Case-level data	BS2^{G} BS4	BP2 BP5	PP1^{P} PP4^{G}	PM3^{S} PM6^{S}	PS2^{S} PS4^{G}	
Functional and Computational data	BS3^{G}	BP4^{P}	PP3^{P}		PS3^{G,P}	
Reputable source		BP6^{R}	PP5^{R}			

Harrison et al. Curr Protoc Hum

Evidence codes in Pathogenic direction

Very strong	Description	
PVS1	Null variant were LOF is known mechanism of the disease	Variant type & location
Strong	**Description**	
PS4	Statistical data of enrichment of variant in affected individuals	Population frequency data
PS1	Same amino acid change as already described pathogenic	Variant type & location
PS2	Denovo, confirmed parental status, matching phenotype	Case level data
PS3	Well established functional studies	Functional studies

Harrison et al. Curr Protoc Hum Genet. 2019

EVIDENCE CODES CLASSIFICATION

Classification	Evidence codes
Pathogenic	1 very strong, 1 strong, 2 supporting evidence
Likely pathogenic	1 strong +1-2 moderate/ supporting
Likely benign	2 benign and no contradictory criteria
Benign	BA1

Bayesian Integration-

Combine baseline probability & evidence code

Harrison et al. Curr Protoc Hum Genet. 2019

Post_P Range	**Classification**
Post_P > 0.99	Pathogenic
0.90 < Post_P ≤ 0.99	Likely pathogenic
0.10 ≤ Post_P ≤ 0.90	Uncertain significance
0.001 ≤ Post_P < 0.10	Likely benign
Post_P < 0.001	Benign

Case 1- What is in a report?

Protein change

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[$]
***HNF1B* (-)** (ENST00000617811.5)	Exon 5	c.1091C>A **(p.Ser364Ter)**	Heterozygous	Renal cysts and diabetes syndrome (OMIM#137920)	Autosomal dominant	Pathogenic

Name of the gene

Complementary DNA variant

Variant was absent in both parents

Case 1

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[$]
***HNF1B* (-)** (ENST00000617811.5)	Exon 5	c.1091C>A **(p.Ser364Ter)**	Heterozygous	Renal cysts and diabetes syndrome (OMIM#137920)	Autosomal dominant	Pathogenic

Population frequency data	• Variant absent in 1000 genomes, gnomAD- **PM2**
Variant type & location	• stop codon and premature truncation **PVS1**
Case-level data	• Phenotype matching/ denovo- **PM6**
Functional analysis	• Not available
Computation & prediction data	• variant is damaging by MutationTaster2

Case 2

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***ATP6V1B1* (+)** (ENST00000234396.10)	Intron 11	c.1144-1G>T **(3' Splice site)**	Homozygous	Distal renal tubular acidosis with progressive sensorineural hearing loss (OMIM#267300)	Autosomal recessive	Pathogenic

Population frequency data	• Minor allele frequency-minor allele frequency of 0.005%-**PM2**
Variant type & location	• stop codon and premature truncation **PVS1**
Case-level data	• Phenotype matching
Functional analysis	• Not available
Computation & prediction data	• variant is damaging by MutationTaster2

Variants of uncertain significance

A genetic variant **with insufficient or conflicting evidence** supporting its involvement in disease

Cannot be classified as P/LP, or as benign/likely benign

Uncertainty for the clinician and chance of misinterpretation

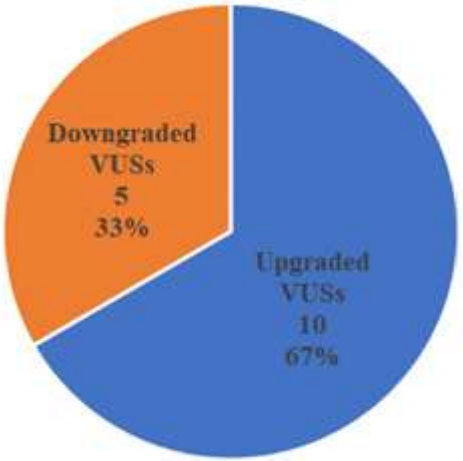
Assuming is harmful than not knowing

RECLASSIFICATION

Availability of new data – upgrade / down

Lim et al reclassify the variants in re
disease

4.5 years after initial results in 413 pe
15 VUS was reclassified



Lim et al, Kidney International

Way out of VUS: Variant Reclassification

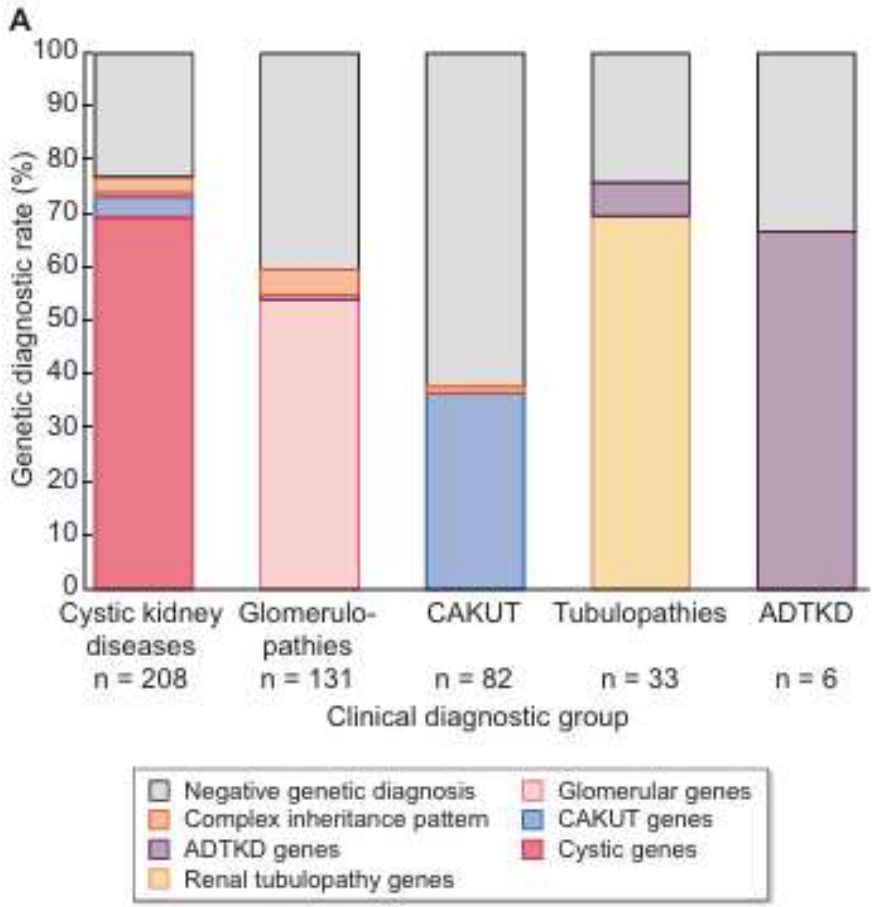
- Segregation analysis
- Monitor patients for new findings
- Follow up testing for additional variants
- Wait for new evidences –cases being reported
- Identify similar patients
- Functional studies
- Interval reanalysis

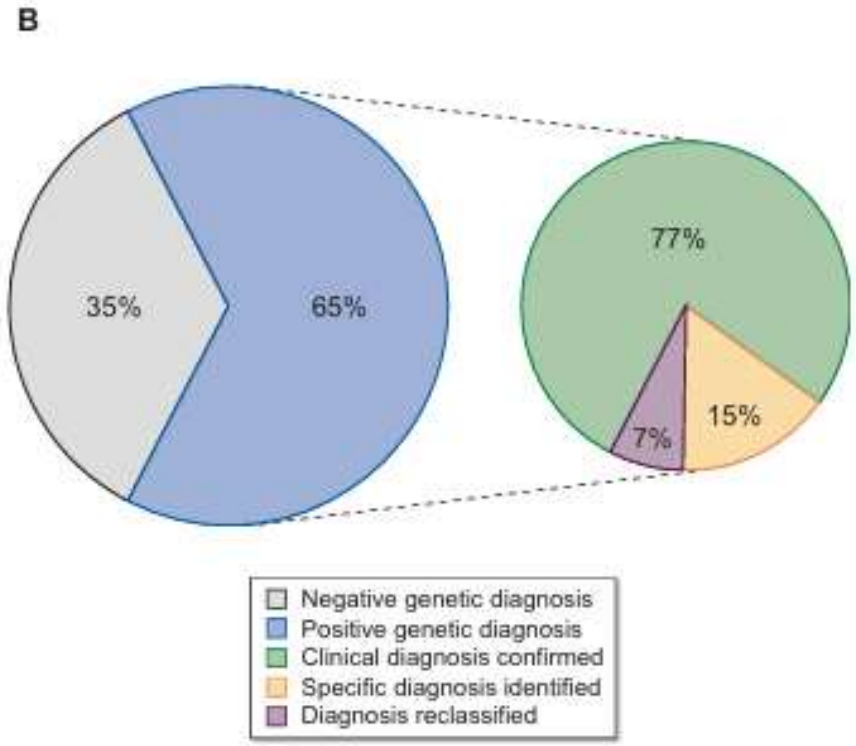
Collaboration with genetic expert

RENAL BIOPSY

Walsh N et al. J Med Genet 2024

Clinical utility of genetic testing in early-onset kidney disease seven genes are the main players





COL4A3
COL4A4
COL4A5
HNF1B
PKD1
PKD2
PKHD1

66%

A.Domingo-Gallegoetal. Nephrol Dial Transplant 2022

Ethical legal and social issues (ELSI)

Ethical	Legal	Social
Informed consent Scope/implication/limitation	Discrimination-Employment/Insurance	Stigmatisation
Autonomy-choose/decline	Ownership of genetic data	Cultural issues
Confidentiality/privacy	Family third party implications	Designed children
Fear of stigmatisation	Legal liability of misinterpretation	Family dynamics
Incidental finding	Who is responsible for reclassification	Psychological issues for children
Reproductive decision making		Flawed public perception

Conclusion

Genetic testing is an unavoidable gadget for the pediatric nephrologist

The availability & affordability has led us to confirm and solve clinical queries

The increasing amounts of data generate increasing challenges in

interpretation

These tests have their limitations

Reclassification of the variants should be actively pursued

THANK YOU

Voiding dysfunction in children

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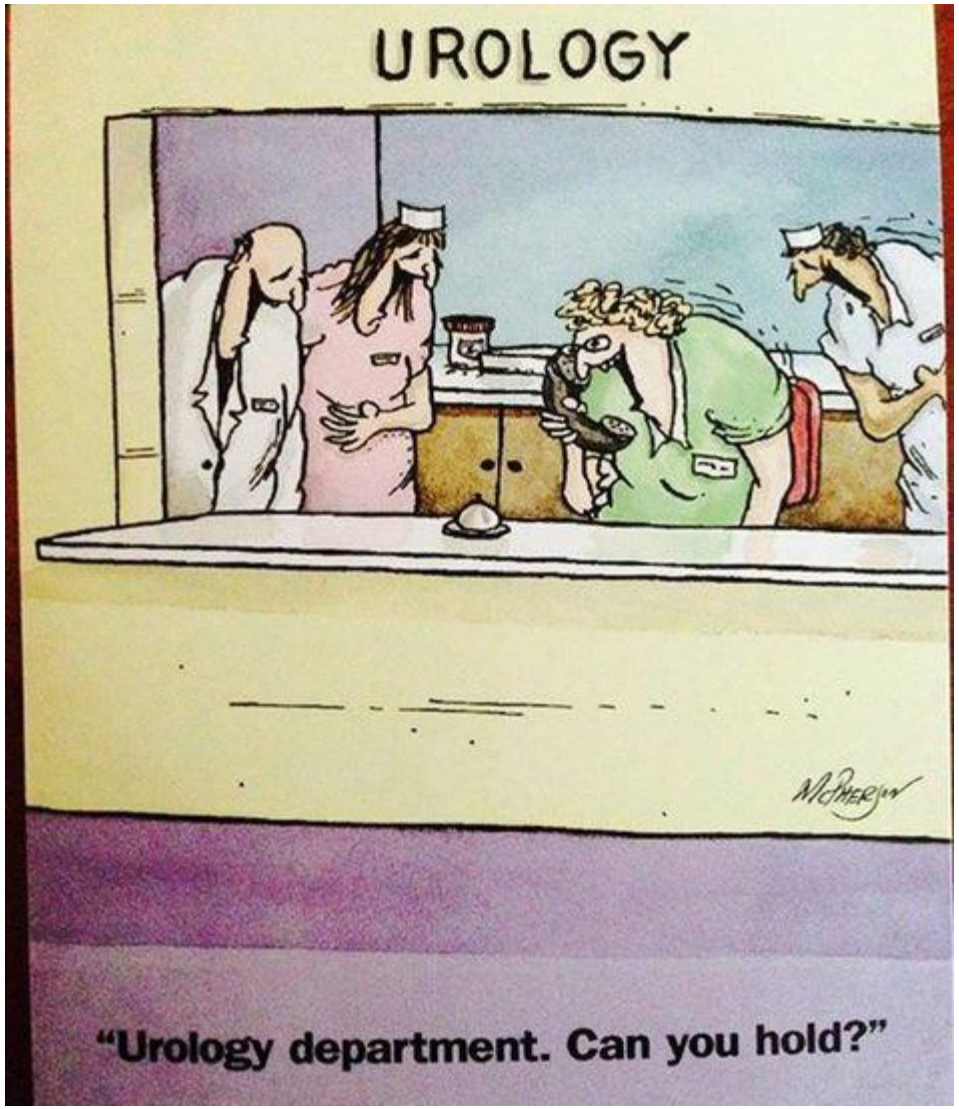
Govt Medical College, Thiruvananthapuram

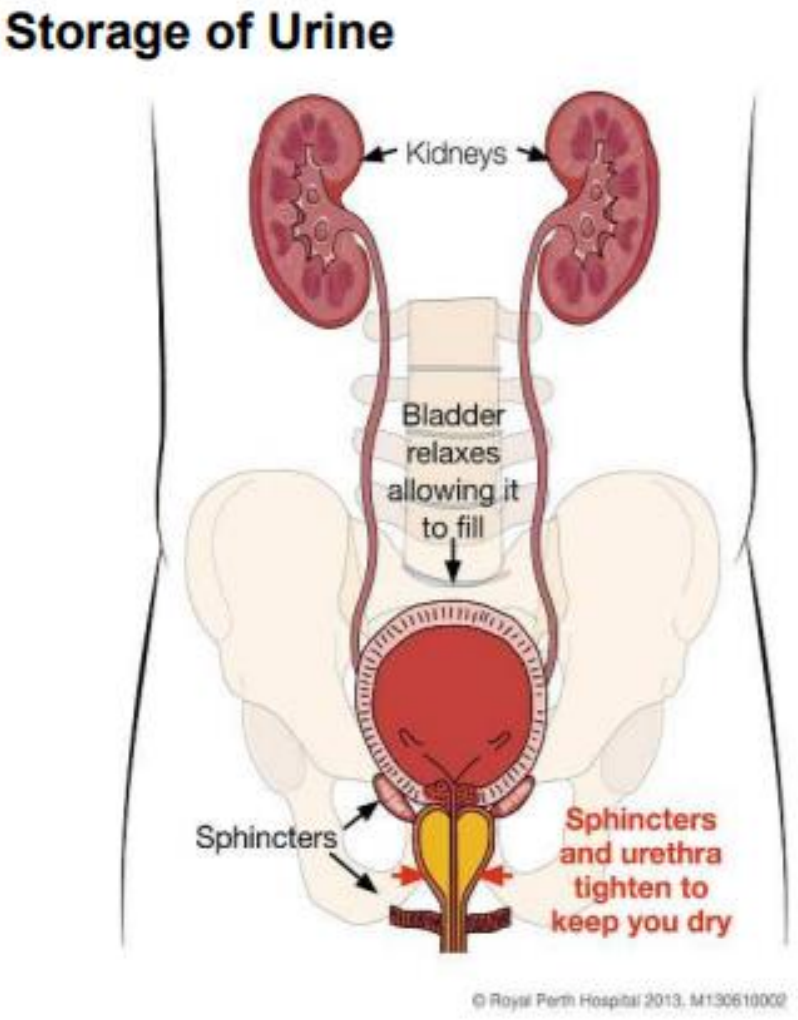
Introduction

- Voiding Dysfunction is seen in 4.2% to 32% of children with lower urinary tract symptoms
- Most common non-surgical pediatric urological diagnosis
- Broadly encompassing term applied to any and all voiding problems in children
- Mostly treatable



Pediatric Nephrology 2016;31(10):1773

Normal voiding cycle

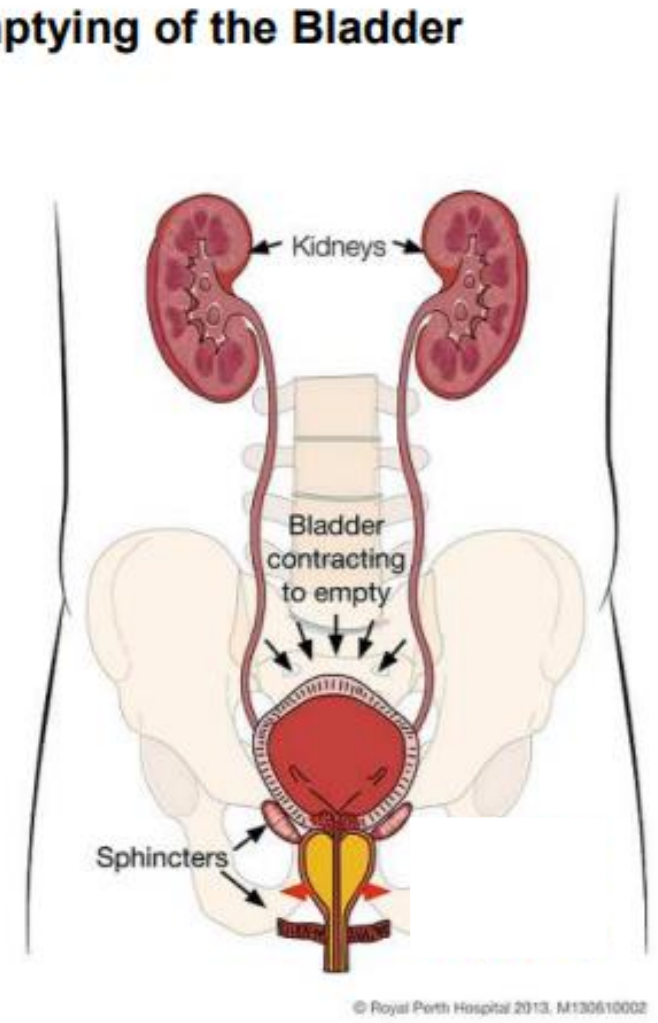


Storage:

- Bladder relaxation (under control of T12 – L2 spinal cord control) and urethral sphincter contraction (under control of S2, S3, S4) are involuntary and automatic.
- When bladder reaches full volumes, message transmitted through spinal cord to pontine micturition center.

Emptying:

Internal and external sphincter relaxation followed by bladder contraction



Micturition in young infants

- Micturition is purely reflexive
- Occurs whenever the bladder is sufficiently distended
- At 18 – 24 months, voiding comes under some cortical control
- At about 3 years, complete control is achieved
- cortex takes over control

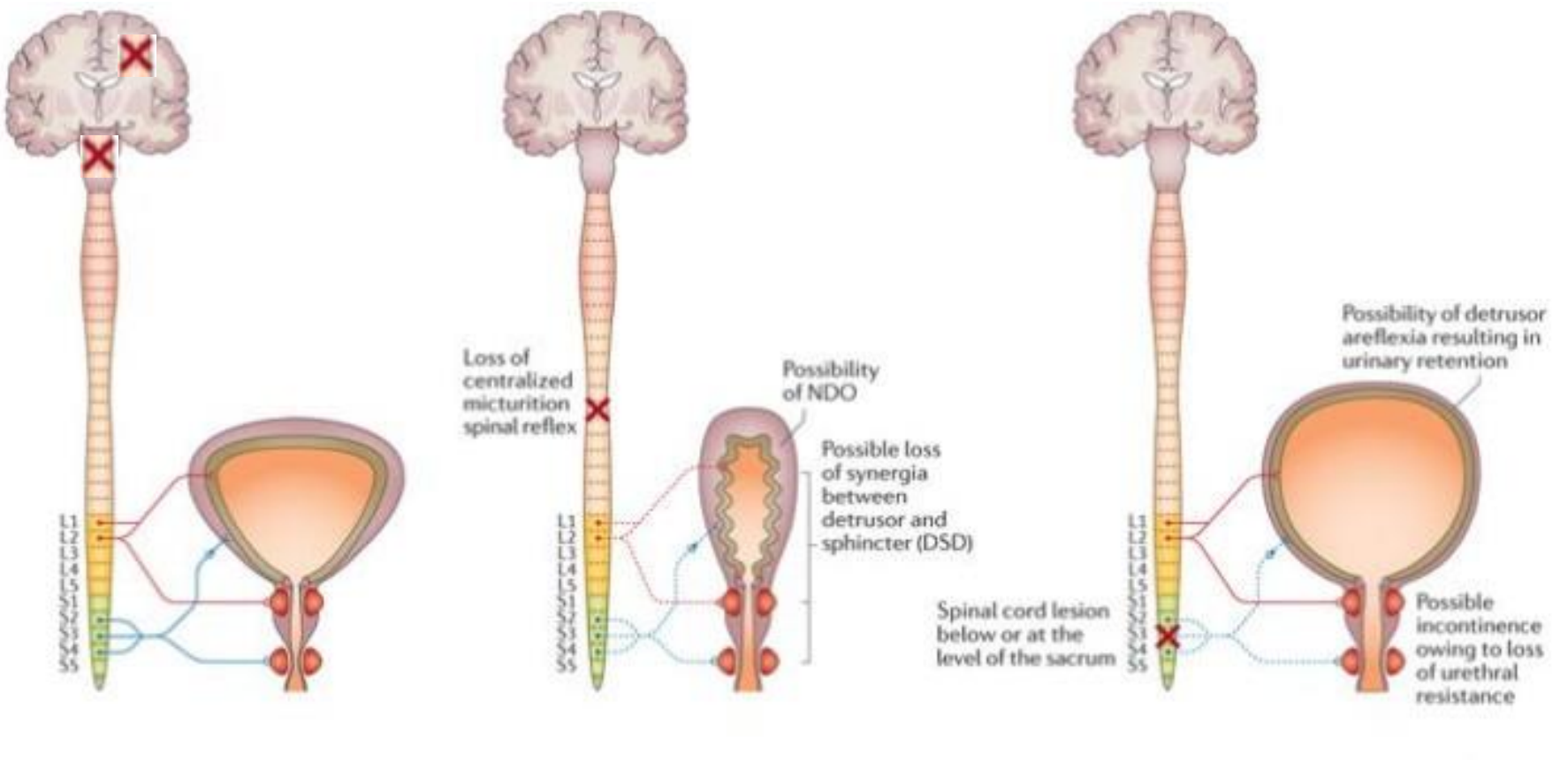
Neural voiding control

Cerebral Cortex - provides the highest level of control and is responsible for social and voluntary control of voiding

Pontine micturition center – coordinates synergy between detrusor and sphincter, controls switch between storage and emptying

Thoracolumbar spine – responsible for normal bladder relaxation

Sacral micturition center – reflexive voiding



If any of these go wrong → neurogenic voiding dysfunction

Definitions

- Bladder and Bowel Dysfunction (BBD) is an umbrella term that encompasses lower urinary tract dysfunction (LUTD) and bowel dysfunction.
- LUTD symptoms are classified according to their relation to the storage and/or voiding phase of bladder function.
- Lower urinary tract symptoms (LUTS) can manifest as urgency and frequency with or without incontinence, or recurrent UTI.

Possible diagnoses in children with LUTS

- Overactive bladder
- Dysfunctional voiding
- underactive bladder
- voiding postponement
- Stress incontinence
- giggle incontinence
- vesicovaginal reflux incontinence
- enuresis.

Subtypes of daytime incontinence

Subtypes	Symptoms	Signs
Overactive bladder	• Frequency • Voiding urgency • Incontinence • Constipation • Enuresis	• (Cystometric) detrusor overactivity • Holding maneuvers • Bell shape/ tower shape pattern • Thick bladder wall • Low volume voids

Subtypes of daytime incontinence

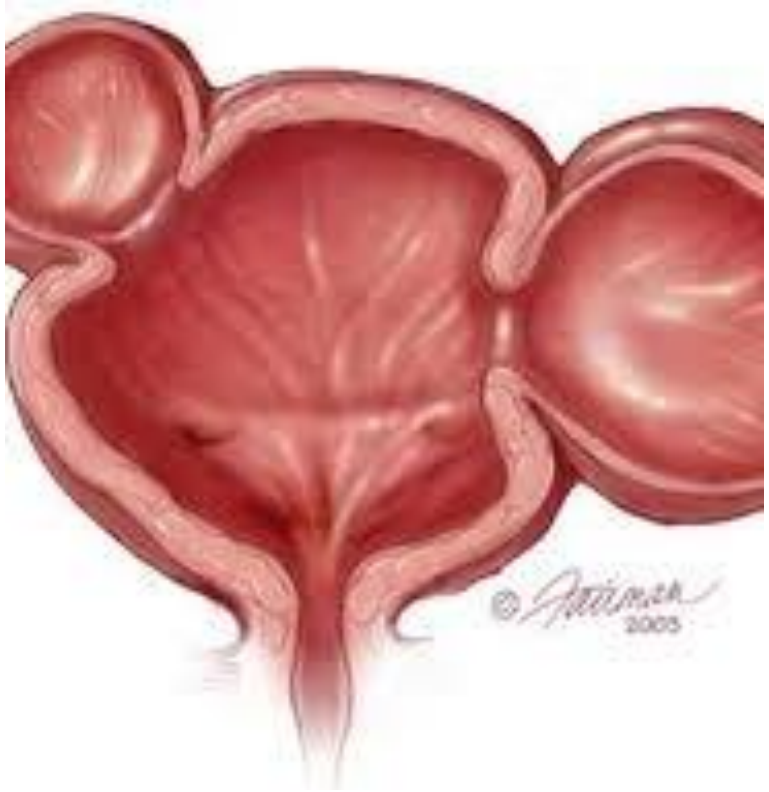
Dysfunctional voiding	• Failure to relax the sphincter during voiding • Normal micturition frequency • Incontinence • Constipation • UTI's • Enuresis	• Post void residual • Staccato or interrupted flow pattern Normal amount of voids
Underactive bladder	• Low micturition frequency • Incontinence • Constipation • UTI's	• Post void residual • Staccato or interrupted flow pattern • Frequent big volume voids • (Cystometric) weak detrusor contractions
Voiding postponement	• Low micturition frequency • Incontinence	• Normal flow pattern • Normal fluid intake • Often associated with behavioural problems

Benign Voiding Dysfunction

- Vast majority of cases
- Self – limiting but distressing to parent/child, episodic
- May be related to stressful events, new school/new sibling
- Often recurs at various times throughout childhood
- May be associated with stool withholding/constipation
- May be associated with episodes of simple cystitis
- Not associated with hydronephrosis, secondary vesicoureteral reflux (VUR), bladder trabeculation

Pathologic Voiding Dysfunction

- Persistent/chronic/unremitting
- Not generally self-limiting; requires intervention
- Can be progressive and if severe may lead to bladder and renal dysfunction (Hinman syndrome – non-neurogenic neurogenic bladder dysfunction)
- Often associated chronic constipation/stool impaction/encopresis
- Urinary tract imaging may be abnormal - hydronephrosis, abnormal bladder



Evaluation of Abnormal Voiding

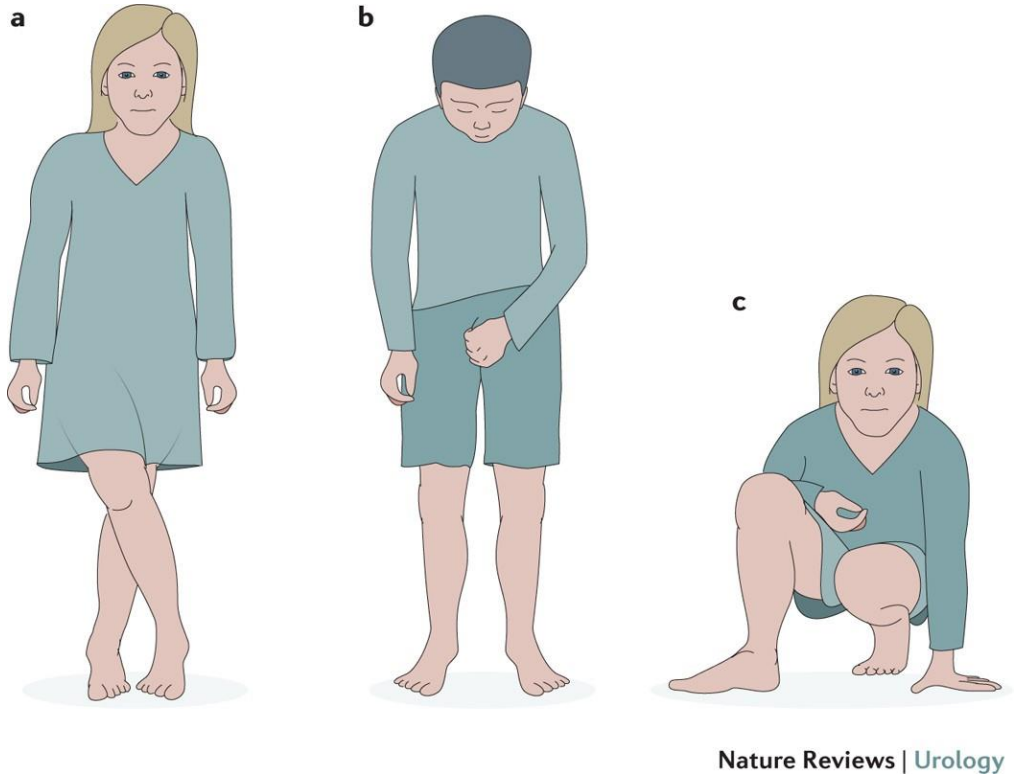
- Full medical history, expanded voiding history
- Physical exam (spine, coordination, GU exam)
- Labs
- Imaging

Lower urinary tract dysfunction – The Great imitator

- Patients won't always present with incontinence
- Common complaints
  - recurrent UTI ("UTI every month")
  - running to the bathroom - very severe urinary urgency or urge incontinence
  - pain – penile/testicular/vaginal pain
  - vulvo vaginitis
  - dysuria

Full Voiding History

- Toilet training (when, easy, difficult?)
- Characteristics of the complaint (urgency/frequency, holding/long voiding intervals, dribbling/leakage/full accidents), strong/weak/intermittent stuttering stream, occurs daytime and/or nighttime)
- H/o constipation/encopresis
- Other medical history (developmental delay), lower extremity coordination (spinal cord)



“small bladder” vs “large bladder"

- Frequent voider
- + frequent warnings/urges to void
- +/- accidents
- OAB

- Infrequent voider
- Distended, myopathic bladder
- Floppy bladders
- No warnings until very urgent need to void
- +/- accidents

BRISTOL STOOL CHART

	Type 1	Separate hard lumps	Very constipated
	Type 2	Lumpy and sausage like	Slightly constipated
	Type 3	A sausage shape with cracks in the surface	Normal
	Type 4	Like a smooth, soft sausage or snake	Normal
	Type 5	Soft blobs with clear-cut edges	Lacking fibre
	Type 6	Mushy consistency with ragged edges	Inflammation
	Type 7	Liquid consistency with no solid pieces	Inflammation

Psychosocial history

- Behavioral problems
- School maladjustment
- Bullying
- Effect of incontinence
- Activity/ lifestyle restriction
- Motivation for treatment

Bladder diary

Date | Time	Urine volume	Drinks volume	Leakage	Urge	Description
Date and Time am/pm	The exact amount in mL	The exact amount in mL / oz	Did you experience any accidental leakage? Rank it 0-4	How strong was the urge to go? Rank it 0-4	

Evaluation

- Physical Exam
  - Abdomen: masses (constipation, suprapubic distention/tenderness)
  - GU:
    - Female – introitus patent/labial adhesions (may indicate trapped or vaginal voiding), erythematous, malodorous, discharge (infection)
    - Male - +/ circumcised/phimosis/ballooning, meatal caliber/stenosis
  - LE: normal neuro exam, +/- sacral dimple/pitting, coordination, high arched feet/toe curl
- Labs - Routine Urinalysis (signs of infection, proteinuria)
  Urine culture if indicated, fasting blood sugar if indicated

Further evaluation

- Uroflowmetry and assessment of post-void residual (PVR)*
  - Small vs large capacity, overactivity (high peak stream), intermittency (stuttering stream), bell shaped normal voiding
- Renal and bladder ultrasound – rule out renal anomaly, bladder thickening and trabeculation

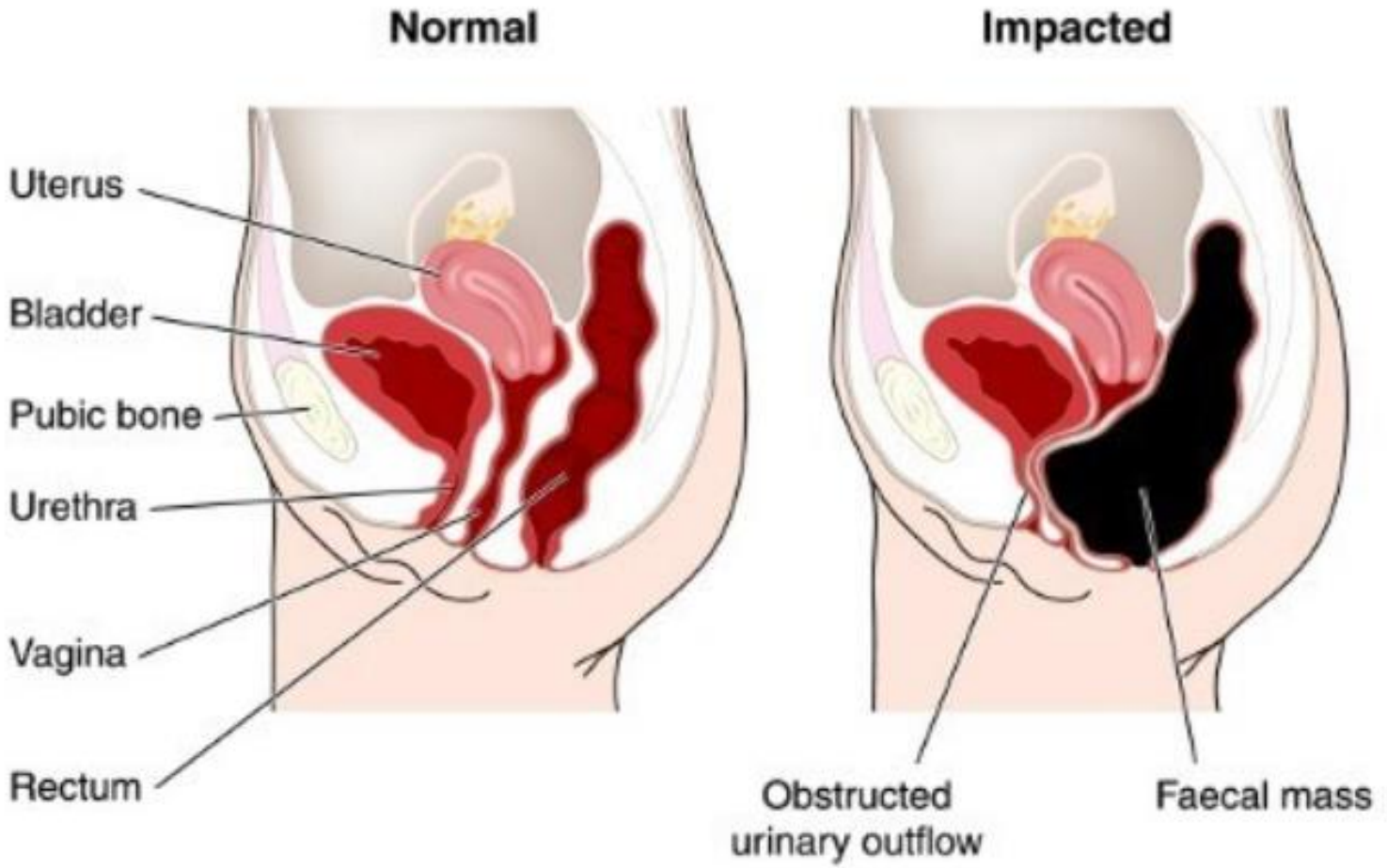
Thickening
- >3mm when distended (>25% expected volume)
- >5mm when non-distended (<10% expected volume)

- Rarely VCUG – formal evaluation of reflux and obstruction

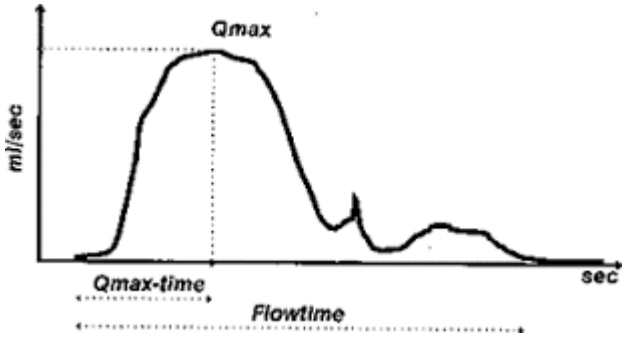
X-ray KUB

–

constipation, bony structures

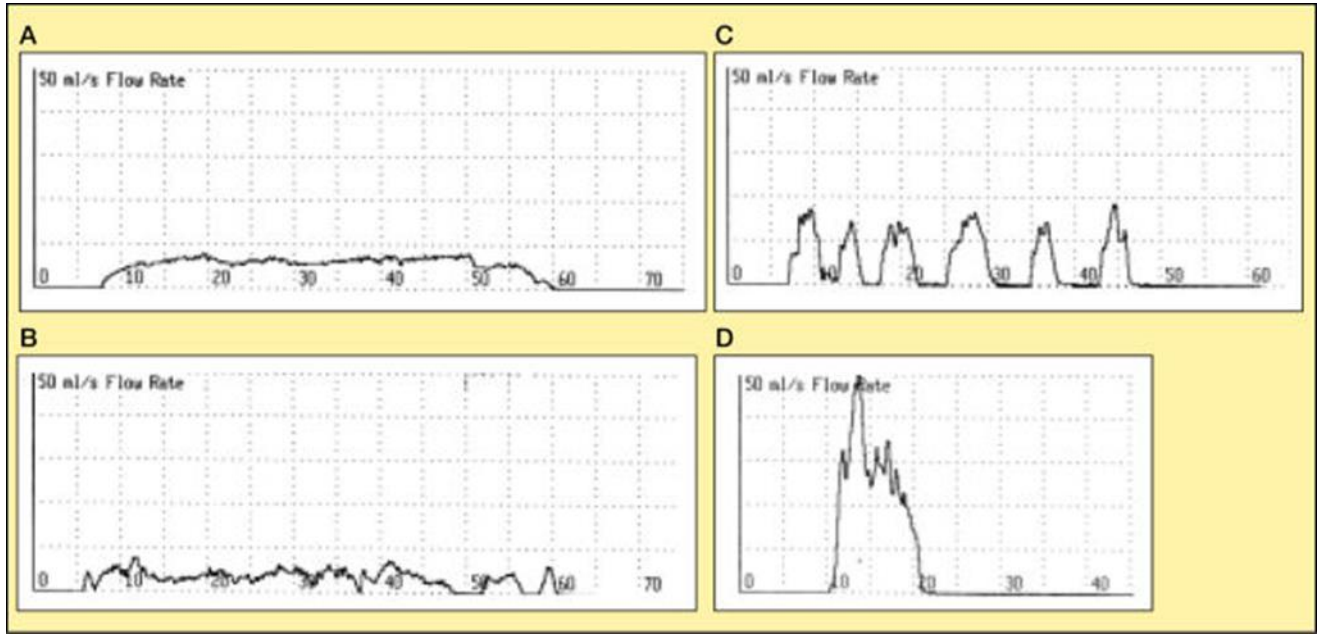


Uroflowmetry/EMG



Simple, in clinic test to measure bladder capacity, urine flow characteristics including peak flow, time to initiate voiding, time to completion of voiding

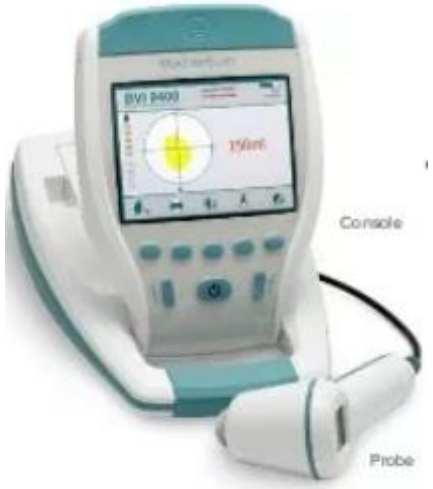
- High peak flow may indicate bladder overactivity
- Stuttering stream/intermittency may indicate DSD
- Prolonged emptying/weak stream/small capacity may indicate obstruction or constipation
- If patch electrodes available for EMG, can assess if normal neural signals precede or are concomitant with voiding



(A) obstructive, or "breadloaf," pattern; (B) detrusor impairment pattern; (C) Valsalva voiding pattern; and (D) superflow pattern. Voided volumes should be greater than 150 mL

Post void residue

- Measures the amount of urine left after voiding
- Most children empty their bladders completely, but it is normal to retain up to 10% of bladder capacity
- Greater than 10% residual suggests incomplete emptying from:
    - Impatient voiding (stopping short)
    - Weak bladder from history of prolonged



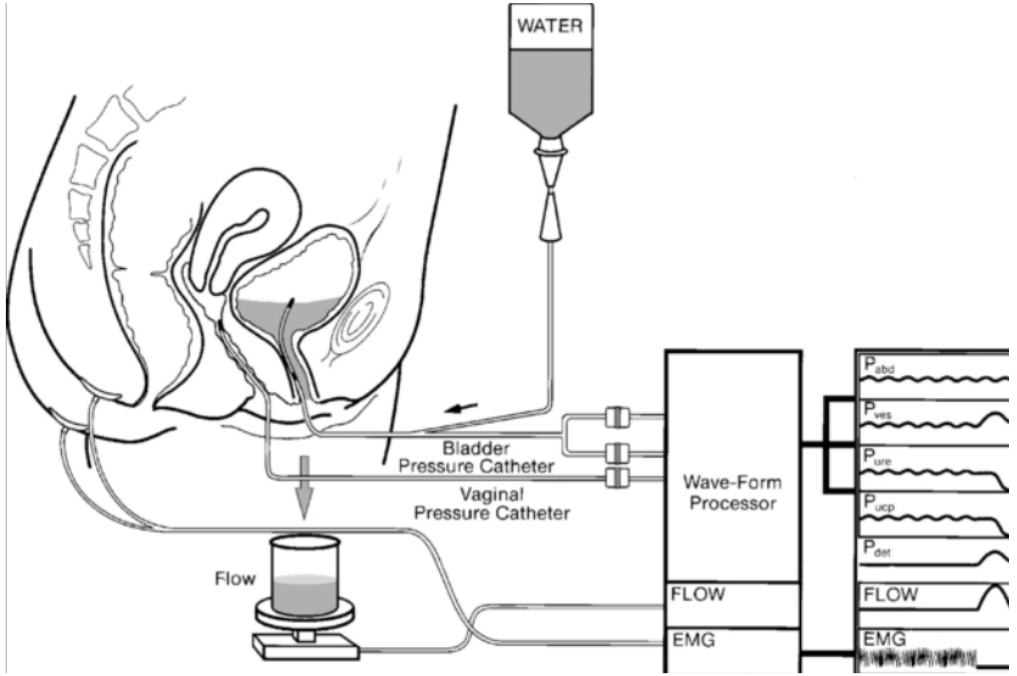
Bladder capacity = (age +2) * 30 ml

Age <2 years – Weight (kg) * 8 ml

Urodynamics/Video-urodynamics

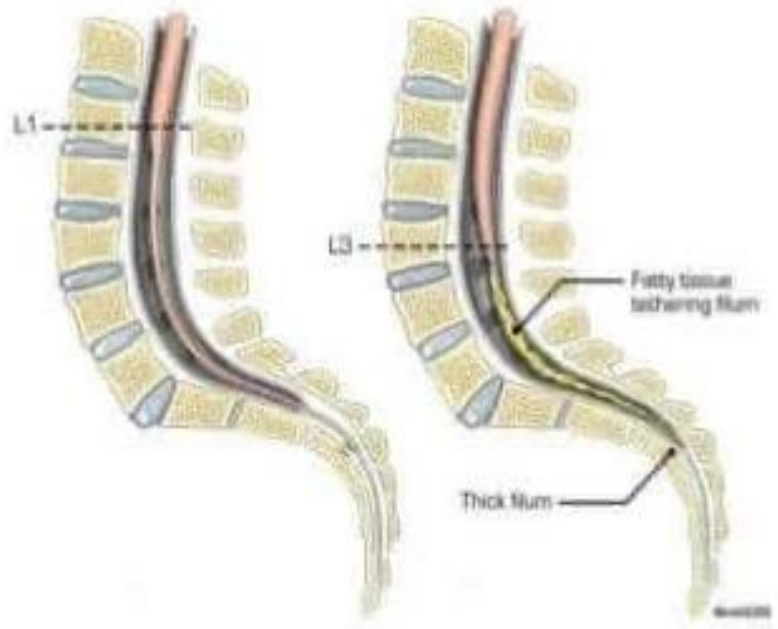
• Formal assessment of bladder function, capacity, manometric evaluation of compliance, voiding pattern, sphincter coordination/relaxation, pelvic floor innervation

• With video/fluoroscopy – visual evaluation of voiding, shape of bladder, assessment for VUR



Tethered Spinal Cord

- Neurologic disorder
- Caused by tissue attachments that limit the movement of the spinal cord within the spinal column and can cause an abnormal stretching of the spinal cord
- After infancy, greatest prevalence in children age 6 during growth spurts and elongation of the spinal cord resulting in worsening stretching by tethered attachments
- MRI spine



Treatment

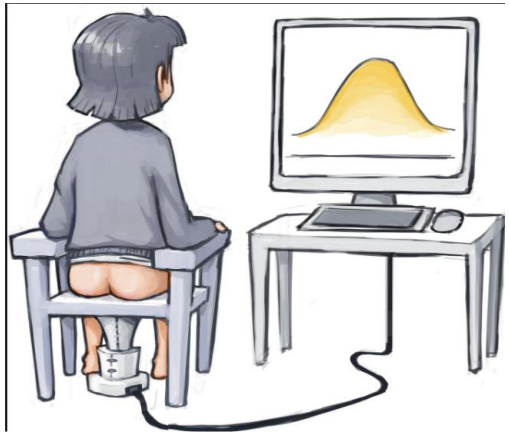
Urotherapy

- defined as bladder re-education or rehabilitation aiming at correcting any correctable anomalies of the filling and voiding function of the bladder sphincter unit.
- Multidisciplinary team work

Treatment options for Voiding Dysfunction

Individualize based on patient presentation

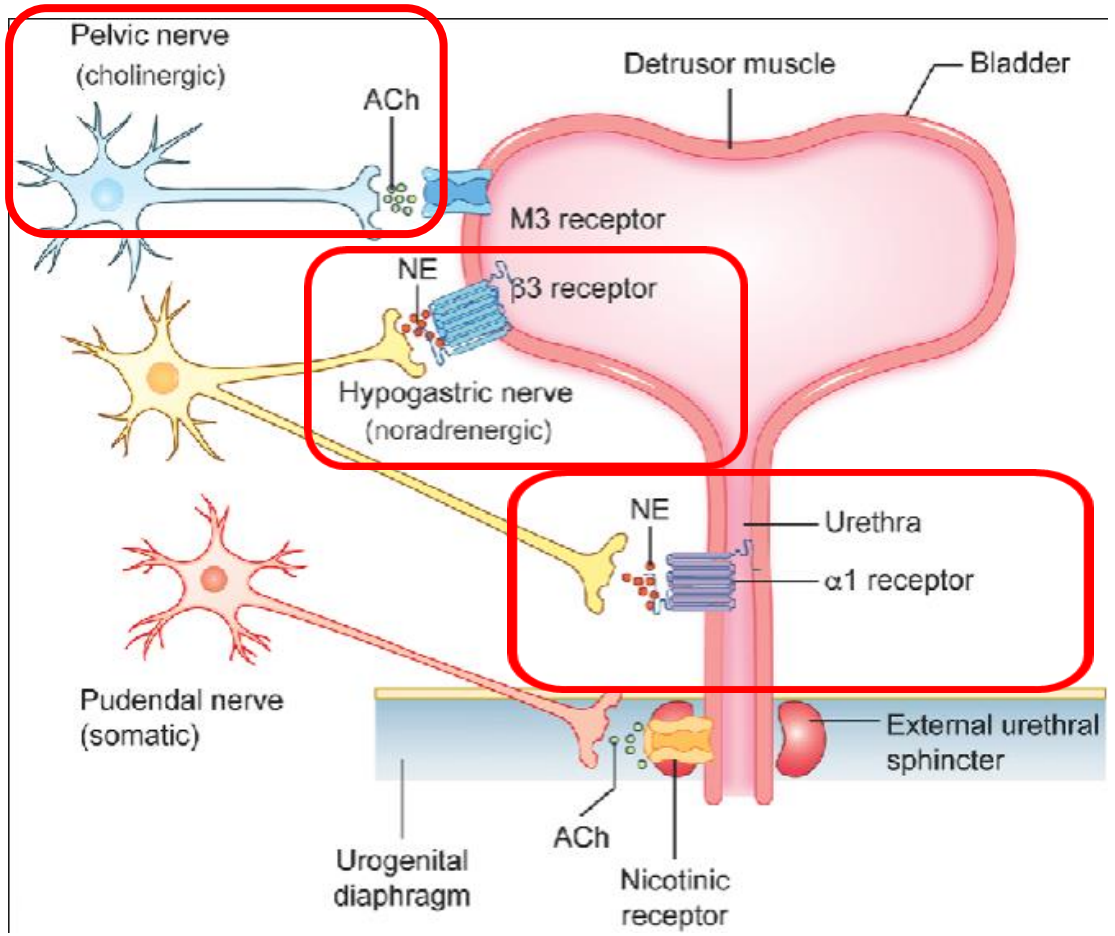
- Strict voiding schedule, diary, alarm watch, school note
- Treatment of constipation (hydration, dietary fiber, fiber gummies, laxatives, Mineral oil, Mag Citrate cleanse)
- Anticholinergic therapy +/- Clean Intermittent Catheterization (CIC) (elevated PVR) +/- alpha blocker (external sphincter relaxation to address dyssynergic sphincter)
- Prompt treatment of UTIs
- Biofeedback to train child to recognize bladder sensation and learn to control urethral sphincter relaxation



Pharmacotherapy

Release of Ach → Bladder contraction
Anticholinergic medications → bladder relaxation

β3-adrenoceptor agonist → Detrusor relaxation (Mirabegron)



Alpha agonists →sphincter contraction
Alpha blockers → sphincter relaxation

Case 1

Appu is a 9-year-old boy brought with daytime incontinence and bedwetting

At home and at school

- He is the middle child of three siblings. He has a 12-year-old brother and a 6-year-old brother. His older brother wetted his bed until he was 10 years old. Appu likes playing football and video games with his friends after school. He enjoys going to school and loves math.
- During summer he went on a summer camp and his family doctor prescribed desmopressin to manage bed wetting during the camp but it did not help

Appu...

- He is wetting day and night; both his underpants and his pants are often wet. He usually walks around with it. It often starts with a big wet spot that gets bigger and bigger.
- Mother sends him to the toilet when she sees him holding up, visible by holding manoeuvres, like wiggling.
- After school, when he is playing football outside or videogames, he is wet more often. The imperative urge to urinate is particularly bothersome to him.
- In total, his micturition frequency is about 9× per day.
- He doesn't have to strain while voiding.
- His fluid intake is about 7 glasses a day.
- At night, he wears diapers. He is a deep sleeper and he never wakes up for peeing.
- He has no poo problems, no faecal incontinence, his bowel movements are daily and Bristol stool chart scores 3-4.

Appu…

- there are no suspicions of any behavioural problems.
- His school results are fine and he has normal concentration. He likes to go to school and see his friends.
- Family situation: happy and healthy family situation.
- Impact of his bladder problems: He feels embarrassed when he needs to go often to the toilet especially when he is at school. His wet pants are frustrating but not everyone can see it. Only his best friend knows about his wetting problems. He doesn’t like to stay over with friends.
- The prescribed desmopressin during summer camp wasn’t effective and he was still wet. He doesn’t want to use that again.
- He has never been bullied.

Appu…

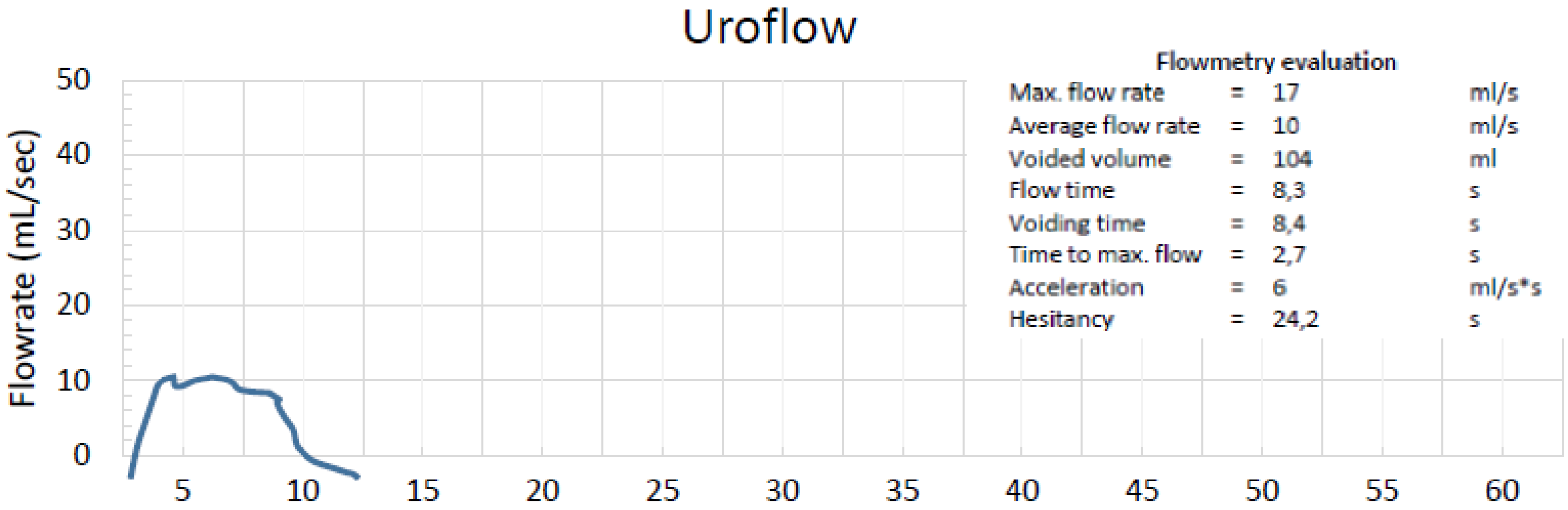
- Physical examination - Neurologically and anatomically, no abnormalities.
- Ultrasound of the kidneys: normal length, normal size, normal ureters.
- Bladder wall thickness after voiding 4 mm.

Bladder diary

Time	Mict vol (ml)	Urine incontinence	Drink (ml)
8.30			200
10.00			200
11.15	70		
11.30		Under pant wet	100
12.30	80		
14.00	90		200
17.00	70	Jeans wet	250
18.00			400
18.30	100		
19.30	100		
Total	6 times		1350

Time	Mict vol (ml)	Urine incontinence	Drink (ml)
8.00			150
10.00	60		200
11.30			200
12.00	20	drops	
13.00			200
13.30	90		
15.30			200
17.00	50	Underpants wet	
18.00			200
18.15	100		
19.00	80		200
19.20	120		
19.40	110		
20.00	120		
Total	9 times		1350

Uroflowmetry



Conclusion

- Urinary incontinence during day and night.
- Based on symptoms and bladder diary, a diagnosis of an overactive bladder is made.
- He has no constipation or other complaints.

Treating Appu

- Ensure motivation
- Since he has a small bladder volume, prescribed Oxybutynin 2.5 mg twice a day, before school and after school, to help him to control his bladder urgency.

Final goal:

- At the end of the urotherapy treatment, he has less or no wetting accidents during the day and night. He and his parents are satisfied.

Treating Appu

Short term goals:

1. Explanation & demystification:

- He and his mother have gained an adequate understanding of how the bladder works an what goes wrong in an overactive bladder. They are aware of why it is difficult to stay dry during the day:

2. Voiding regimes: He and his mother know what average fluid intake is appropriate for his age and how to properly distribute the fluid intake throughout the day.

- How to void: he has gained insight into his toilet position, knows how to adjust it, and what aids are needed for this.
- When to void: He understands that he should go to the toilet ‘’when you feel you have to go, you need to go’’
- How often to void: He understands that when and how often he should go to the toilet., a bladder diary will be his feedback tool
- Inhibit urgency by prescribing anticholinergics, this will give him some relief regarding urgency complaints.

Long term goals:

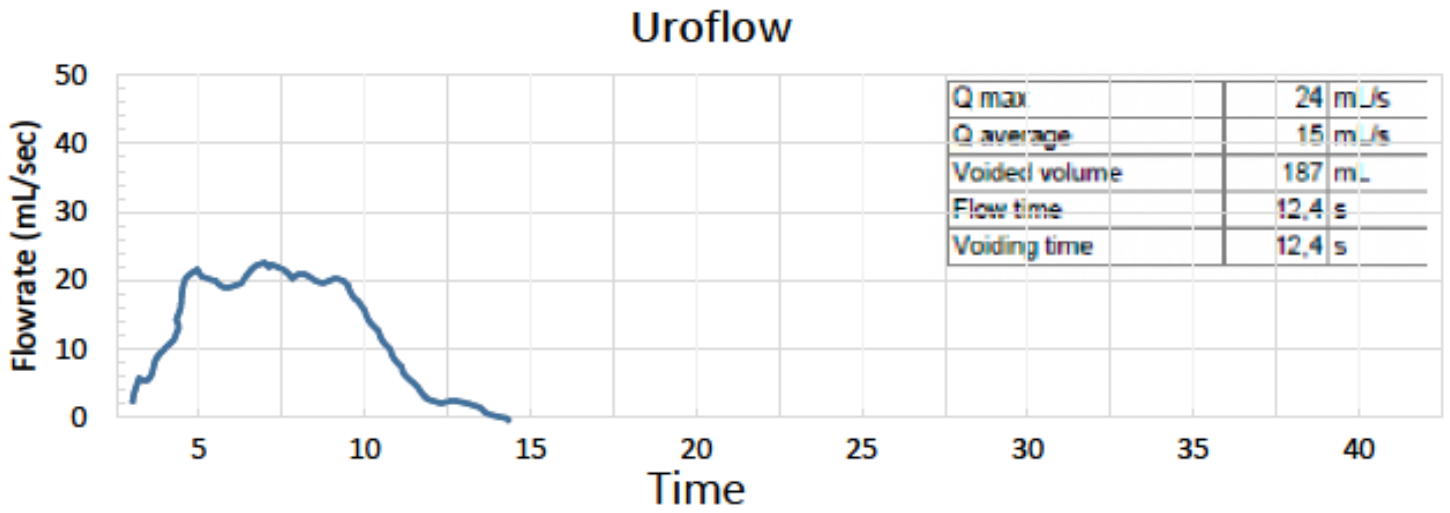
- 1. An increase in his maximum voided volume, according to his expected bladder
- capacity
- 2. He will be able to inhibit urgency, increase the time that he can hold his urine
- 3. He will be dry at night

Trainin result at 3months

He has fewer wetting accidents during the day, 2-3 per week and when he is wet, it's only his underpants, not his trousers anymore. With full days program and distractions when he is playing with friends, he becomes wet. He is aware that it will take him effort to stay dry during the day.

He and his mum are satisfied with the results. He has less urgency complaints, he had bowel movements every day. His voiding frequency has improved to 6-7 times a day and his bladder volume increased to max 200 mls.

Wetting still occurs during the night, and he is wearing a diaper during the night. He would also like to become dry at night.



Training results from past week

Day	Number of Drinks/	voidings	Dry/wet	Notes from his mom
Monday 1 December	6 glasses	6		Normal school day, went to tennis after school
Tuesday 2 December	7	8		Played with friends after school, went to the toilet timely
Wednesday 3 December	6	7		Wet just before dinner, had an exciting day, due to his brother's birthday.
Thursday 4 December	7	9		Did great, had a few drops in his pants. Smaller than 2 euro coin.
Friday 5 December	5	8		went to school, trained hard.
Saturday 6 December	8	7		He was dry till afternoon then he became wet. He didn't notice his bladder due to playing with his father and brother.
Sunday 7 December	6	7		We went to the forest.
Monday 8 December	5	6	Still dry ...till phone call	

Six months later

- After completing his bladder training, Appu learned during the training how to stay dry during daytime.
- The most difficult moments are still after schooltime, while playing with friends or videogames.
- He voids 6-7 x per day. He has measured his maximum voided volume at home, and it has increased to 250mls, although this volume is still small according to his expected bladder
- capacity (EBC – 330ml).
- Beware that constipation can be a contributory factor for OAB, incontinence and bedwetting and hence always check defecation habit/bowel movement – may develop constipation due to
- has no severe side effects of Oxybutynin, no dry mouth, and he still has bowel movement every day, Bristol stool chart is 3 and he has no faecal incontinence.

- At night he is still wet, and he is motivated to train -This is the most important factor in our decision to start an alarm treatment.
- The plan is to start a bedwetting training with alarm.
- Due to his small bladder volume, prescribing desmopressin (Minrin) is not preferred.
- alarm treatment in combination with oxybutynin will be sufficient.

6 week later

- Appu proudly told us that he has achieved 14 dry nights in a row.
- He is still dry during day and during night.
- He is able to continue his good drinking, voiding and bowel habits.
- He may stop his alarm treatment.

Appu has a happy ending…

- *Ending phase*
- Three months later he is still dry during the night and day, and then the medication can be stopped.
- Again 3 months later, if there are lasting results, the treatment is successfully completed.

Case 2: Dysfunctional Voiding Treatment in a 10 year Old Girl

Ameena is 10 years old and suffers from wetting and UTI's for the past 2 years.

- Ruled out any kidney problems or reflux. She has
- no symptoms of neurological problems with bladder and has mild constipation which is being treated with lactulose.
- **At home and at school**
- a healthy girl, she is the middle child of 3 siblings.
- Happy home
- Well adjusted at school

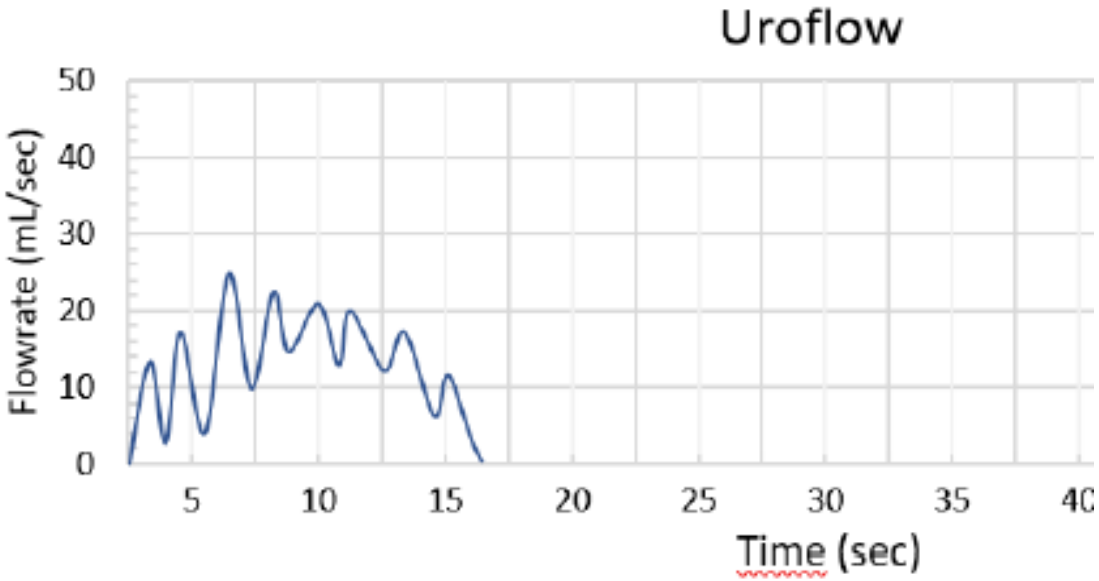
Assessment

- She poops 2-3 times a week with stool like Bristol 4. She has no faecal incontinence or pain when she poops. She doesn’t like to go to the toilet in school to poop and avoids this.
- Once a week, she can have large stools that clogs the toilet. She never needs to run to the toilet when she needs to poop and has no pain in the stomach or bloated belly.
- She pees 3-4 times a day but can avoid peeing in school. She has urgency few times a week and has small leakage of urine 2-3 times a week when she comes home from school.
- She pees with a normal unabrupt stream and has no hesitancy or need to push the urine out.
- At night she has no enuresis but a few nights a week, she wakes up and rushes to the toilet with drops of urine leaking in her underwear. She has no problem waking up at night.

Further evaluation

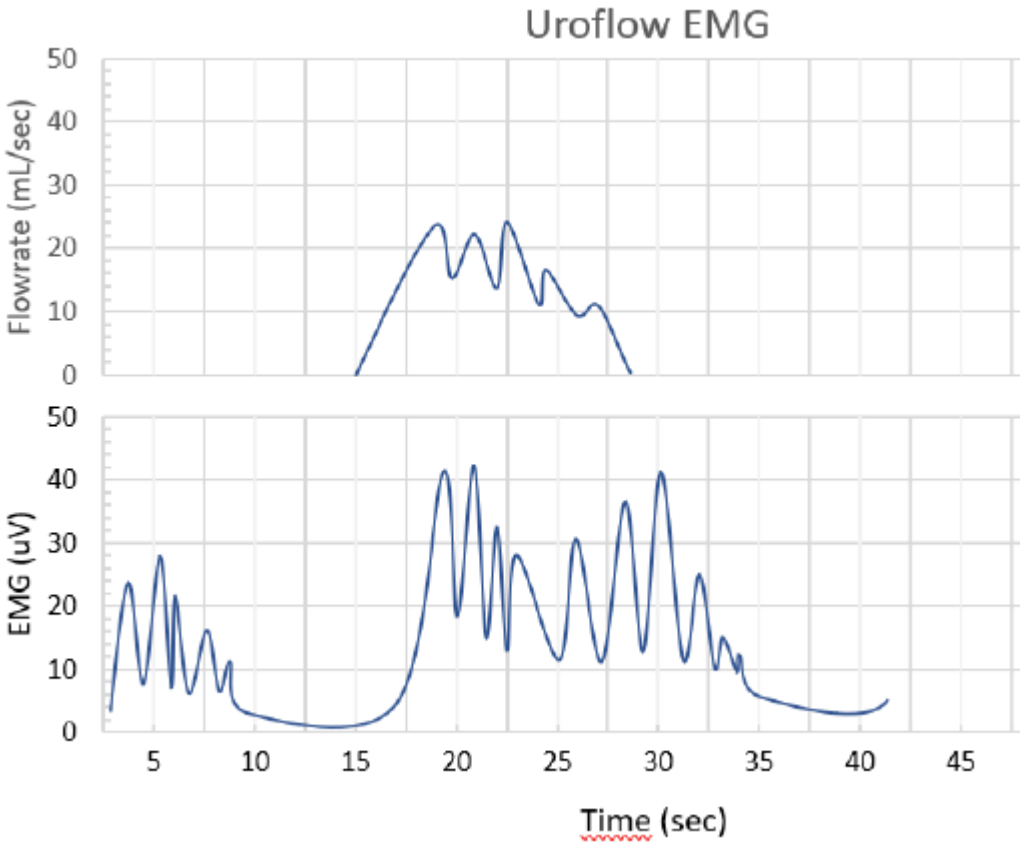
- Transabdominal ultrasound - rectum width 2,4 cm. The detrusor muscles look a bit thick and measures 5 mm, measured while the bladder was empty.

- Uroflow – staccato flow. Qmax- 25ml/s



EMG-uroflow

- She has trouble in relaxing the pelvic floor when she pees.
- This time she voids 250 ml with a staccato shape curve and has about 30 ml residual urine after.
- She didn’t feel that the stream was uneven or that she contracted the pelvic floor.



Managing Ameena

Ameena’s motivation for doing the treatment is assessed as well as her parents’ support.

- Final goal: Complete resolution of urine incontinence and normalisation of voiding function
- Short term goals: Increasing the voiding frequency and be able to relax pelvic floor during voiding.
- Long term goals:

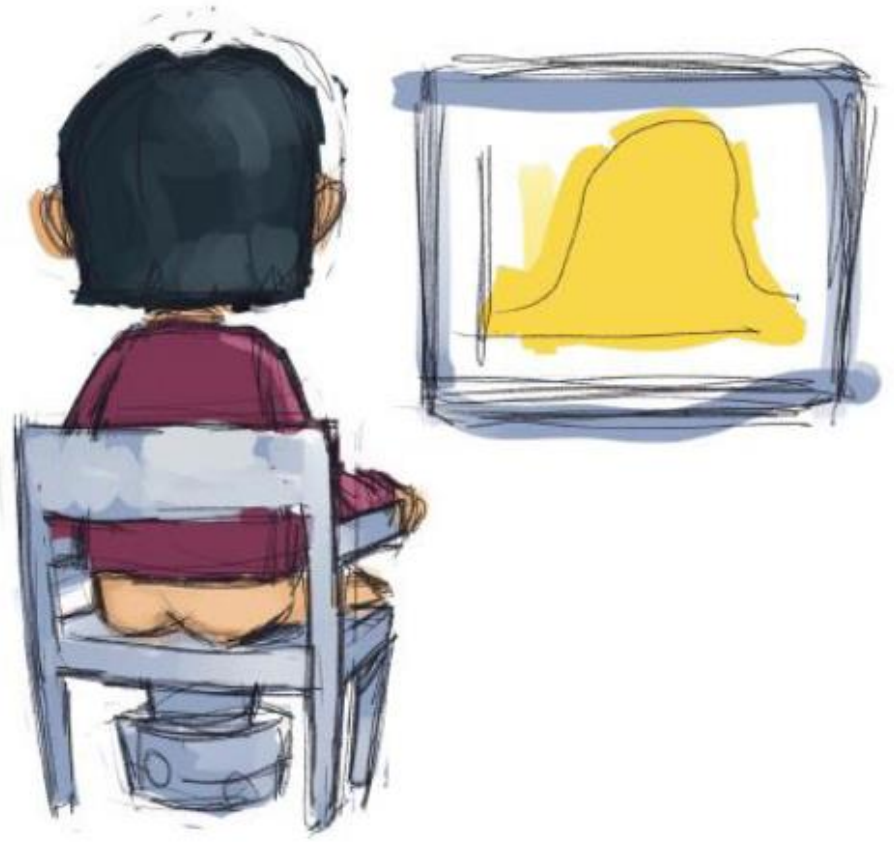
1. Normalization of bladder capacity
2. Normalization of micturition frequency
3. Voiding with relaxed pelvic floor
4. No residual urine

Good micturation habits

- Go to the toilet and pee 3 hourly during daytime. First time in the morning and last time before going to bed.
- Drinking should be done spread out through the day with at least 6-8 glasses of water based drinks.
- She is to focus on trying to relax the pelvic floor when peeing and listen to the urine stream. If it loses power, she shall take a deep breath and exhale slowly with semiclosed mouth in order to relax the pelvic floor optimally. She should also relax the gluteus muscles, abdomen and thighs during voiding.

Biofeedback program

- play a video game with the pelvic floor on the computer for a few minutes.
- By contracting and relaxing the pelvic floor, she is controlling a fish catching bubbles in a 5 second contraction and 5 seconds relaxation.
- She can do this but gets tired quickly and starts to help by contracting the gluteus muscles. The game is then stopped.



correct posture

incorrect posture

Sitting position on the toilet

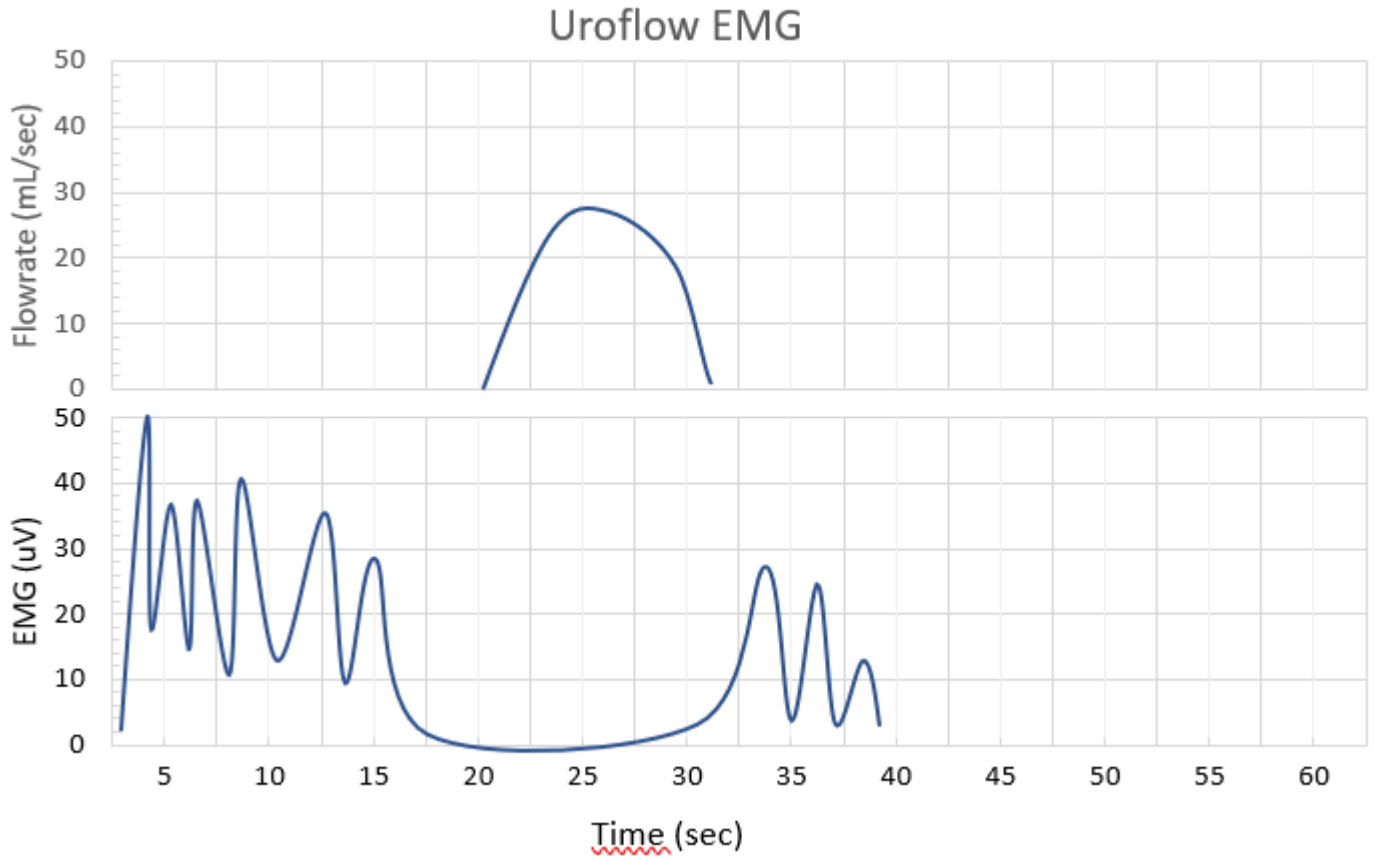
To void effectively, a correct sitting position is vital. Sitting with good balance makes it easy to relax the abdomen and pelvic floor. The child should sit with the back upright or slightly forward leaning, maybe supporting the elbows on the thighs. The feet are preferable supported on a foot stool if the floor cannot be reached. Sitting back on the toilet with support for the thighs also helps.

2 months later

- She now pees 6-7 times a day and uses the toilet 1-2 times during schooltime.
- Her urgency has been much less since the first visit and her urine incontinence has improved and has happened 1 time in the past weeks.
- Her urgency during night-time has also been better with no urine in the underwear during the night.
- Her bladder diary shows a normalization in micturition frequency.
- She drinks better than last time, and she has no urine incontinence on these days.
- Her bladder capacity has increased to 91 % of EBC and this is normal.
- She has been working on relaxation on the toilet when she pees.

Uroflow EMG

- better relaxation this time with a completely silenced pelvic floor. She pees 208 ml with Q-max 28 ml/sec in 13 seconds. She has no residual urine. She no longer has dysfunctional voiding.



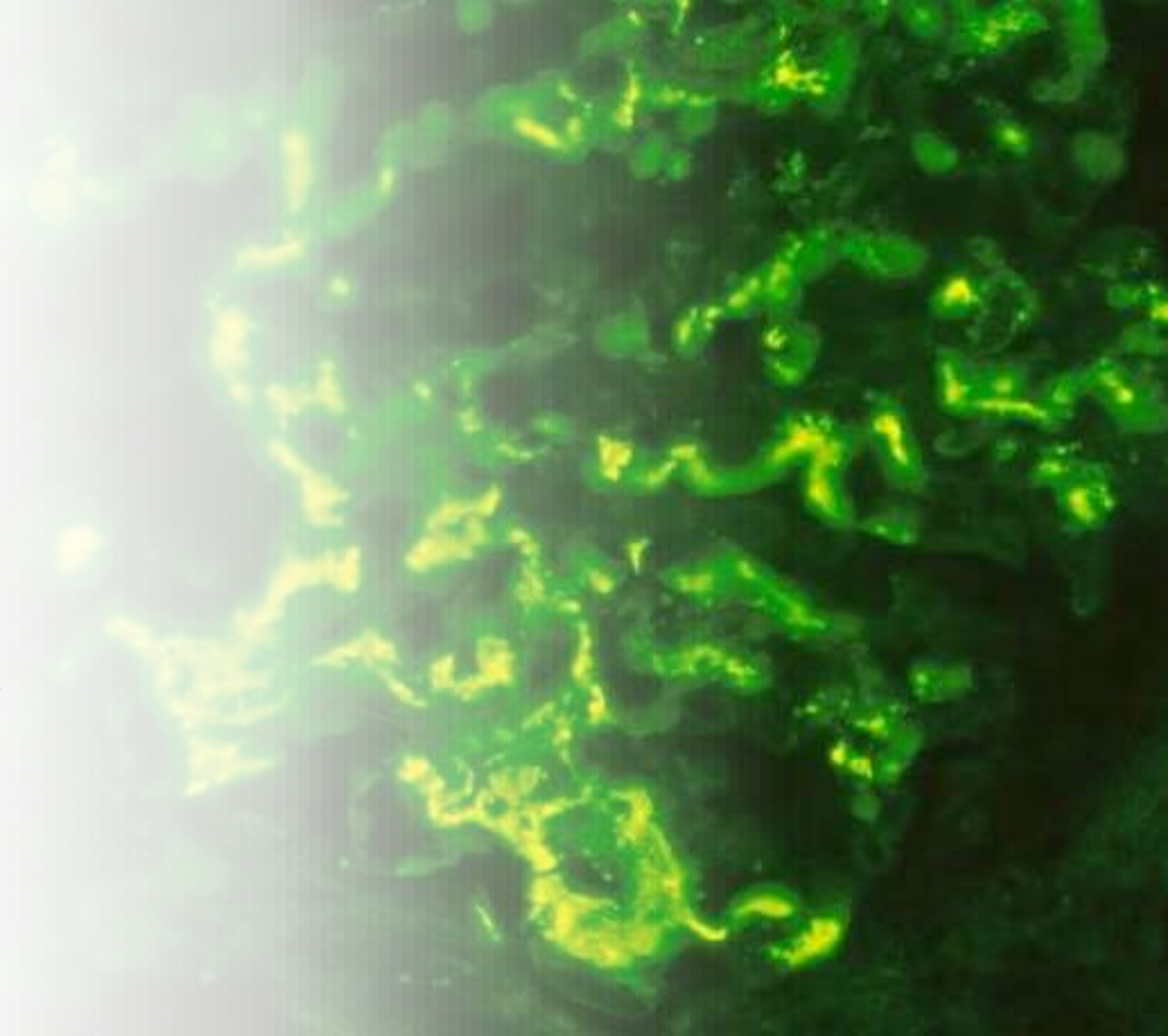
Thank you

Current concepts and recent advances in IgA nephropathy

Dr Satish Balan MD DM DNB

Senior Consultant Nephrologist

KIMSHEALTH Trivandrum



The case

- 15 year old boy presented with painless macrohematuria following respiratory illness
- No edema, no other symptoms
- BP 110/80 normal for age
- Creatinine was 0.7 mg/dL
- Proteinuria was 2+ urine showed plenty of RBC
- Follow up after two weeks – normal creatinine, RBC 10-12 and proteinuria 2+ with ACR 1680. Decided to follow up
- After two more weeks, RBC 10-12 and ACR 1620

Renal biopsy done

Turned out to be IgA nephropathy

Oxford MEST C classification M1 E0 S1 T0 C0

What do we understand about IgA nephropathy ?

first described in 1968 in a one page submission – IF was a new tool at that time

Not many believed him but soon had many converts

MILESTONES IN NEPHROLOGY
Mark A. Knepper, Feature Editor
J Am Soc Nephrol 11: 1957–1959, 2000

Les dépôts intercapillaires d'IgA - IgG

par MM. J. Berger et N. Hinglais (*)
with comments by
LILIANE STRIKER
Reprinted from J. Urol. Nephrol. (Paris) 74: 694–695, 1968

RESUME

Sur les biopsies rénales de 25 malades, ont été mis évidence par immunofluorescence des dépôts intercapillaires fixant le sérum anti-IgA et moins intensément les sérums anti-IgG et anti-β_1 C-globuline. En revanche, il n'y avait aucune fixation sur ces dépôts, des sérums anti-IgM, anti-fibrinogène, anti-albumine, anti-coeruléoplasmine, anti-α_2-macroglobuline et anti-β-lipoprotéine. Les dépôts intercapillaires étaient présents dans tous les glomérules.

L'existence de dépôts intercapillaires n'avait été reconnue en microscopie optique que dans 3 cas. Dans la moitié des cas, le diagnostic histologique avait été celui de glomérulonéphrite focale: en effet, une partie des glomérules présentaient des lésions focales hyalines ou quelquefois nécrotiques, mais les autres glomérules paraissaient normaux. Dans les autres cas, le diagnostic histologique avait été celui de glomérulonéphrite inclassée, de néphrite chronique, d'altérations artériolaires isolées ou de rein normal.

La présence de dépôts denses et finement granuleux situés entre la membrane basale et les cellules intercapillaires a été vérifiée par la microscopie électronique dans les 10 cas qui ont été étudiés par cette technique.

Tous les patients avaient une protéinurie modérée et une hématurie microscopique. Dans la moitié des cas, étaient survenues une ou plusieurs hématuries macroscopiques, suivant habituellement une angine. La fonction rénale était normale dans la grande majorité des cas. Trois malades étaient hypertendus.

La durée d'évolution de la néphropathie depuis sa découverte jusqu'à la biopsie allait de quelques mois à douze ans.

Il apparaît donc que dans la plupart des cas de glomérulonéphrite «focale» chronique, il existe en plus des lésions focales, des dépôts intercapillaires diffus. Cette constatation, outre son intérêt théorique, a une utilité pratique: l'immunofluorescence permet de faire très aisément le diagnostic de cette variété de glomérulonéphrite dans les cas où la microscopie optique ferait croire à tort que le rein est normal ou atteint d'autres lésions.

(*Clinique néphrologique* [Professeur J. Hamburger], *Hôpital Necker, Paris.*)

(*) Chargé de recherches au C.N.R.S.

GUEST COMMENTARY

Liliane Striker

Department of Medicine, Division of Nephrology, Laboratory of Renal Cell Biology
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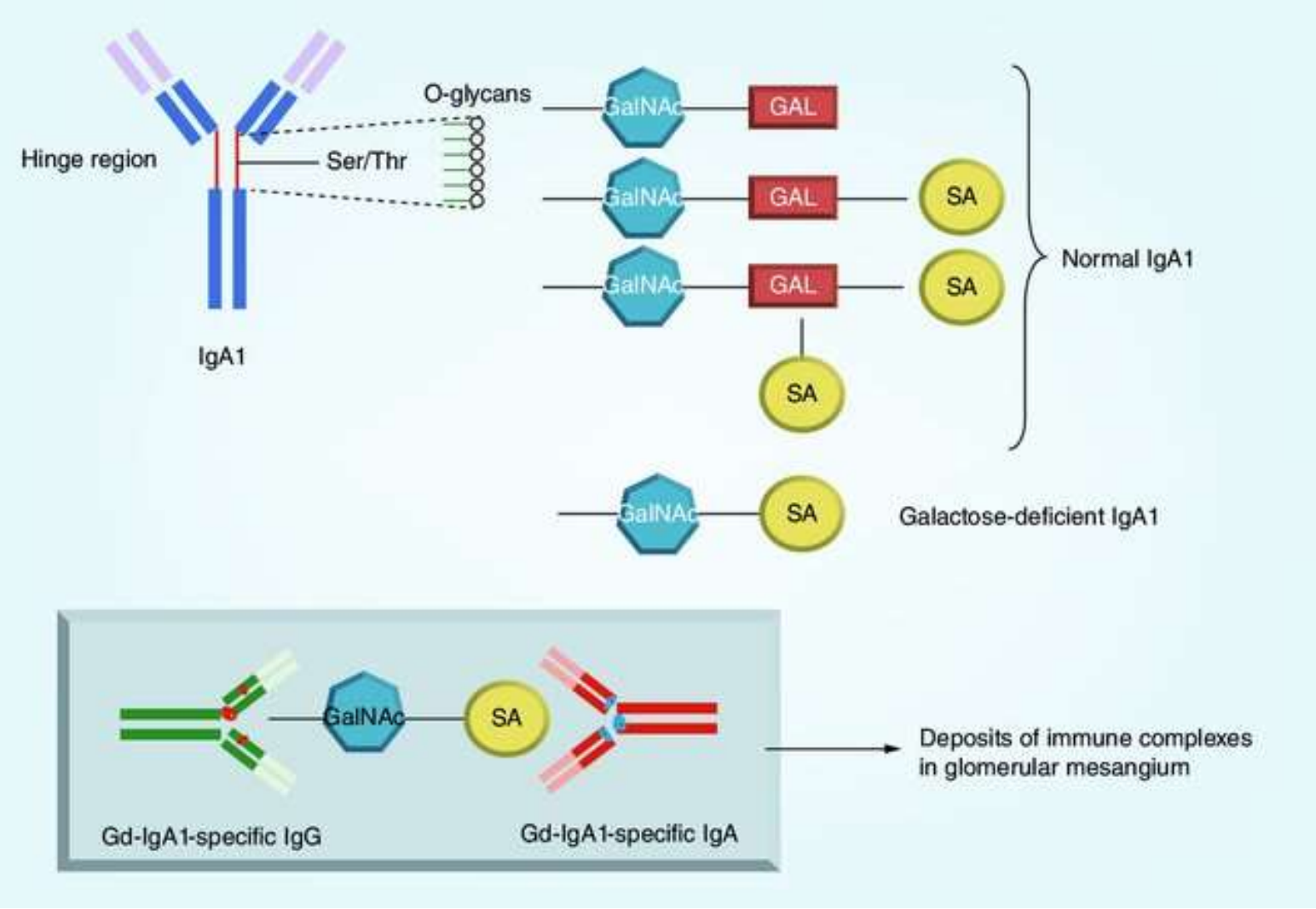
This month, the editors have chosen to waive the usual rule that the author of the original manuscript comment on the work and its circumstances for the JASN readership. Dr. Jean Berger, who recently retired as Professor of Pathology, has chosen not to revisit the past. Because I was one of the few pathologists mentored by Dr. Berger between 1964 and 1970, I was asked to comment on a small article that appeared in French in 1968 in the Journal d'Urologie et de Néphrologie (1). This article dramatically altered the face of clinical nephrology.

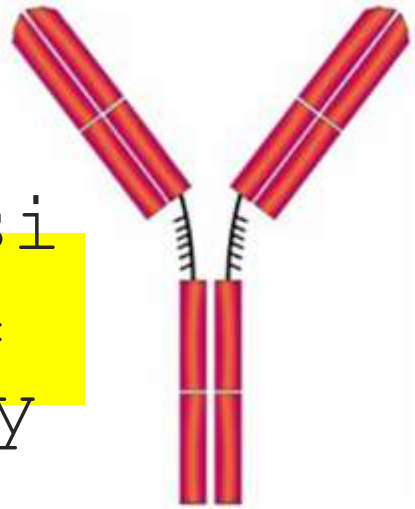
Dr. Berger presented on a series of patients with recurrent hematuria who had unusual biopsy findings at the winter meeting of the French-speaking Société de Néphrologie, which was held in Paris. All of these patients had focal and segmental glomerular lesions by light microscopy. However, they had a characteristic immunofluorescence pattern that consisted of the presence of deposits of immunoglobulin IgA and that was distributed in a diffuse fashion and delineated the mesangial regions of the glomeruli while the peripheral loops were uninvolved. IgA was associated with less conspicuous deposits of IgG and C3. This presentation was received with interest but a certain degree of skepticism. Was this really a new disease as claimed by its father, or was this an immunofluorescence finding with little general significance? Many of the members of the audience knew little about IgA; furthermore, immunofluorescence microscopy was still considered an experimental research tool with little clinical application and/or significance. However, Dr. Berger was considered to be a brilliant investigator. The importance of this discovery did not escape the members of the Société de Néphrologie for long, and in the ensuing months and years, antibodies to IgA were applied to a wide variety of renal diseases.

The French Society of Nephrology was the most exciting forum. The meetings were held in the old "amphitheater" at Necker's Hospital with antiquated wooden benches,

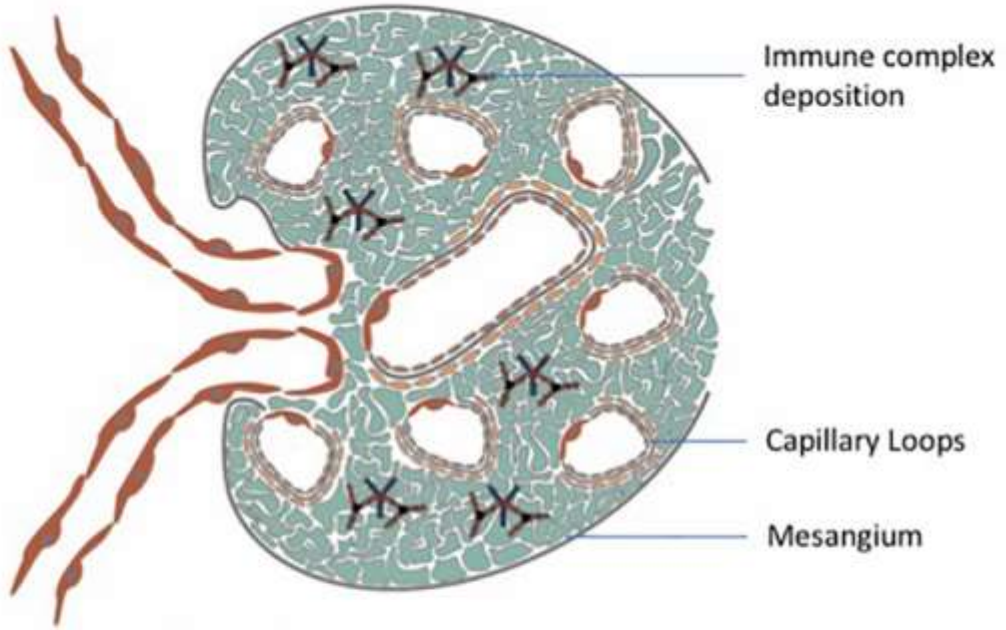
Current understanding of pathogenesis



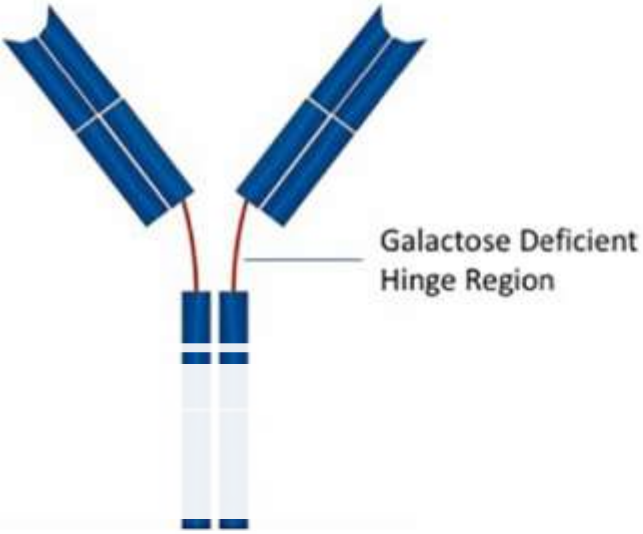
Pathogenesis – the 4 hit theory



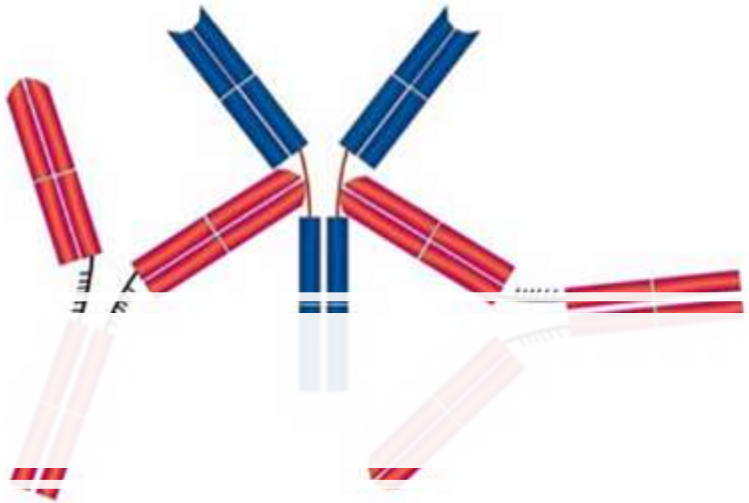
Hit 2: Anti-Gd-IgA1



Hit 4: Mesangial Immune Complex Deposition

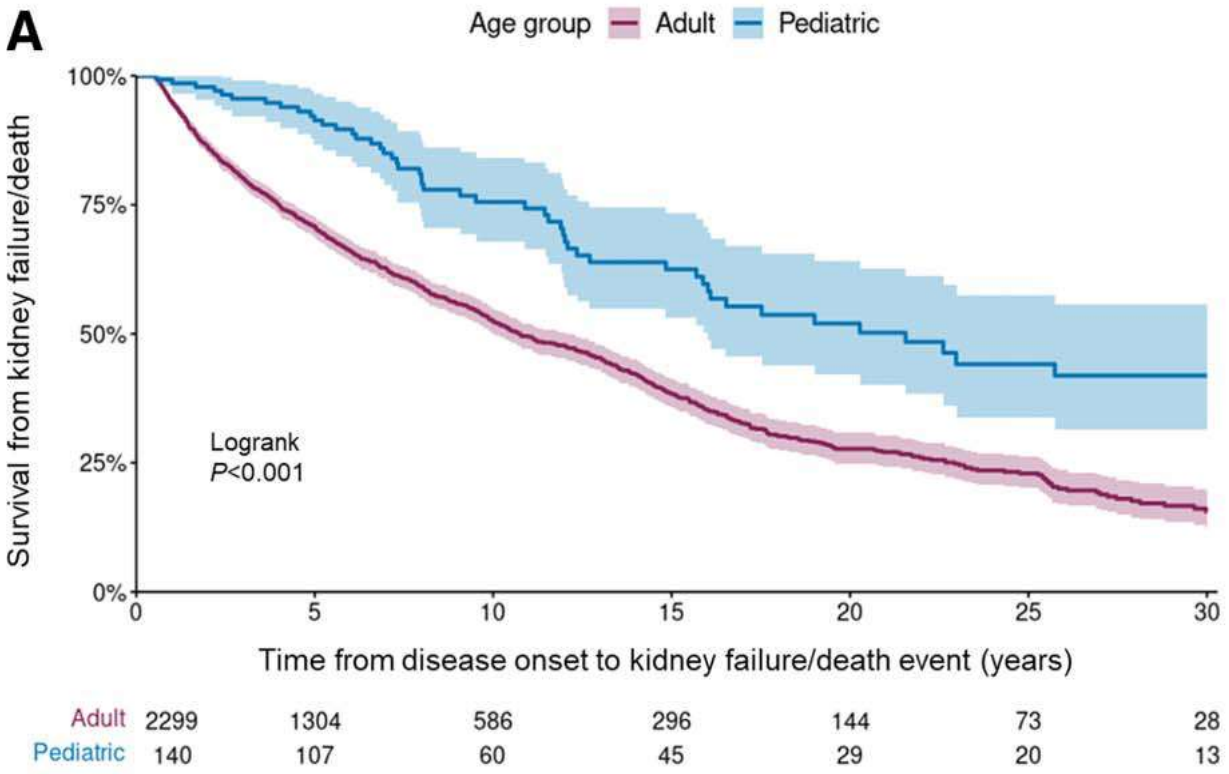


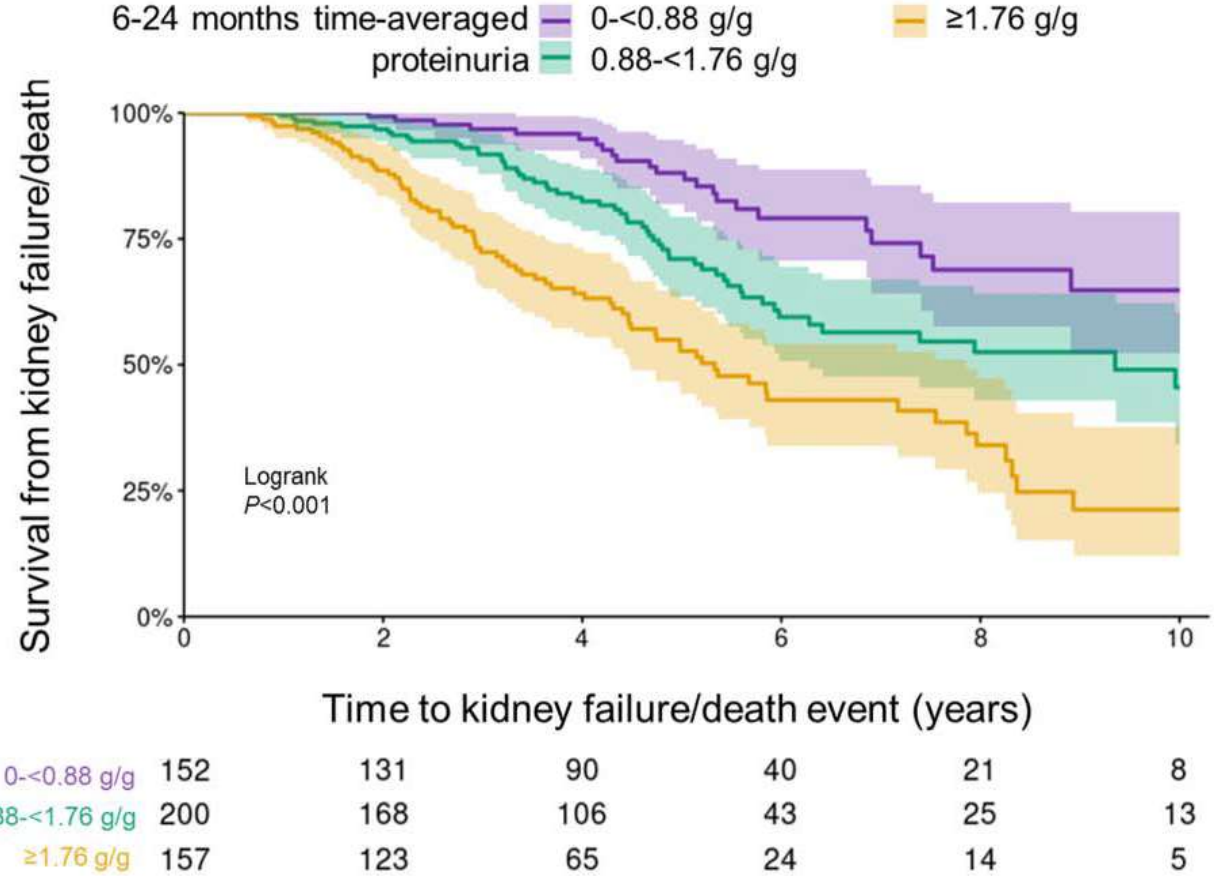
Hit 1: Galactose Deficient IgA1



Hit 3: Anti- Gd-IgA1 - Gd-IgA1 complexes

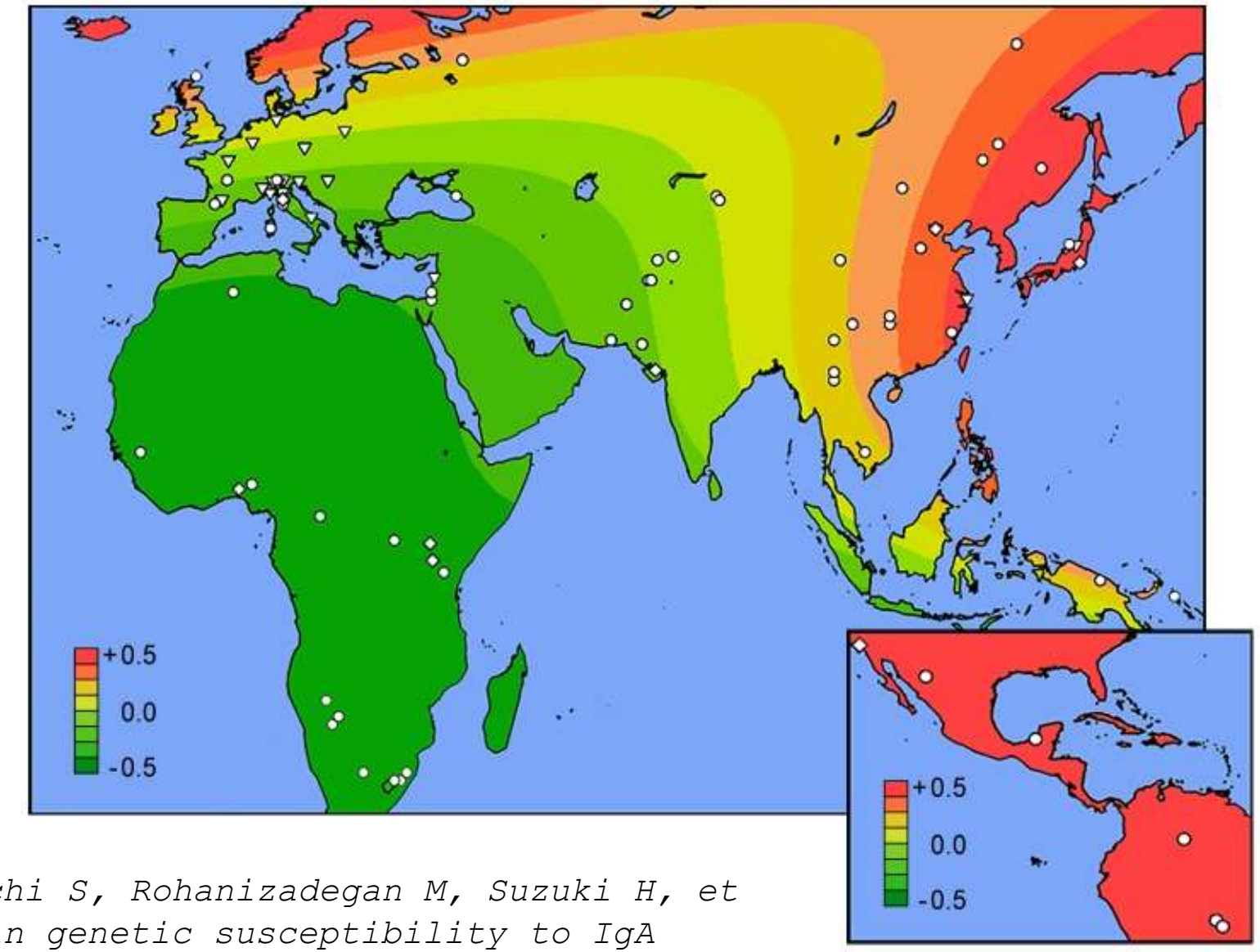
Outcomes in children/adults with IgAn *(UK National Registry of Rare Kidney Diseases (RaDaR)*





Pitcher D, Braddon F, Hendry B, Mercer A, Osmaston K, Saleem MA, Steenkamp R, Wong K, Turner AN, Wang K, Gale DP. Long-term outcomes in IgA nephropathy. Clinical Journal of the American Society of Nephrology. 2023 Jun 1;18(6):727-38.

Geospatial risk analysis



Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8(6):e1002765. doi: 10.1371/journal.pgen.1002765. Epub 2012 Jun 21. PMID: 22737082;

DIAGNOSIS AND PROGNOSTICATION

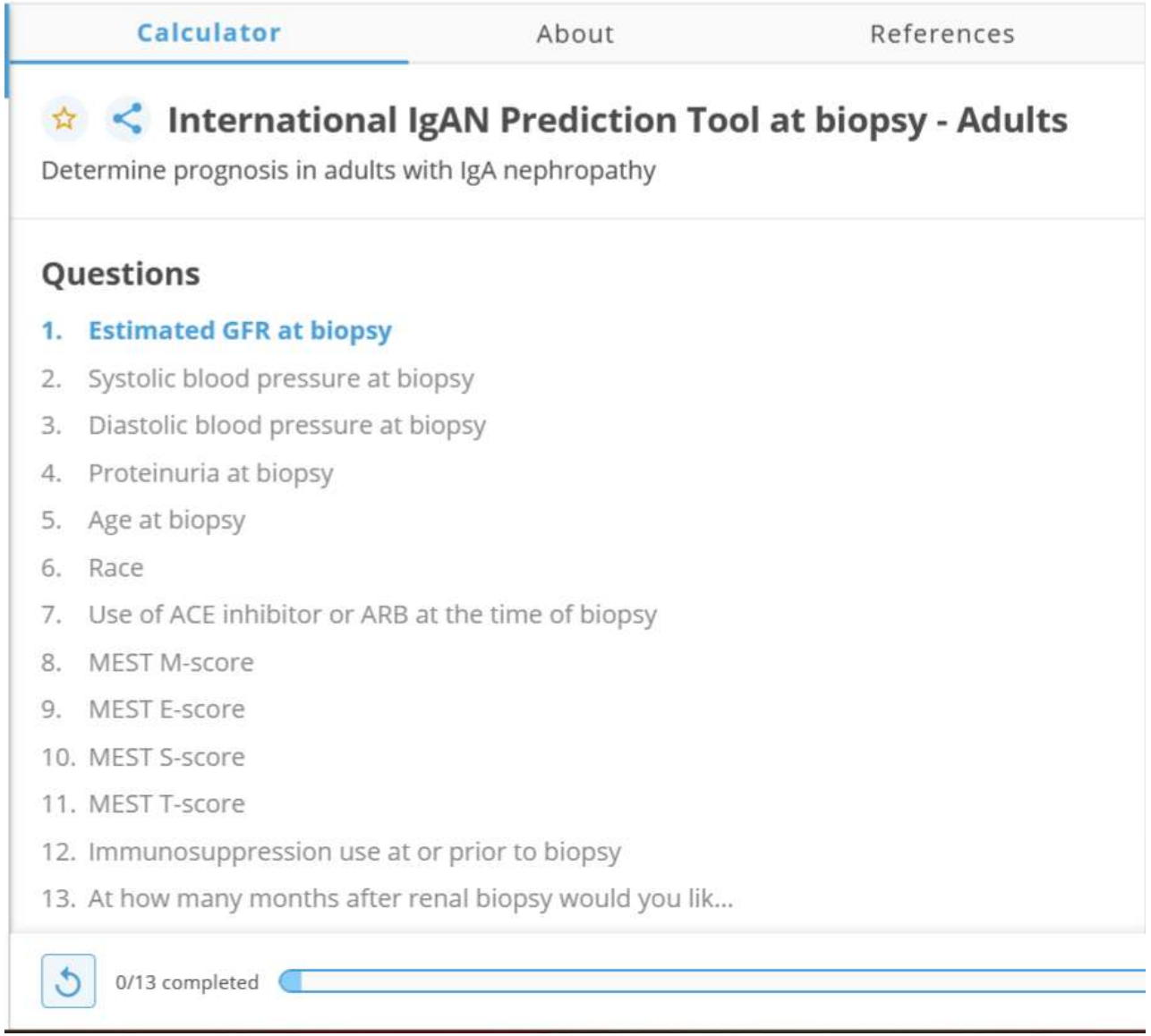
OXFORD CLASSIFICATION OF IGA NEPHROPATHY

MEST	DESCRIPTION	SCORE
M	Mesangial Hypercellularity	M0: <50% Glomeruli M1: >50% Glomeruli
E	Endocapillary Hypercellularity	E0: Absent E1: Present
S	Segmental Glomerulosclerosis	S0: Absent S1: Present
T	Tubular Atrophy	T0: Absent or <25% tubules T1: 26-50% tubules T2: >50% tubules
C	Crescent	C0: Absent C1: 1-24% Glomeruli

Oxford IgA classification - MEST C score

- Can be used for prognostication but not for treatment

IgA nephropathy risk score

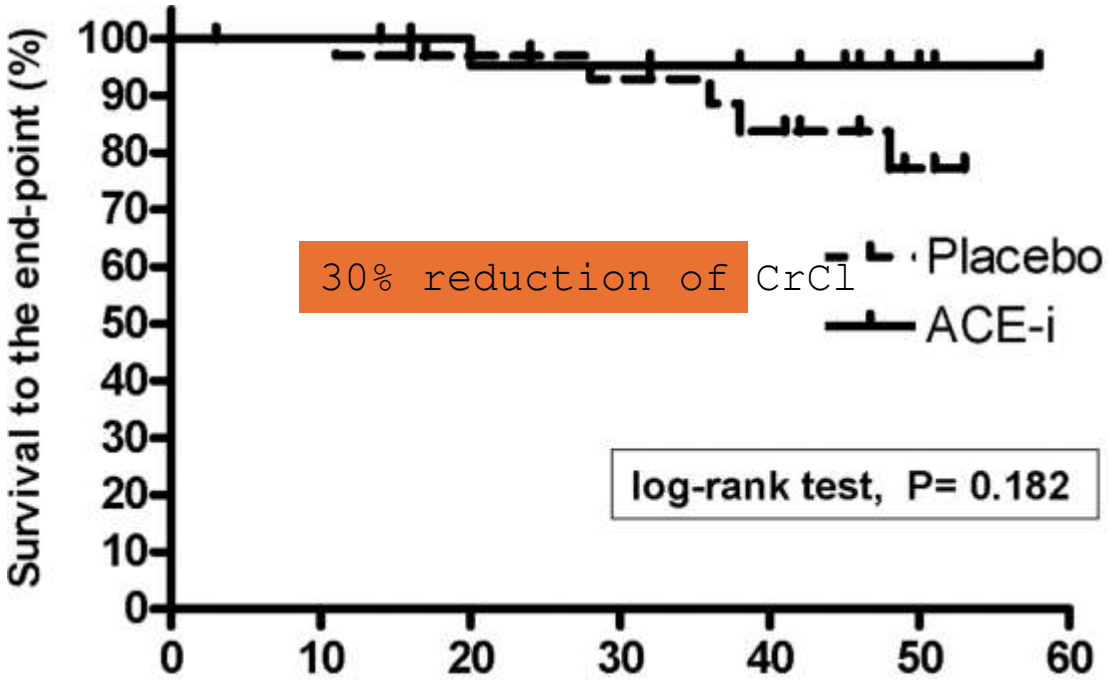


Our case

- 15 year old boy
- Normal renal function and normal blood pressure
- M1 S1
- Proteinuria ACR 1680 with microhematuria

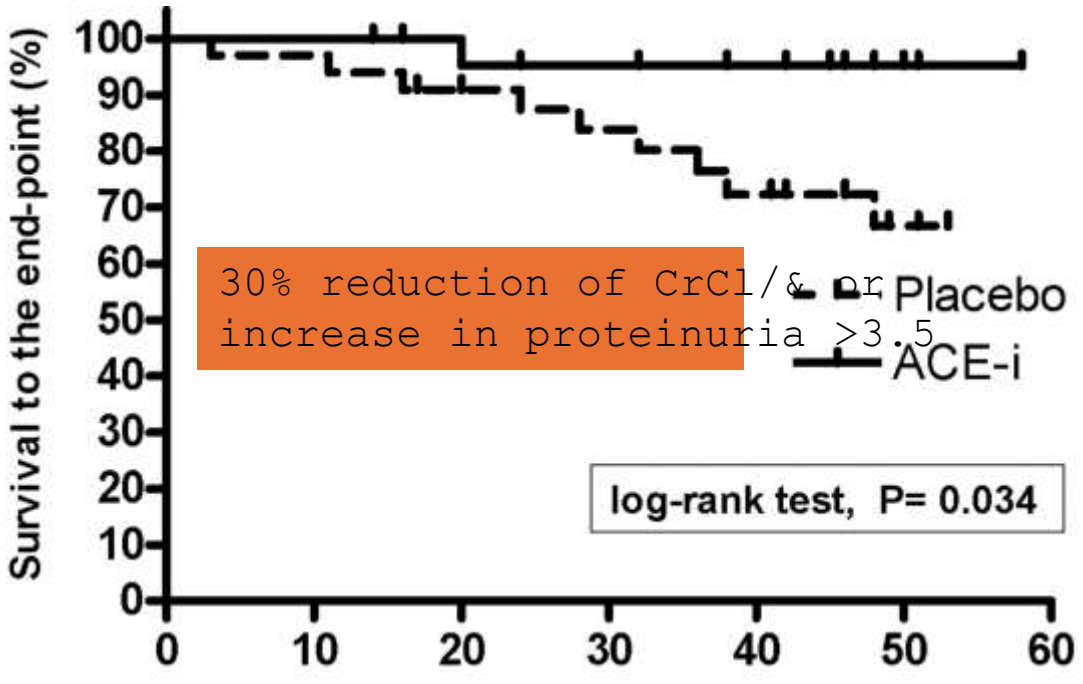
- What should we start for him?

Evidence for the use of RASi



Subjects at risk

ACEI	32	23	20	17	15	8
PLACEBO	34	32	26	23	16	6



Subjects at risk

ACEI	32	23	21	17	15	8
PLACEBO	34	32	27	24	17	6

Coppo, Rosanna; Peruzzi, Licia*; Amore, Alessandro*; et al, on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group. IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA*

RASi

- Child was started on telmisartan 20 mg per day and increased to 40 mg per day
- BP around 90-100 systolic on this
- After about two months proteinuria dropped to ACR 820mg/g

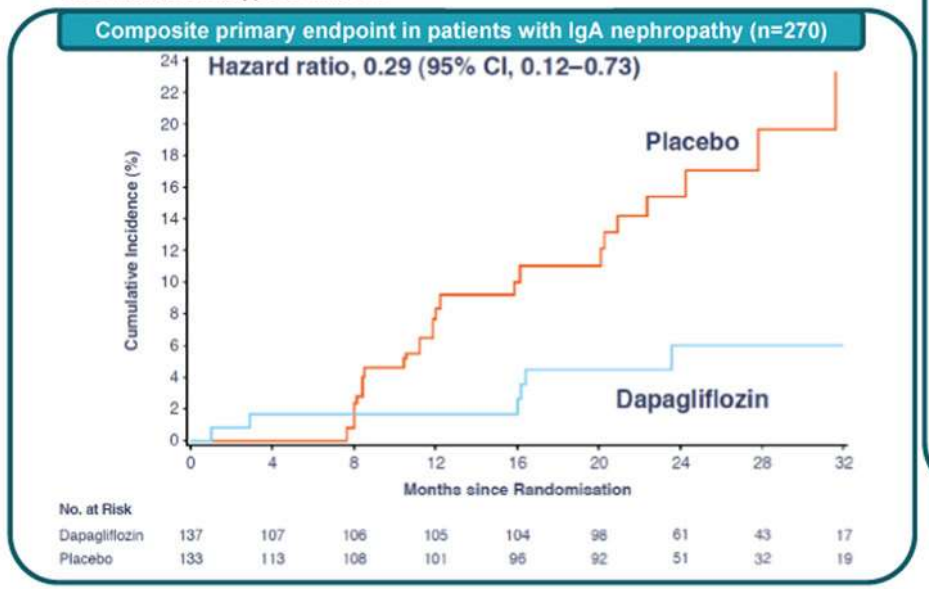
SGLT-2i in IgAn – DAPA CKD SUBGROUP

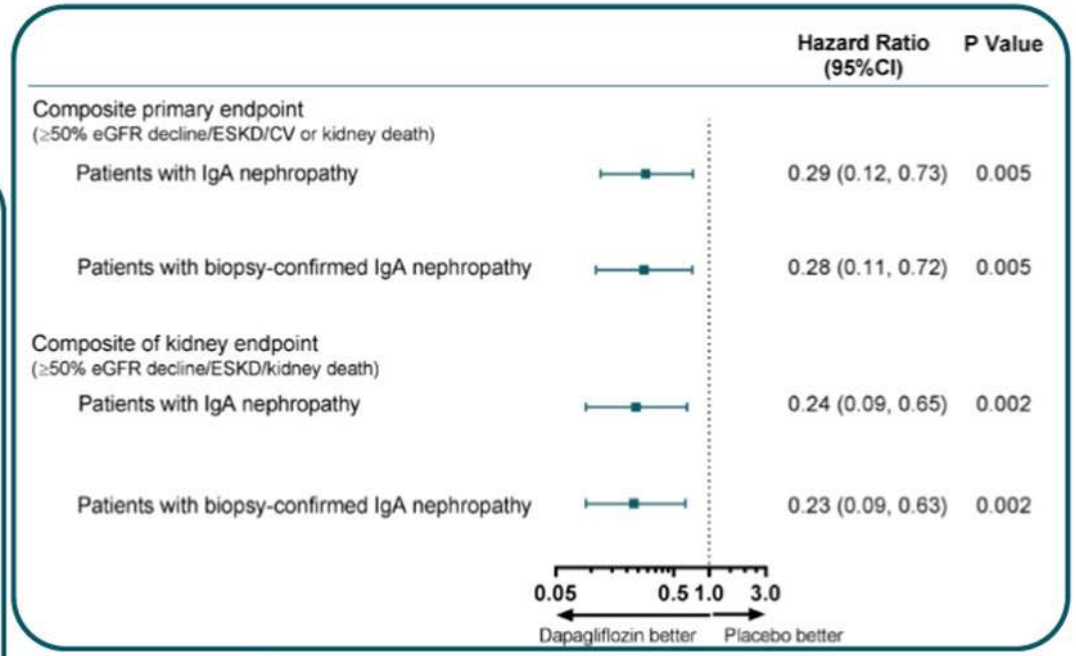
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m²
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**





IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

CONCLUSION:

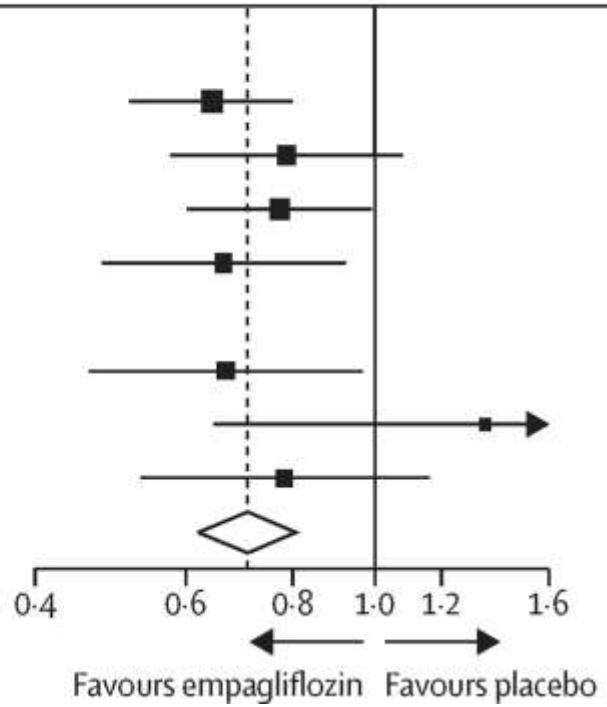
In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

kidney INTERNATIONAL ISN

Wheeler et al, 2021

EMPA KIDNEY TRIAL IGA NEPHROPATHY SUBGROUP

	Events/participants		Hazard ratio (95% CI)	$p_{heterogeneity}$
	Empagliflozin	Placebo		
Causes of kidney disease				0·62
Diabetic kidney disease	137/1032	189/1025	0·64 (0·52–0·80)	
Hypertensive or renovascular disease	72/706	87/739	0·79 (0·58–1·08)	
Glomerular disease	115/853	139/816	0·77 (0·60–0·99)	
Other disease or unknown	60/713	89/725	0·67 (0·48–0·92)	
Types of glomerular diseases				0·25
IgA nephropathy	51/413	67/404	0·67 (0·46–0·97)	
Focal segmental glomerulosclerosis	17/98	13/97	1·35 (0·65–2·81)	
Other glomerulonephritis	47/342	59/315	0·78 (0·53–1·16)	
All participants			**0·71 (0·62–0·81)**	



1.Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial *Judge, PK et al. The Lancet Diabetes & Endocrinology, Volume 12,*

Nephrol Dial Transplant, 2024, 39, 907–909
https://doi.org/10.1093/ndt/gfae029
Advance access publication date: 2 February 2024

SGLT2 inhibitors: approved for adults and cats but not for children with CKD

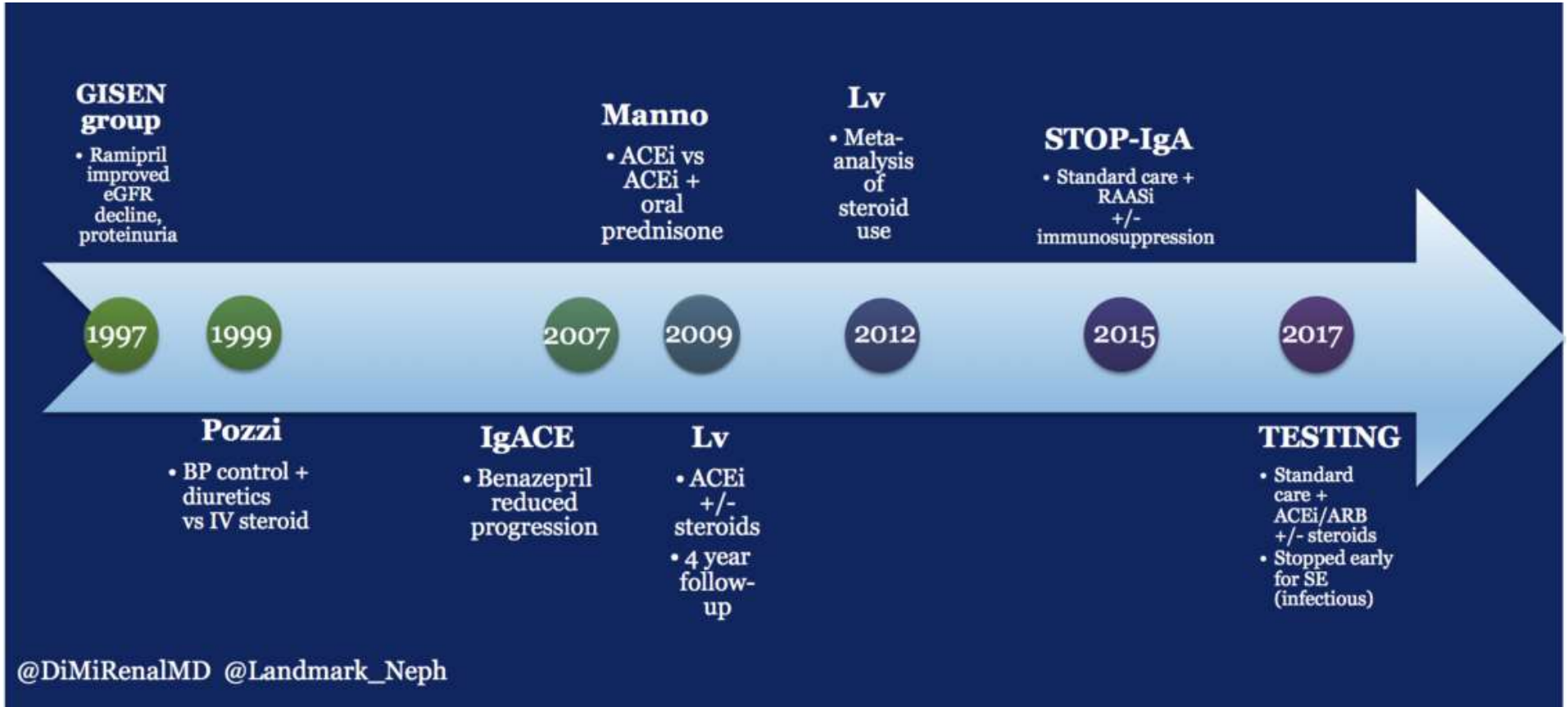
Oliver Gross [1], Dieter Haffner [2], Franz Schaefer[3] and Lutz T. Weber[4]

OUR CASE

- After about two months of telmisartan, proteinuria dropped to ACR 820mg/g
- SGLT2i was not started as there is lack of evidence in children
- Small study by Choi et al in 22 children showed safety and some efficacy
- Sooner or later will need to use

Steroids in children

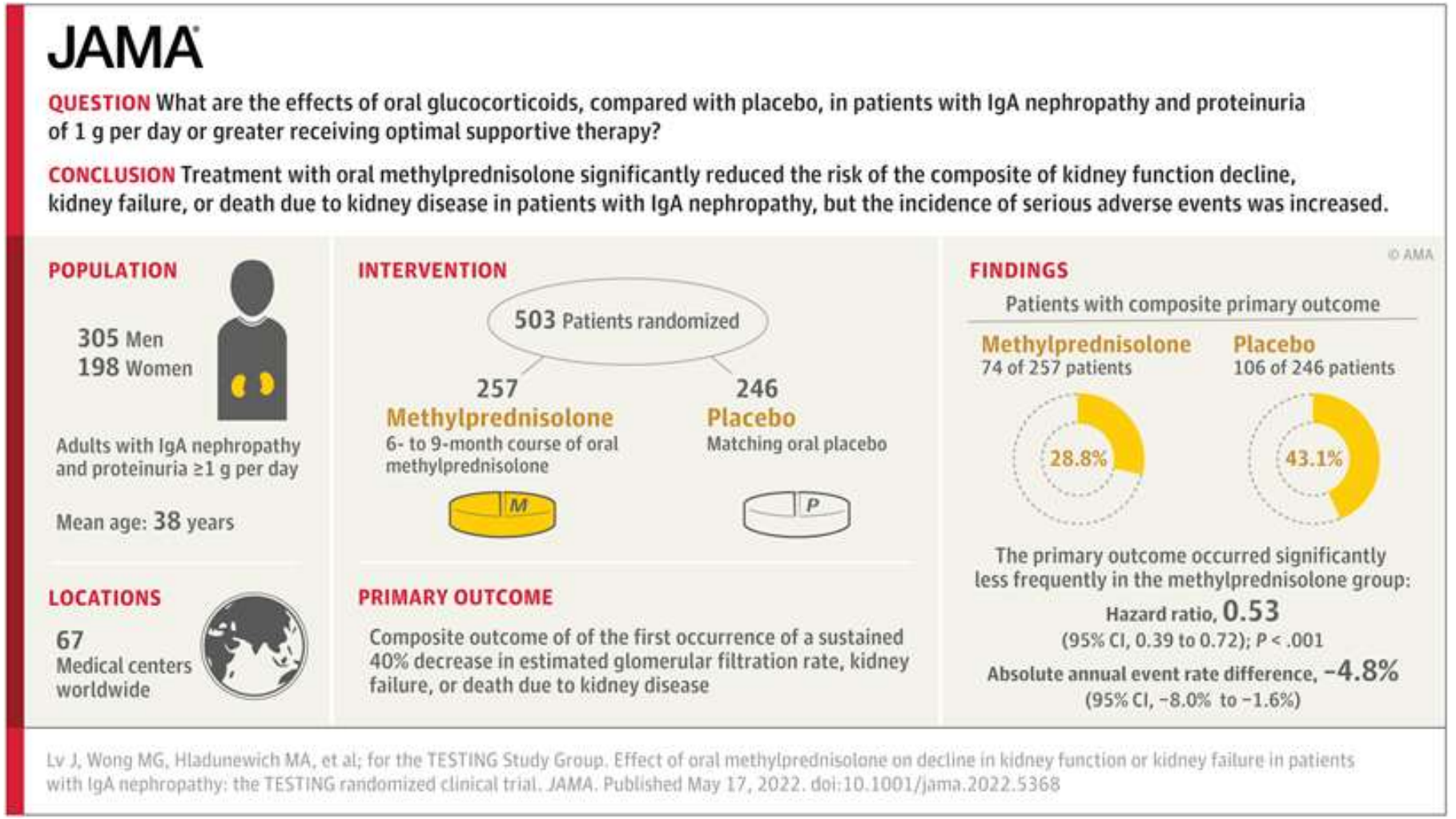
- In general use of steroids more in children with IgAn and proteinuria >1g than in adults



TESTING TRIAL and steroids

- The TESTING trial started in May 2012
- Steroids given 0.6-0.8 mg / day of oral methylprednisolone
- Stopped in November 2015 – excess deaths in steroid group after 262 patients randomised
- Protocol changed to 0.4mg/kg per day, restarted March 2017 and protocol revised to 500 patients instead of 750 as originally envisaged
- Published in JAMA 2022
- Lv J, Wong MG, Hladunewich MA, et al. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA*. 2022;327(19):1888-1898. doi:10.1001/jama.2022.5368

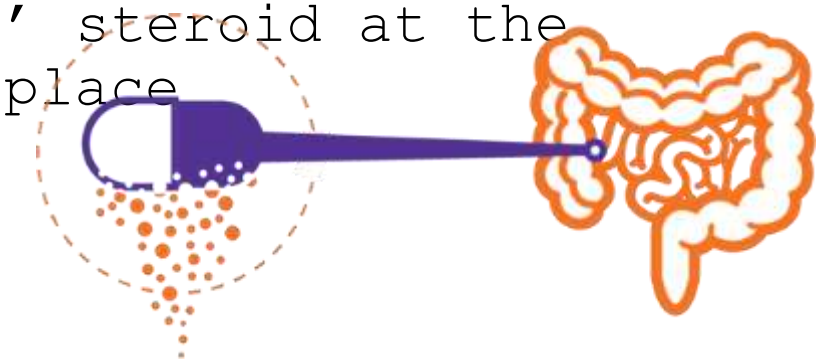
The TESTING trial



Lv J, Wong MG, Hladunewich MA, et al; for the TESTING Study Group. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. Published May 17, 2022. doi:10.1001/jama.2022.5368

NEFIGARD TRIAL- 2 YEAR RESULTS

- NefIgArd trial was a more nuanced take on steroids
- Targeted release oral budesonide
- Releases only at the site of Peyers patches
- Thus targets the source of abnormal polymeric IgA1 that is Hit 1
- Normal steroid side effects are less since budesonide first pass metabolism >80%
- A ‘perfect’ steroid at the ‘perfect’ place



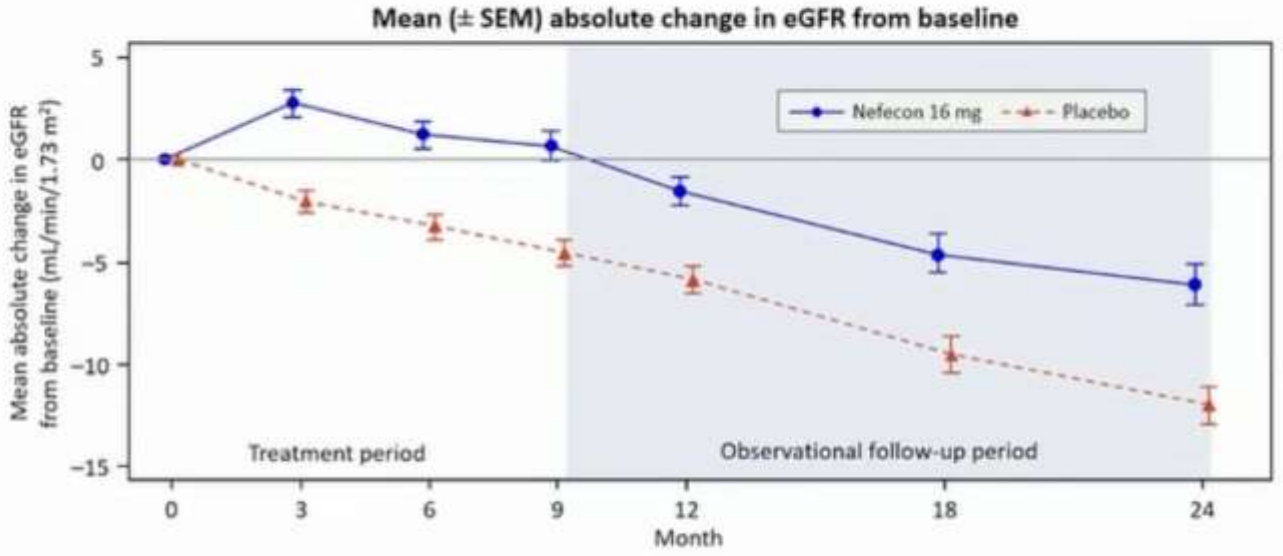
NefIgArd trial

60 ERA CONGRESS MILAN & VIRTUAL JUNE 15-18, 2023

Results: Efficacy (1)

Primary endpoint: time-weighted average change from baseline in eGFR over the 2-year period

- 5.05 mL/min/1.73 m² eGFR treatment benefit in favor of Nefecon vs placebo over 2 years (p<0.0001)
- eGFR benefit at the end of the 9-month treatment period with Nefecon was maintained during the 15-month observational follow-up



Nefecon 16 mg/day, mL/min/1.73 m²	+0.66	−1.52	−6.11
Placebo, mL/min/1.73 m²	−4.56	−5.85	−12.00
Absolute difference, mL/min/1.73 m² (95% CI)	5.21 (3.35–7.58)	4.33 (2.44–6.66)	5.89 (3.35–9.15)

CI, confidence interval; eGFR, estimated glomerular filtration rate; SEM, standard error of the mean; UPCR, urine protein-to-creatinine ratio.

TR budesonide in our case

- Boy was now started on oral budesonide
- As proteinuria <1g did not fit the TESTING trial group, considered safer to start prolonged release oral budesonide
- Initiated on 9mg od for two months
- ACR came down to 450 mg/g
- No rise in blood sugar, gain in weight or Cushingoid features
- Normal renal function

OTHER OPTIONS?

Sparsentan in IgAn - PROTECT trial

Sparsentan a dual endothelin A/angiotensin II receptor blocker DEARA

Endothelin shares many of the negative connotations of the renin-angiotensin system

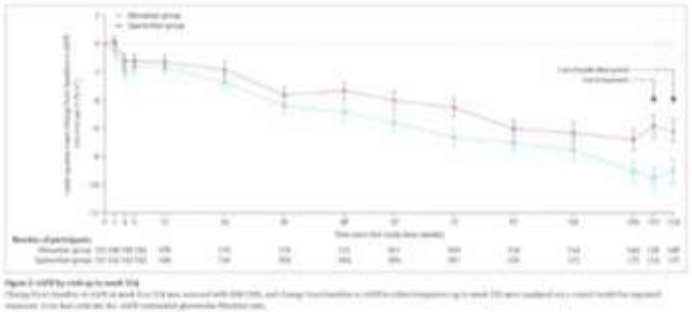
Dual blockade achieves greater results than blockade of one alone

PROTECT trial

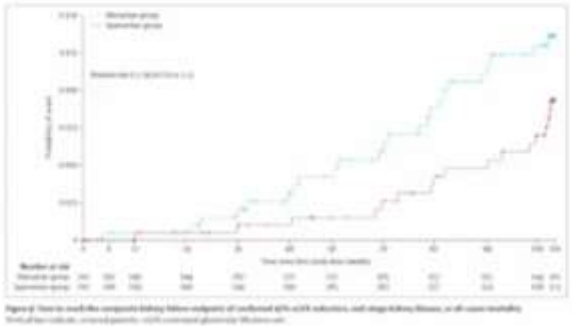
Sparsentan in IgAN: Phase 3 PROTECT Study

Two-year results: *Lancet*, Nov 2023

GFR thru week 114



Composite Kidney Failure



	Sparsentan (n=202)	Irbesartan (n=202)	Difference
UP/C (g/g)	-42.8%	-4.4%	**GMR 0.60** (0.50, 0.72)
eGFR Total slope (mL/min/1.73m2/yr)	-2.9	-3.9	**1.0** (-0.03, 1.94), p=0.06
eGFR Chronic slope (mL/min/1.73m2/yr)	-2.7	-3.8	**1.1** (0.07, 2.12), p=0.04
Absolute ΔeGFR at week 114, 4 weeks post-treatment	-6.1	-9.0	**2.9** (0.45, 5.25)
Composite Endpoint: 40% reduction in GFR, ESRD, or death	18 (8.9%)	26 (12.9%)	**RR: 0.68** (0.37, 1.24)

The Lancet 2023 402:2077-2090

MMF in IgAn – Chinese study MAIN trial

JAMA Network | Open

RCT: Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy

POPULATION

94 Males, 76 Females

Patients with immunoglobin A (IgA) nephropathy with proteinuria ≥0.75 g/d

Mean age, 36.6 y

INTERVENTION

170 Patients randomized

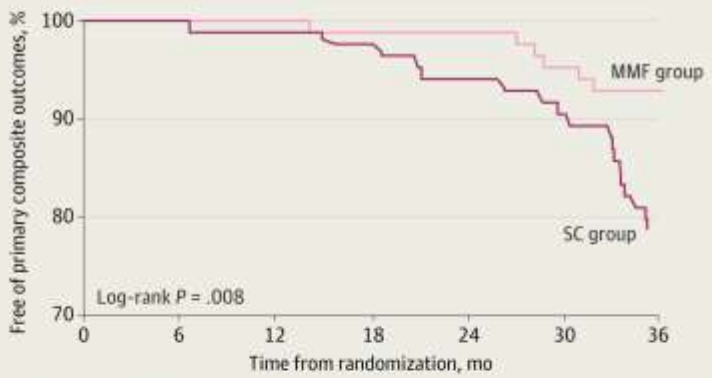
USUAL CARE

85 Supportive care (SC) group
Blockade of renin-angiotensin system with losartan, blood pressure control, lifestyle change, and statin as needed

85 Mycophenolate mofetil (MMF) and SC
SC with oral MMF at 1.5 g/d for 12 mo, then 0.75 to 1.0 g/d for >6 mo

FINDINGS

Addition of MMF to SC, compared with SC alone, significantly reduced the risk of the primary composite outcome and delayed the progression of CKD



Composite kidney outcome, MMF group vs SC group:
7.1% vs 21.2%
aHR, 0.23; 95% CI, 0.09-0.63; *P* < .001

Progression of CKD, MMF group vs SC group:
8.2% vs 27.1%
aHR, 0.23; 95% CI, 0.10-0.57; *P* < .001

SETTINGS / LOCATIONS

1 Kidney center in China

PRIMARY OUTCOME

A composite of doubling of serum creatinine, end-stage kidney disease (dialysis, transplant, kidney failure without kidney replacement therapy), or death due to kidney or cardiovascular cause, and progression of chronic kidney disease (CKD)

Hou FF, Xie D, Wang J, et al; MAIN Trial Investigators. Effectiveness of mycophenolate mofetil among patients with progressive IgA nephropathy: a randomized clinical trial. *JAMA Netw Open*. 2023;6(2):e2254054. doi:10.1001/jamanetworkopen.2022.54054

HCQ in IgAn

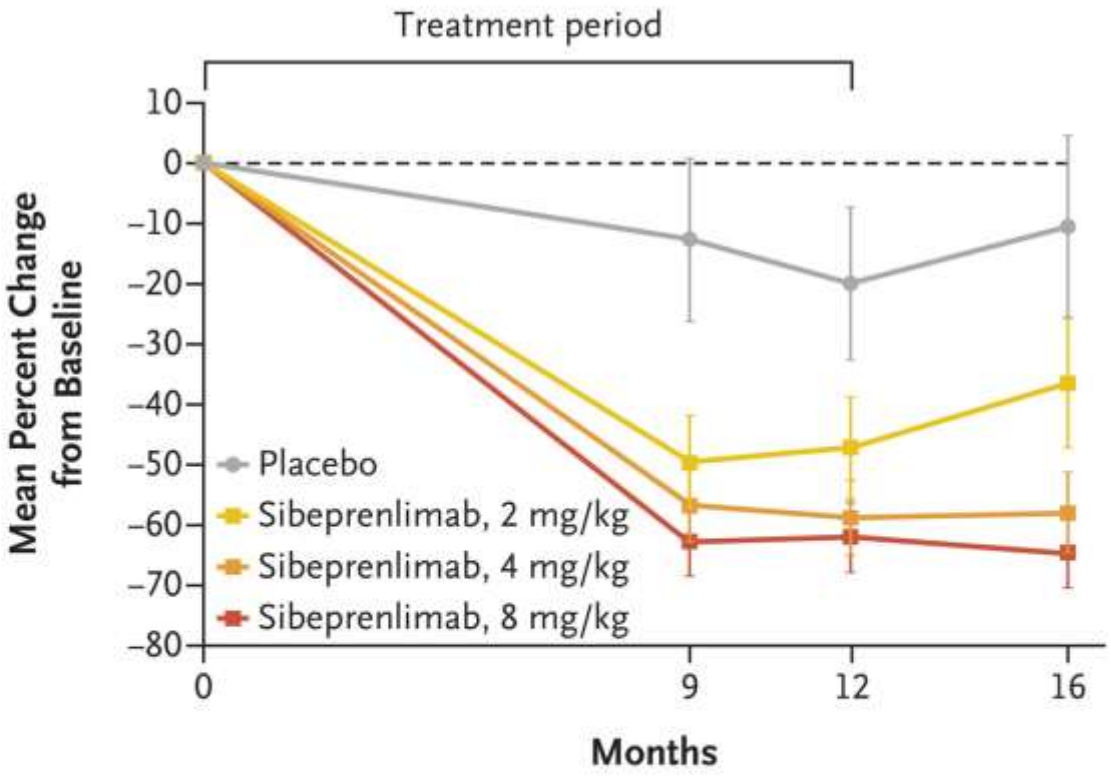
- Used as add on to SOC
- All Chinese trials and showed benefit in reducing proteinuria and one study showed comparable efficacy to steroids given by Manno protocol
- Indian study from AIIMS also showed 10/37 complete remission and 11/37 partial remission and others no response
- So may of benefit – cheaper and lesser side effects than steroids

B cell modulators in IgAn

- Rituximab was disappointing
- BAFF and APRIL are two targets which promote B cell growth and proliferation
- Blisibimod anti BAFF agent has shown efficacy in reducing B cells and stabilising proteinuria but not yet published
- Sibeprenlimab, APRIL inhibitor was found useful in a phase 2 trial

Mathur M, Barratt J, Chacko B, Chan TM, Kooienga L, Oh KH, et al. A Phase 2 trial of sibeprenlimab in patients with IgA nephropathy. *N Engl J Med* (2023) 390:20-31. doi: 10.1056/NEJMoa2305635

Sibeprenlimab in IgAn



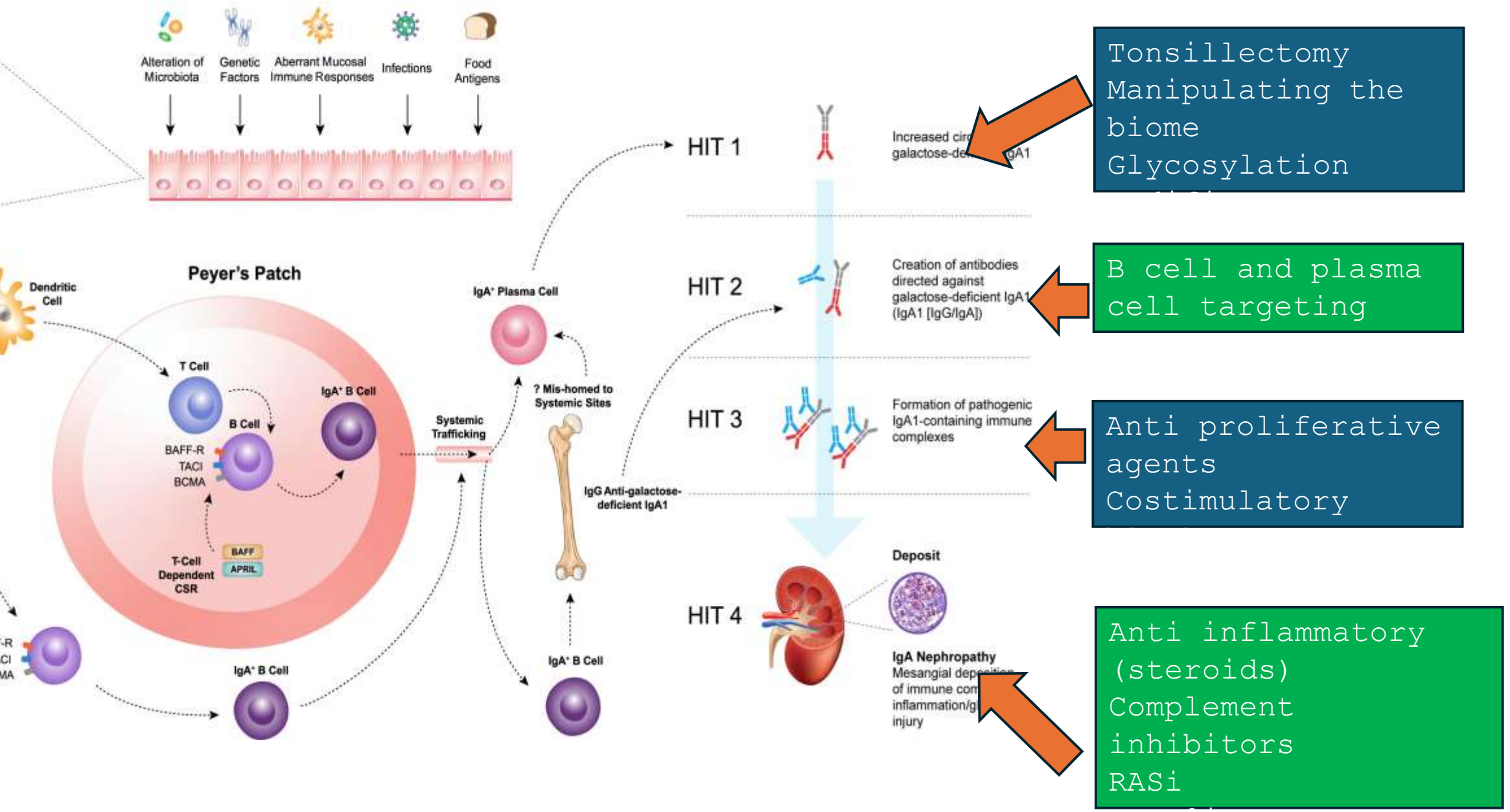
No. of Patients				
Placebo	38	35	35	35
Sibeprenlimab, 2 mg/kg	38	35	35	35
Sibeprenlimab, 4 mg/kg	41	40	38	38
Sibeprenlimab, 8 mg/kg	38	36	37	37

Other biologicals under study

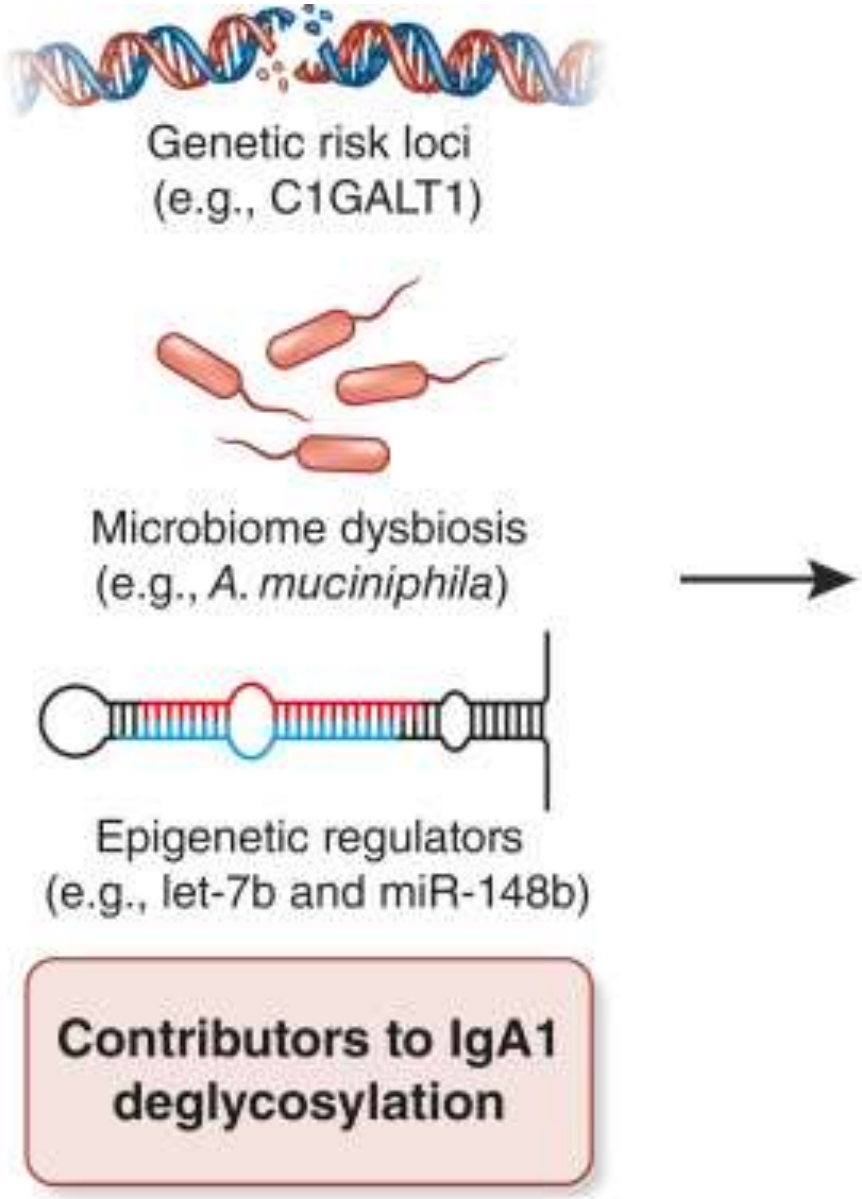
Zigakibart anti APRIL agent

Telitacicept, atacicept are fusion proteins which target the binding site of BAFF and APRIL - Phase 2 trials found useful

Perhaps we will see more of this in future


Alteration of Microbiota
Genetic Factors
Aberrant Mucosal Immune Responses
Infections
Food Antigens
Peyer's Patch
Dendritic Cell
T Cell
B Cell
IgA+ B Cell
BAFF-R
TACI
BCMA
T-Cell Dependent CSR
BAFF
APRIL
Systemic Trafficking
IgA+ Plasma Cell
? Mis-homed to Systemic Sites
IgG Anti-galactose-deficient IgA1
IgA+ B Cell
IgA+ B Cell
HIT 1
Increased circ
galactose-de
gA1
HIT 2
Creation of antibodies directed against galactose-deficient IgA1 (IgA1 [IgG/IgA])
HIT 3
Formation of pathogenic IgA1-containing immune complexes
HIT 4
Deposit
IgA Nephropathy
Mesangial depo
of immune com
inflammation/g
injury
Tonsillectomy
Manipulating the biome
Glycosylation
B cell and plasma cell targeting
Anti proliferative agents
Costimulatory
Anti inflammatory (steroids)
Complement inhibitors
RASi

The microbiome and IgAn



Akkermansia muciniphila

- Found to repurpose enzymes that remove sugar moieties from the hinge region in IgA1 leading to underglycosylated IgA1(gd-IgA)
- This leads to hit 1
- First time someone demonstrated one bacteria doing such sneaky stuff
- Not seen with E coli in mouse models
- A municiphila made a mouse model develop IgA nephropathy

Conclusion

- Last few years exciting times in IgA n
- New paradigm-the 4 Hit theory which seems eminently plausible
- Criteria for defining risk have been on solid ground
- Established the definitive role of RASi and more recently SGLT2i
- Defined the role of steroids and targeted budesonide
- Chinese studies on MMF and HCQ
- Stretching new frontiers with DEARA, BAFF APRIL targeting
- On the fast lane for antibiotic treatment of IgAn???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Thank you

Office practice in childhood kidney diseases:

Early diagnosis & timely referral

Dr Sudarsan K MD, DM (Ped Nephro)

Assistant Professor

Dept of Paediatrics

JIPMER, Puducherry

Case 1

- 5-year-old boy presents to OPD with fever for 3 days. O/E, found to have BP of **109/69** mm Hg
  - Is he hypertensive?
  - Does he require further evaluation?

Definition of hypertension

For children aged 1-13 y	For children aged ≥ 13 y
Normal BP: < 90th percentile	Normal BP: < 120/< 80 mm Hg
Elevated BP: ≥ 90th percentile to < 95th percentile or 120/80 mm Hg to < 95th percentile (whichever is lower)	Elevated BP: 120/< 80 to 129/ < 80 mm Hg
Stage 1 HTN: ≥ 95th percentile to < 95th percentile + 12 mm Hg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥ 95th percentile + 12 mm Hg, or ≥ 140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥ 140/90 mm Hg

AAP 2017 Hypertension guidelines

TABLE 4 BP Levels for Boys by Age and Height Percentile

Age (y)	BP Percentile	SBP (mm Hg)						
		Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%
5	Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	51	51	52	53	54	55	55
SBP	90th	63	64	65	65	66	67	67
DBP	95th	66	67	68	69	70	70	71
	95th + 12 mm Hg	78	79	80	81	82	82	83

Screening BP values

Age, y	BP, mm Hg			
	Boys		Girls	
	Systolic	DBP	Systolic	DBP
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

Refer if BP above this value

Suspect secondary hypertension if...

- ✓ Age < 6 years
- ✓ Thin child with negative family history
- ✓ Acute severe rise in BP
- ✓ Nocturnal hypertension
- ✓ Diastolic hypertension

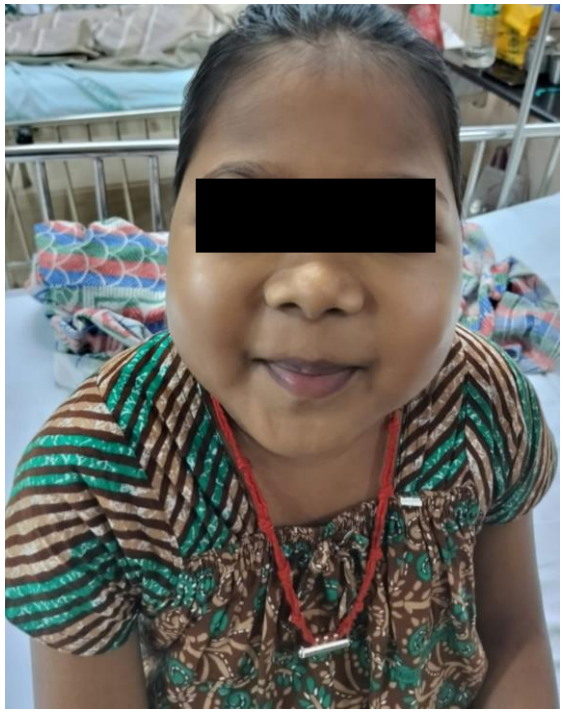
Rx: ACEi/ARB first choice

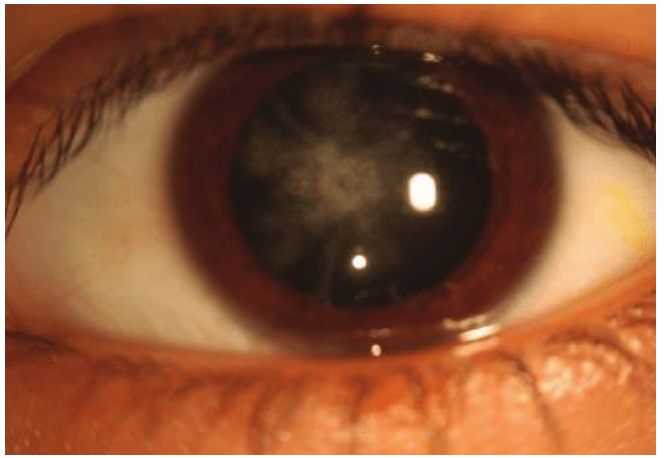
Target: 90th centile (<50th centile in CKD)

Case 2

- 10y/F, k/c/o nephrotic syndrome with multiple relapses in the past
- Brought to you for the first time in relapse
- O/E: Mild pedal edema; very cushingoid, striae over abdomen
- B/E posterior subcapsular cataract noted

Management?

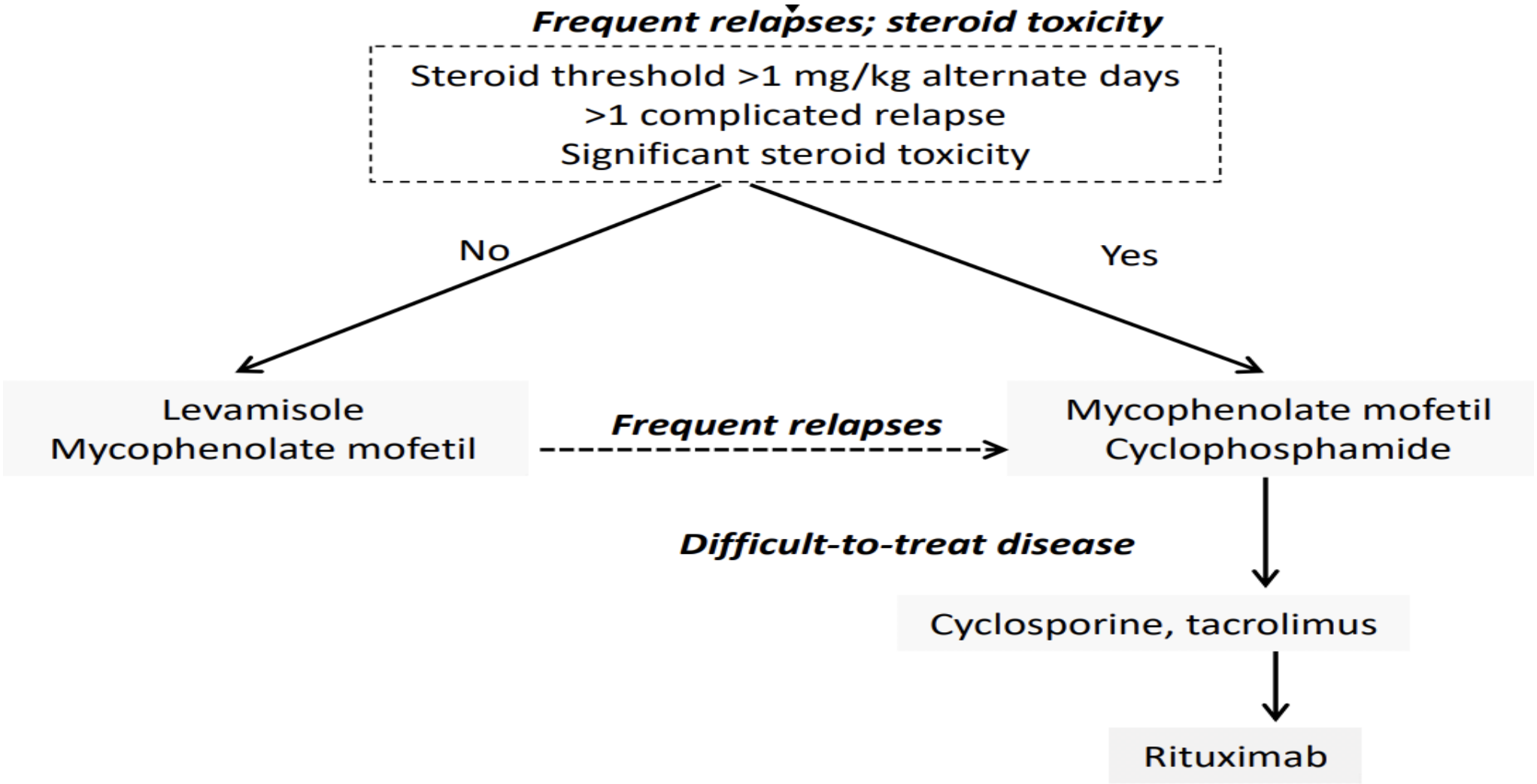




Nephrotic syndrome definitions

Parameter	***ISPN 2020***	***ISPN 2008 [7]***	***KDIGO 2020 [9]***
Nephrotic syndrome	Nephrotic range proteinuria, hypoalbuminemia (albumin <3 g/dL) and edema	Nephrotic range proteinuria, hypoalbuminemia (<2.5 g/dL), cholesterol >200 mg/dL and edema	Nephrotic range proteinuria and either hypoalbuminemia (<3 g/dL) or edema
Steroid resistance	Lack of complete remission despite daily therapy with prednisolone for 6-wk	Lack of complete remission despite daily therapy with prednisolone for 4-wk	Lack of complete remission despite daily therapy with prednisone at 4-weeks^
Prednisolone for initial episode	6-wk daily and 6-wk AD; surface area (BSA) or weight-based dosing#; no indication for prolonged therapy	6-wk daily and 6-wk AD; weight-based dosing#; no indication for prolonged therapy	4-6 wk daily and 4-6 wk AD; BSA or weight-based dosing#; prolong therapy (16-24 wk) if <4-6 yr-old, or if delayed remission
Frequent relapses	≥2 relapses in first 6-months after initial therapy; ≥3 relapses in any 6-months; ≥4 relapses in 1-yr	≥2 relapses in first 6-months after stopping initial therapy; ≥4 relapses in 1-yr	≥2 relapses in 6-months; ≥4 relapses in 1-yr

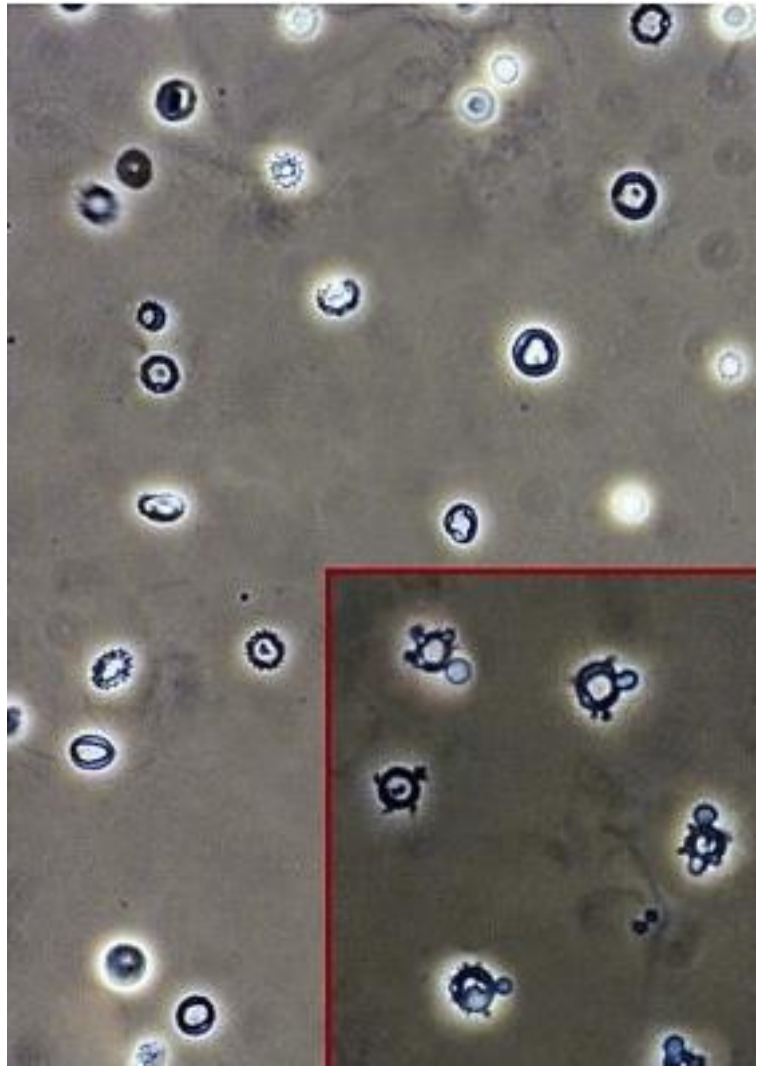
Management of FR/SDNS



Case 3

- 13y/M with 2 e/o gross hematuria so far, both after URI
- No h/o UTI, abd pain, hearing loss, visual problems
- O/E mild pedal edema, BP 132/89 mm Hg
- Urine exam: Up 2+; UpUc 1.8, plenty of RBCs

Differentials?



Case 3: Hematuria

- Confirm if it is hematuria
- Identify if hematuria is glomerular or non-glomerular
- Look for associated proteinuria, deranged renal function, hearing loss, visual disturbances etc.

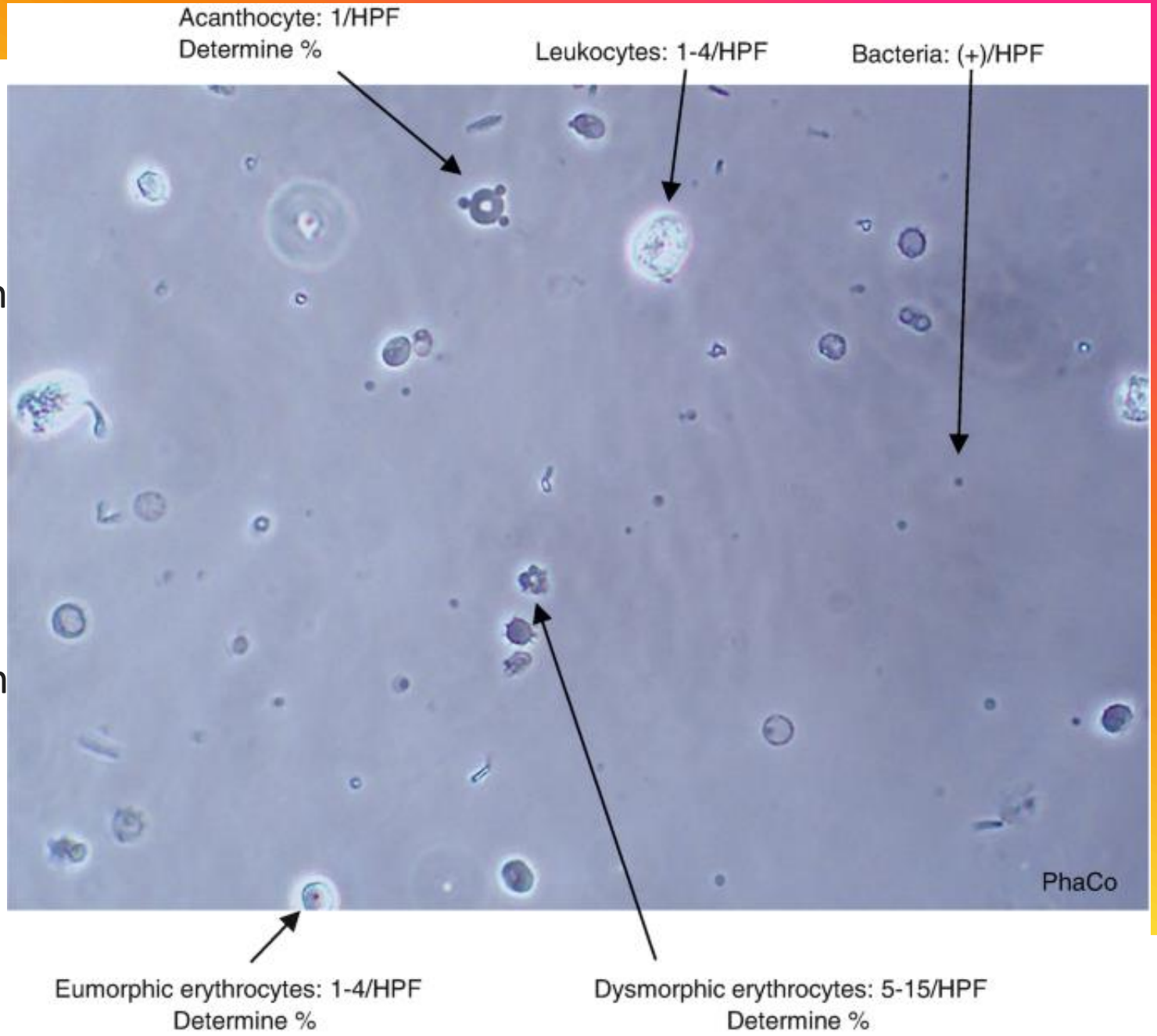
How to check urine

Centrifuge 10 ml of urine for 10 min at 400 g (2,000 rpm)

Suction out 9.5 ml of supernatant urine

Pipette out 50 µl of resuspended sediment to a glass slide, cover with coverslip

Count RBCs per HPF at 400x



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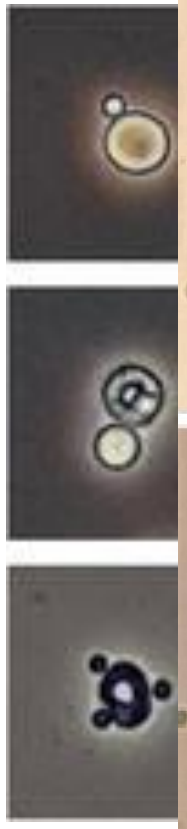
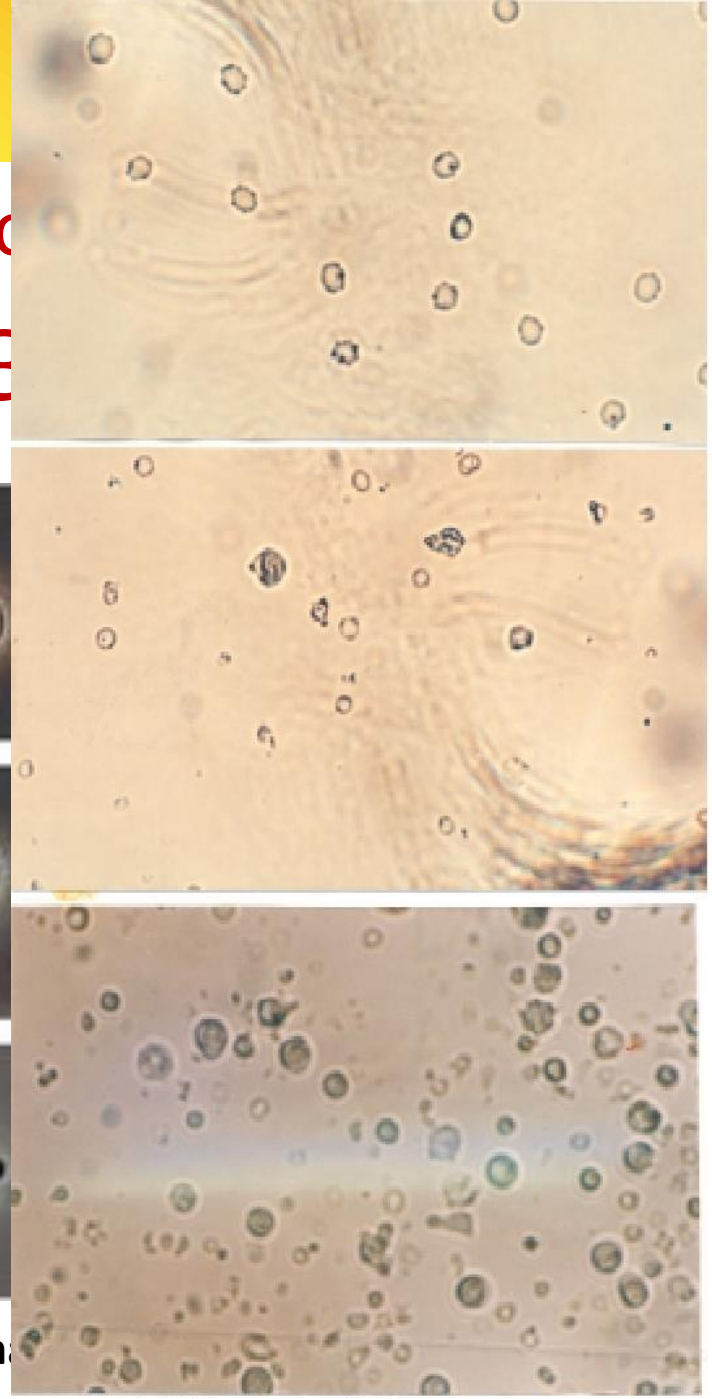
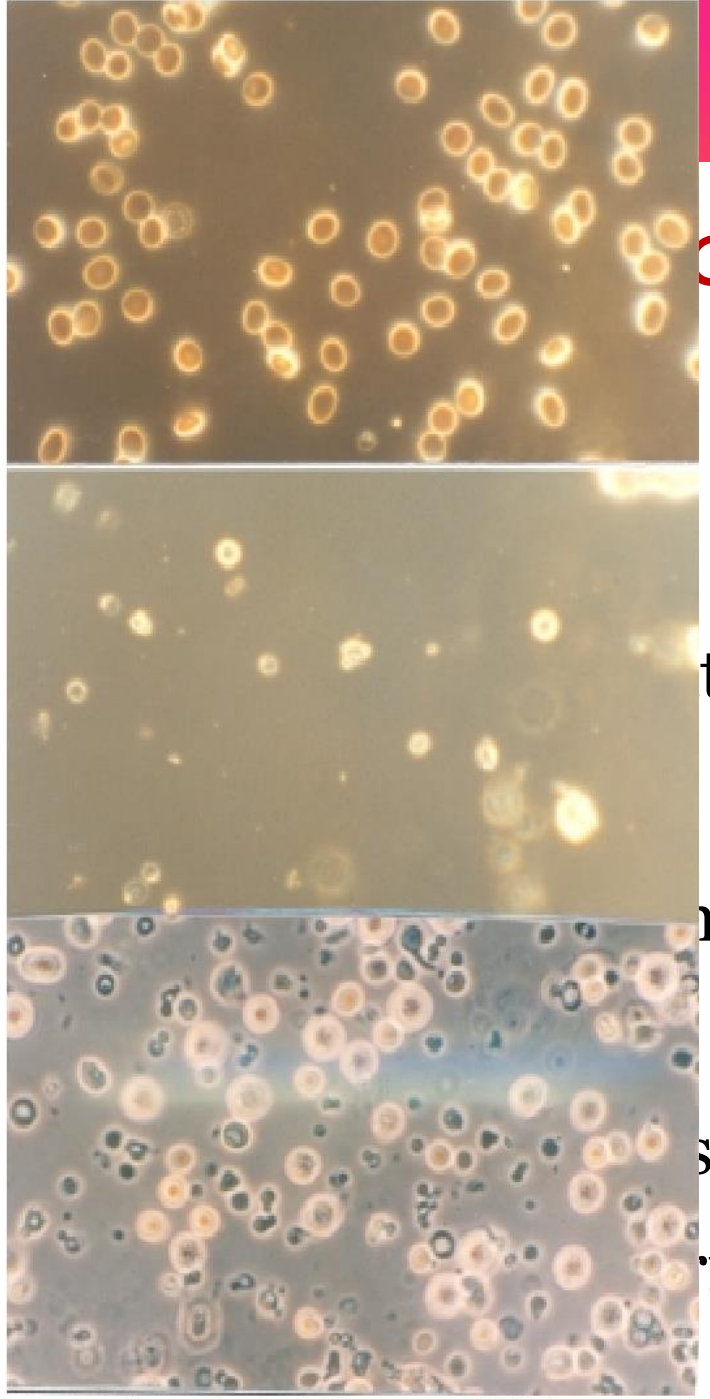




Isomorphic red blood cell ×400

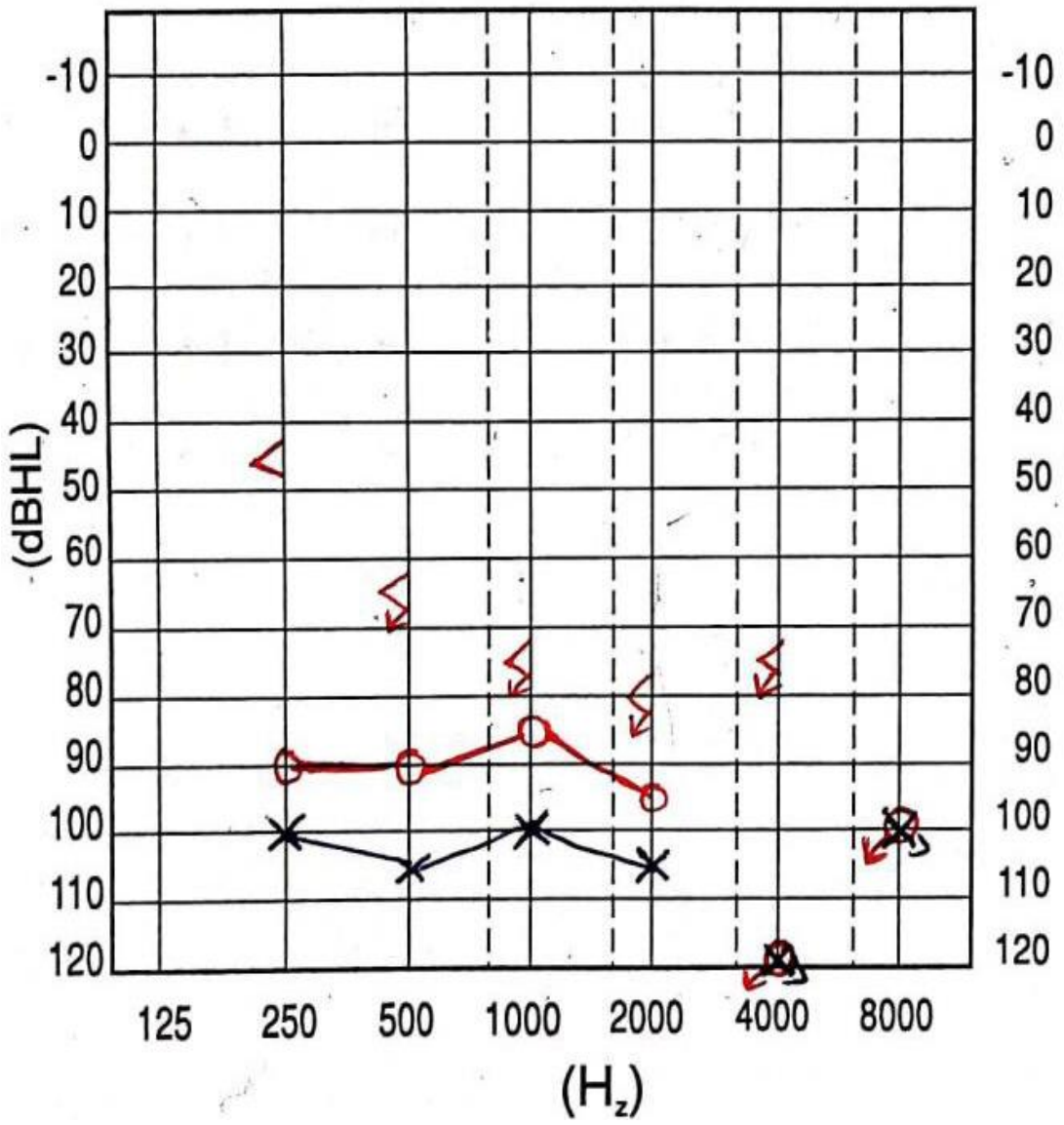
Dysmorphic red blood cell ×400

Dysmorphic red blood cell ×400



Light Microscopy (LM)

Phase Contrast Microscopy (PCM)


-10
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(dBHL)
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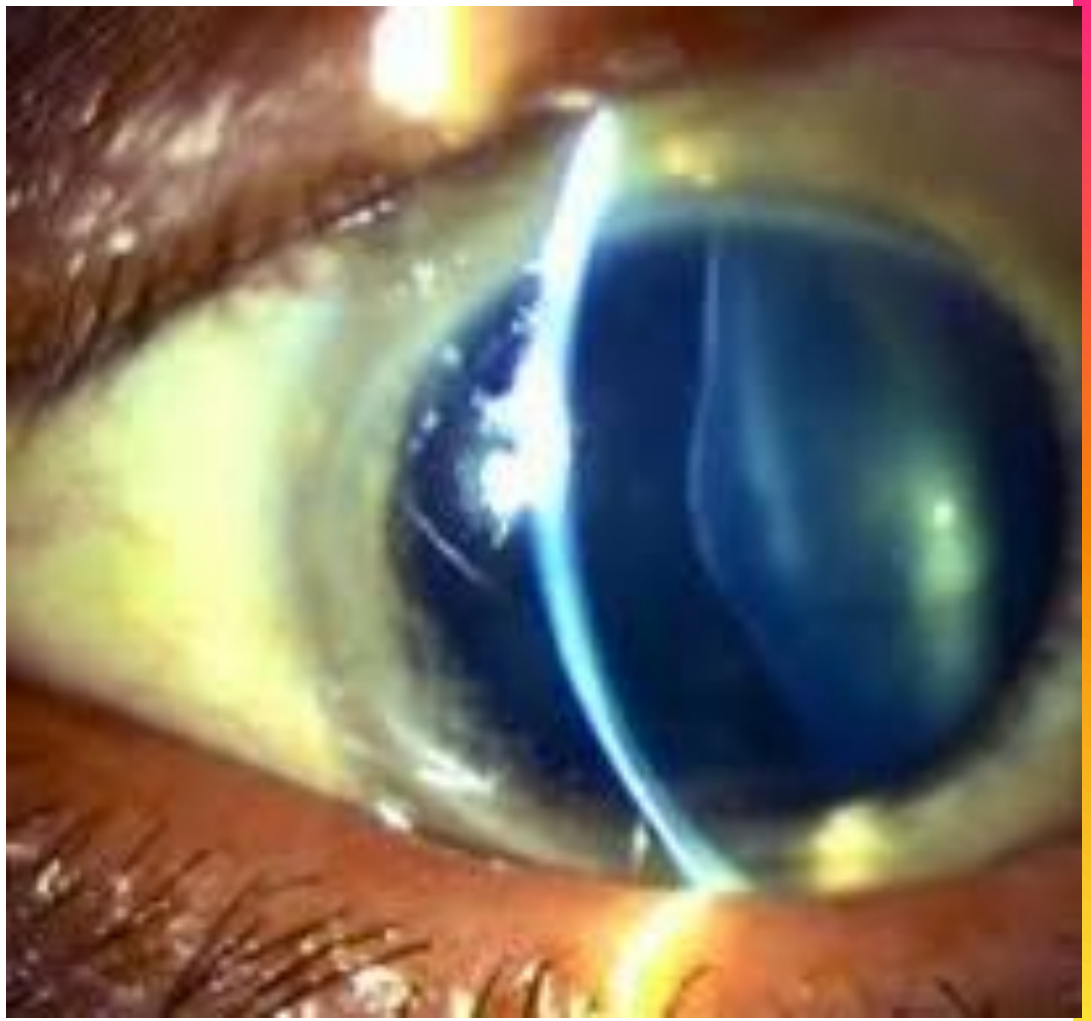
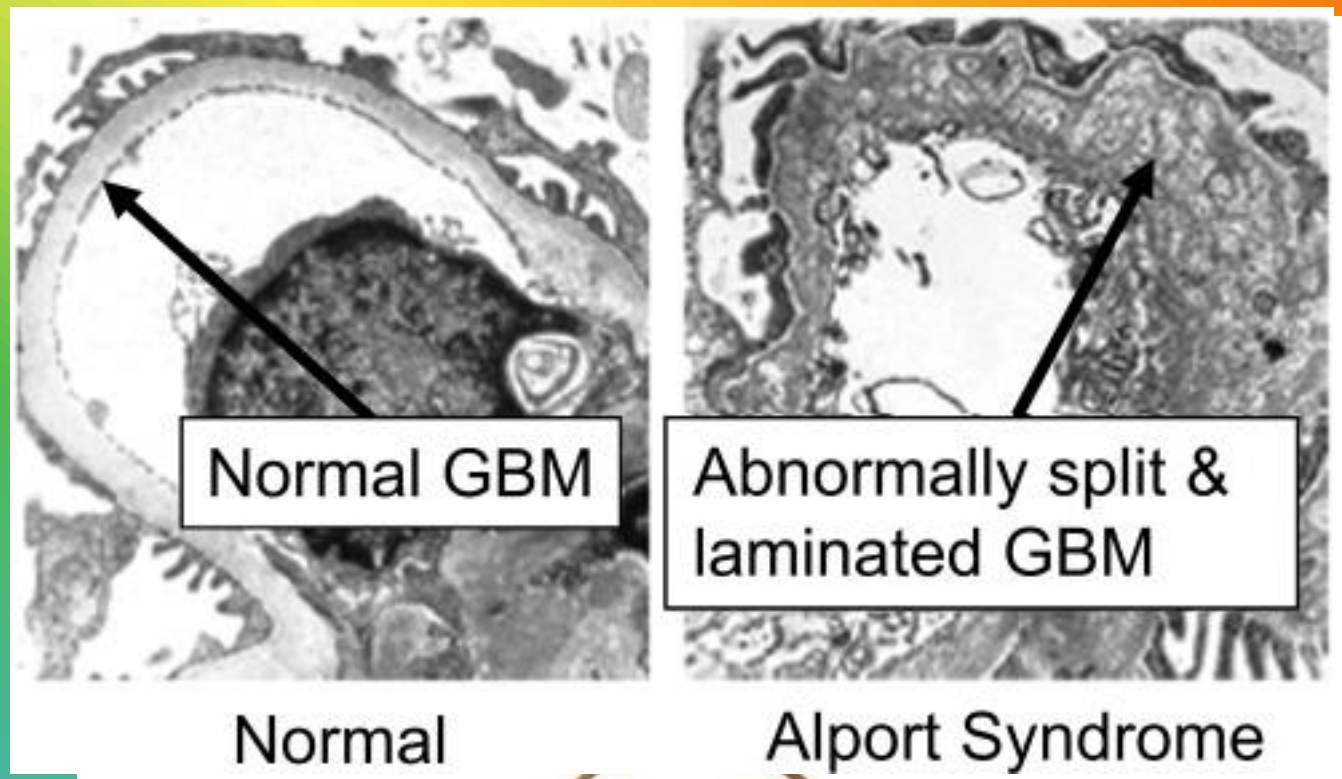
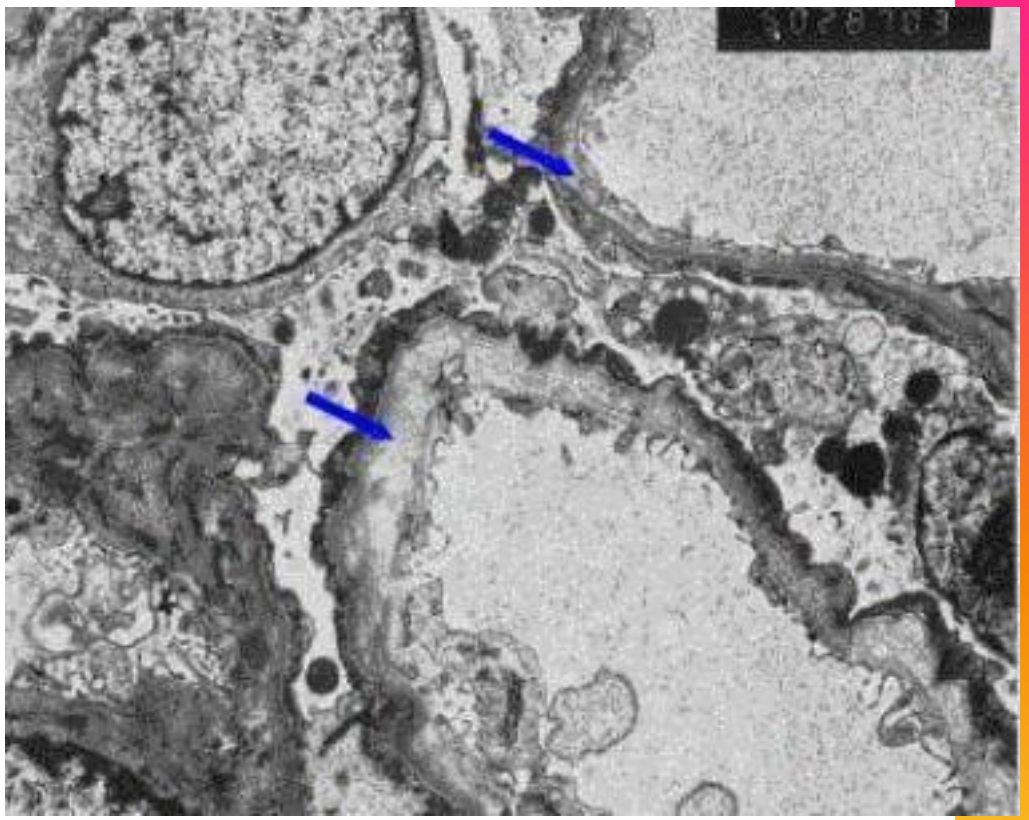
8000
(Hz)

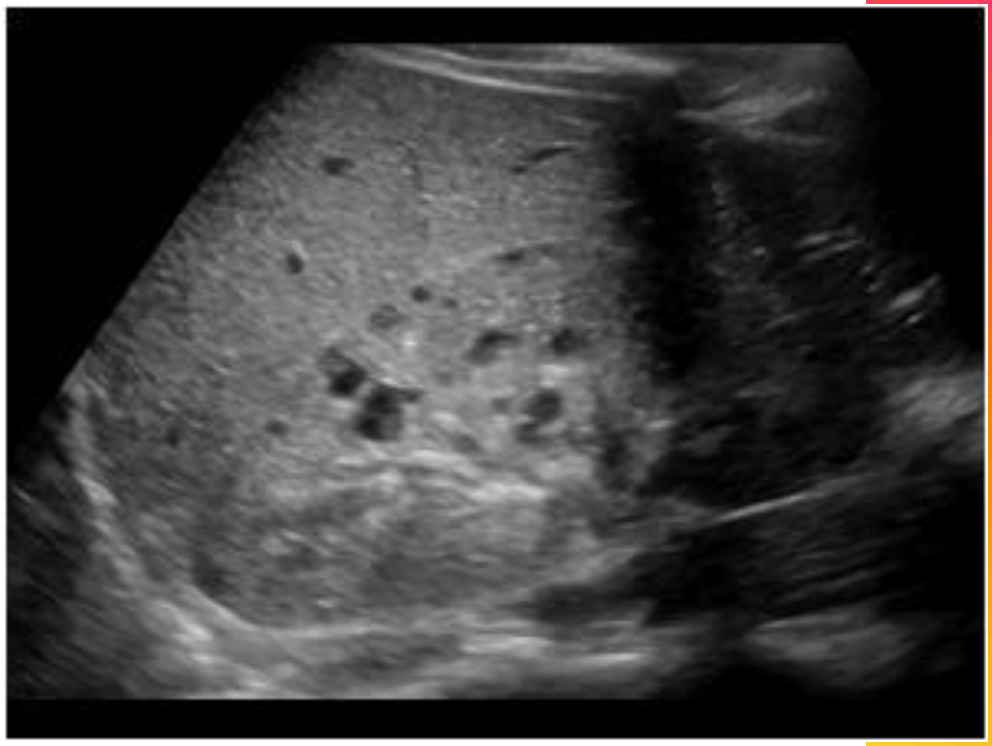



Normal GBM
Abnormally split &
laminated GBM
Normal
Alport Syndrome



Case 4

- 6y/F referred to the nephrologist after undergoing USG for vague abd pain
- O/E Kidneys palpable, BP 118/74 mm Hg
- S/E unremarkable
- Urine exam: Up1+, 15-16 RBCs/HPF
- s. creatinine: 0.7 mg/dL

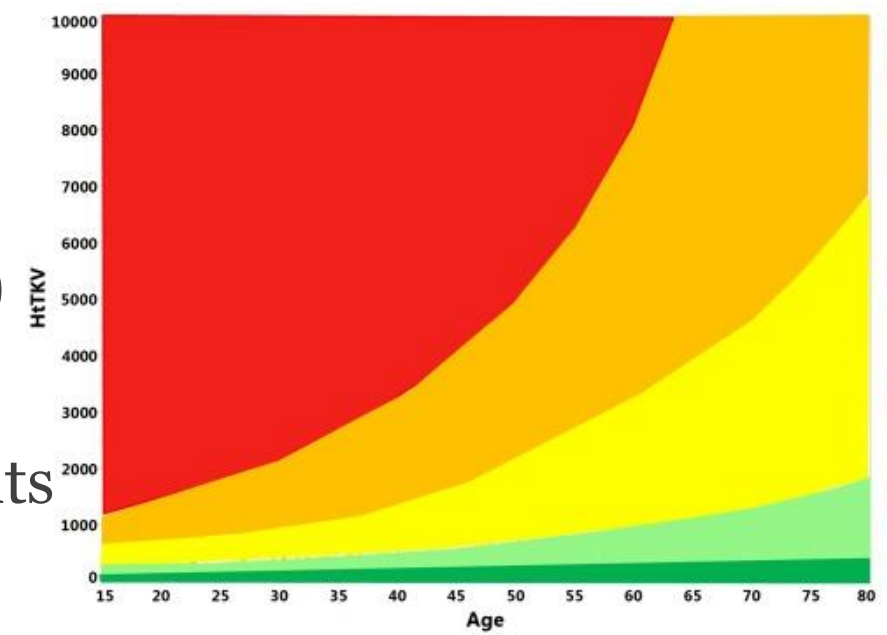


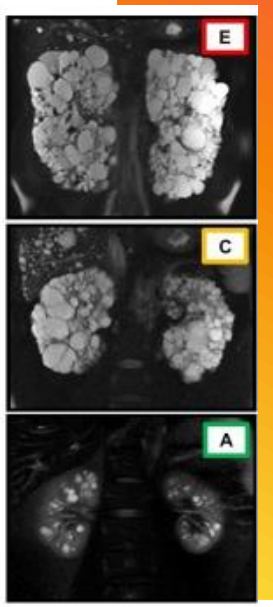
Diagnosis?

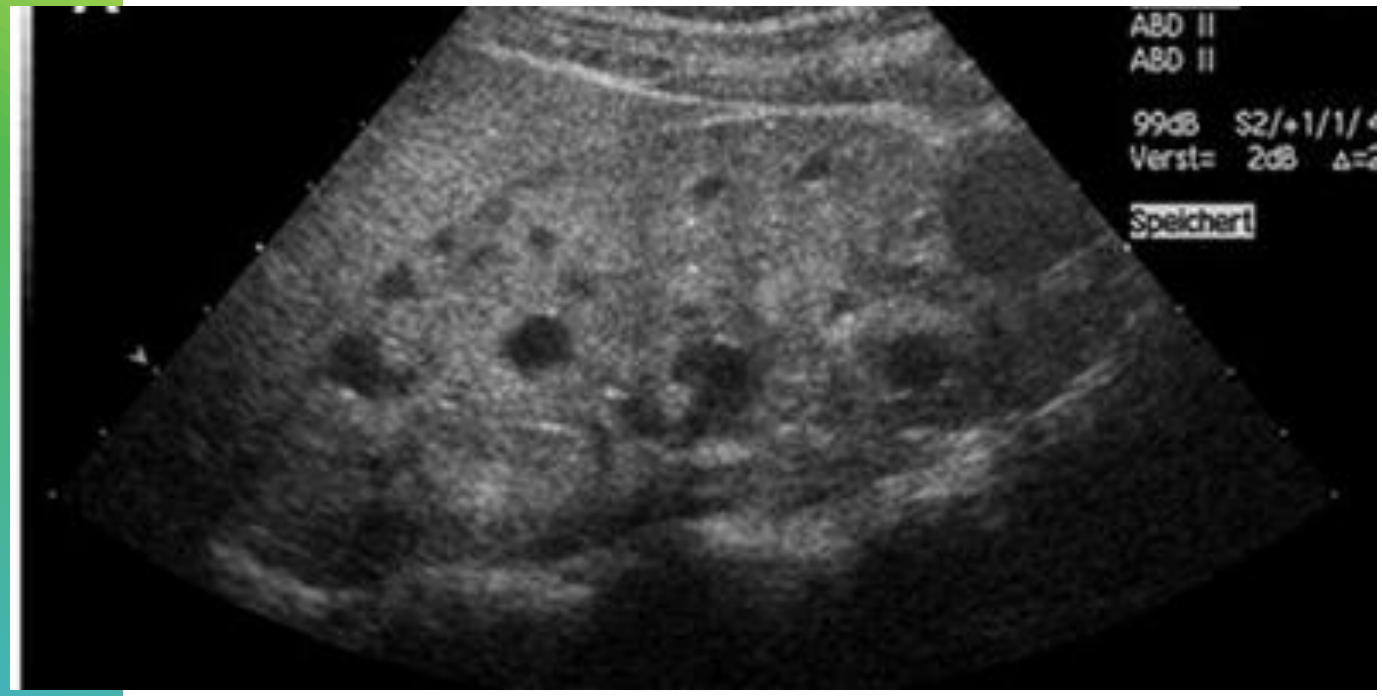
On probing, father gives history of hematuria once few years ago

Case 4: Cystic kidney

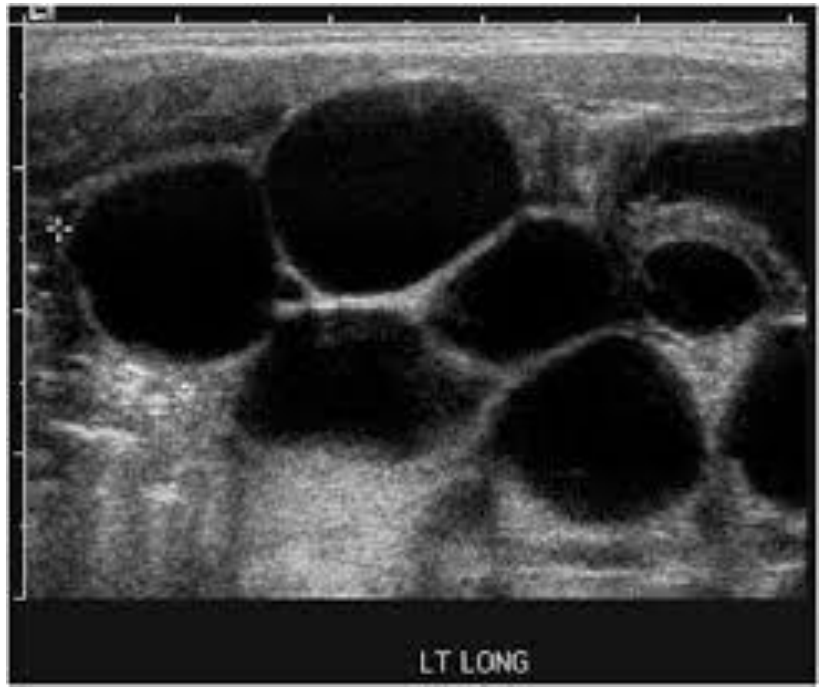
- Meticulous family history and pedigree
- Ultrasound of parents (grandparents also if parents <40y)
- Rx:
  - Salt restriction
  - Plenty of fluids
  - BP control (prefer ACEi/ARB)
  - Screen parents & siblings
  - ?Tolvaptan in high-risk patients







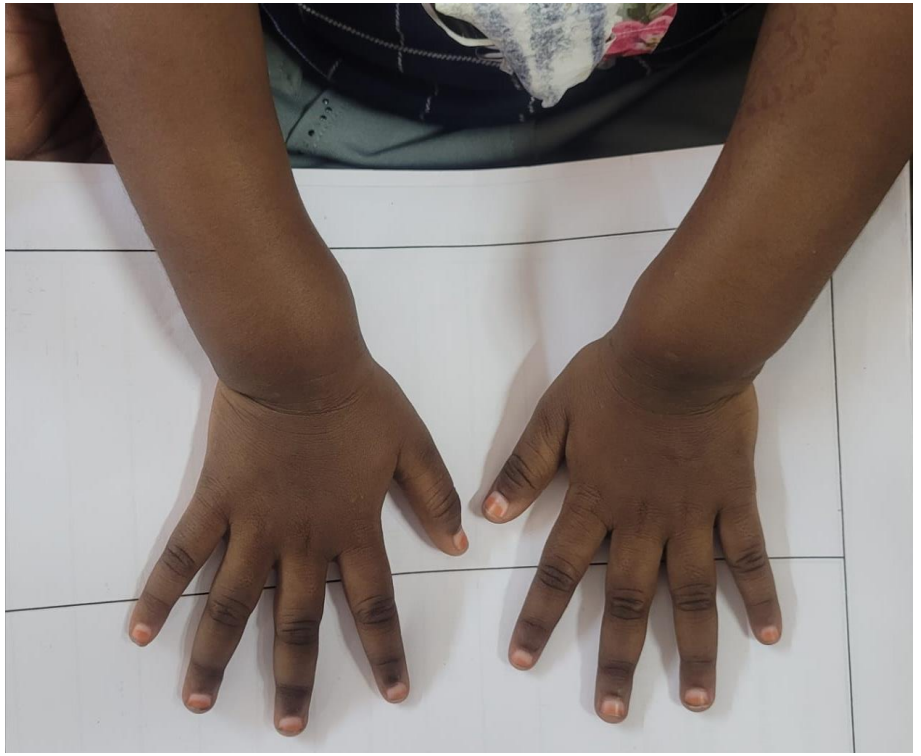
ADPKD

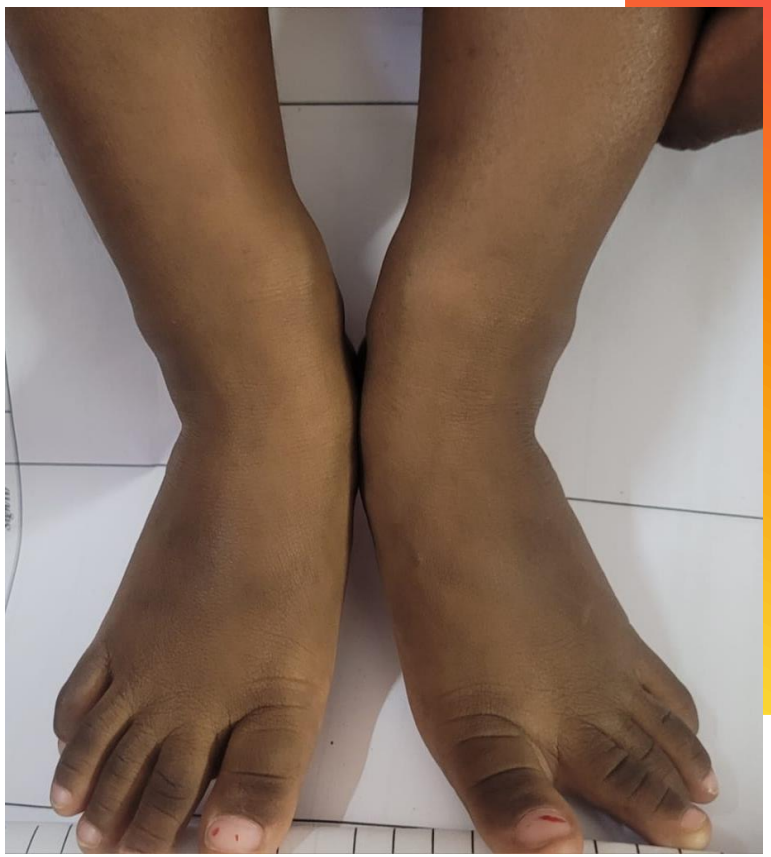


MCDK

Case 5

- 2y/F brought with inability to walk and bent legs
- Seen several GP in the past & recd multiple medications
- O/E



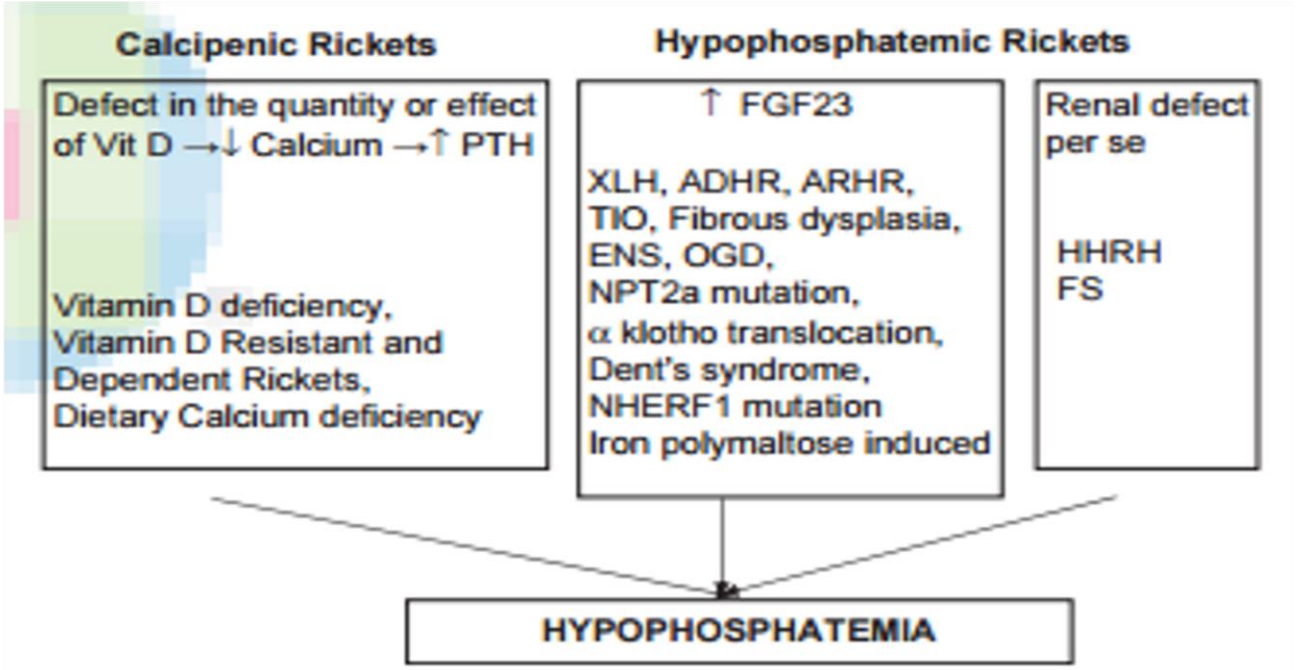


Case 5

- Is it rickets?
- Nutritional Vit D deficiency?
- Calcipenic or phosphopenic rickets?

- History: tetany, seizures, alopecia → think of calcipenic rickets
- LL predominant involvement, mother affected → Phosphopenic

↓Phosphate common denominator



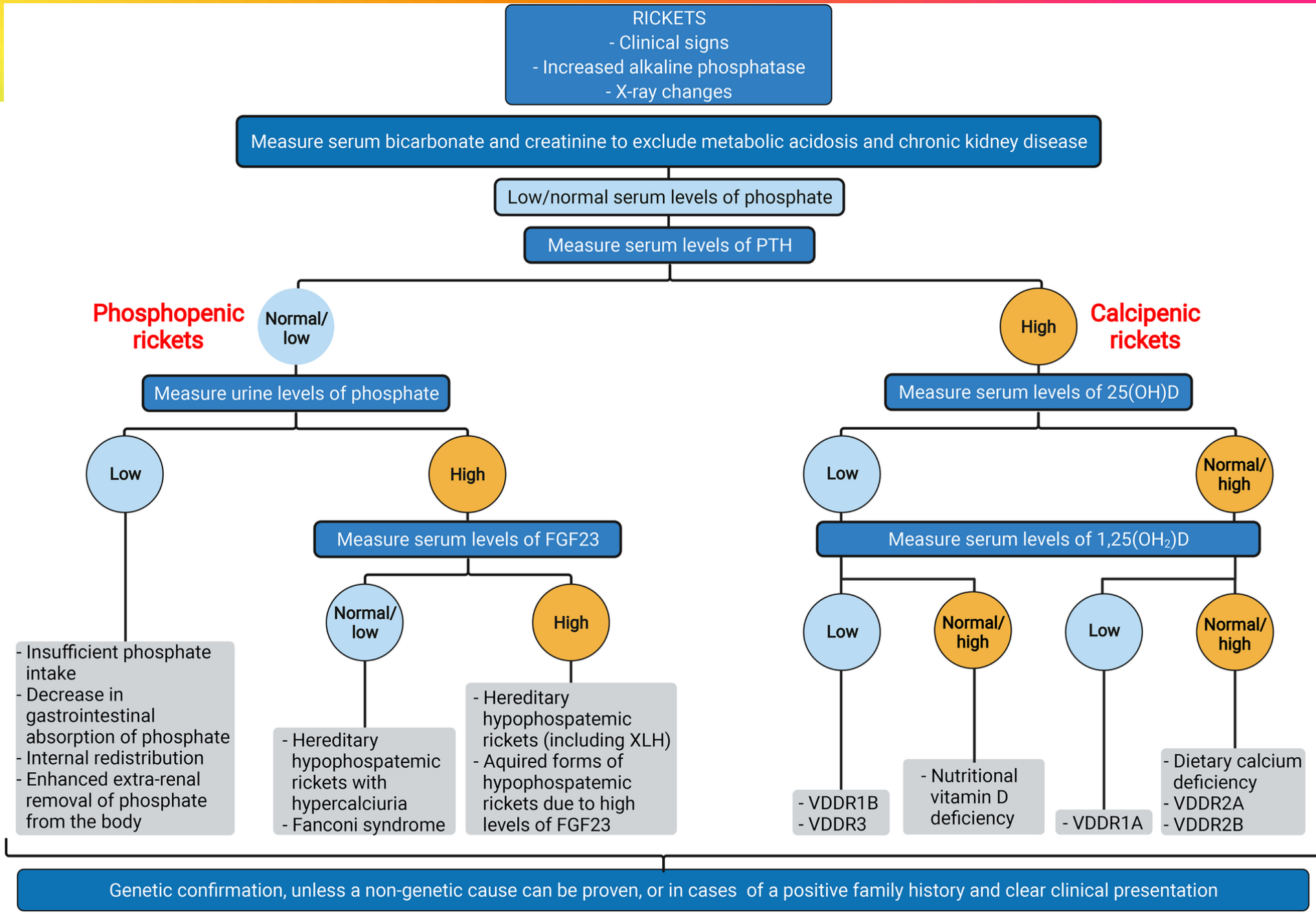
Low PO4 level leads to decreased apoptosis of hypertrophic chondrocytes in growth plate

Lack of invasion of blood vessels and blockade of new bone formation

Rickets

Laboratory findings in rickets

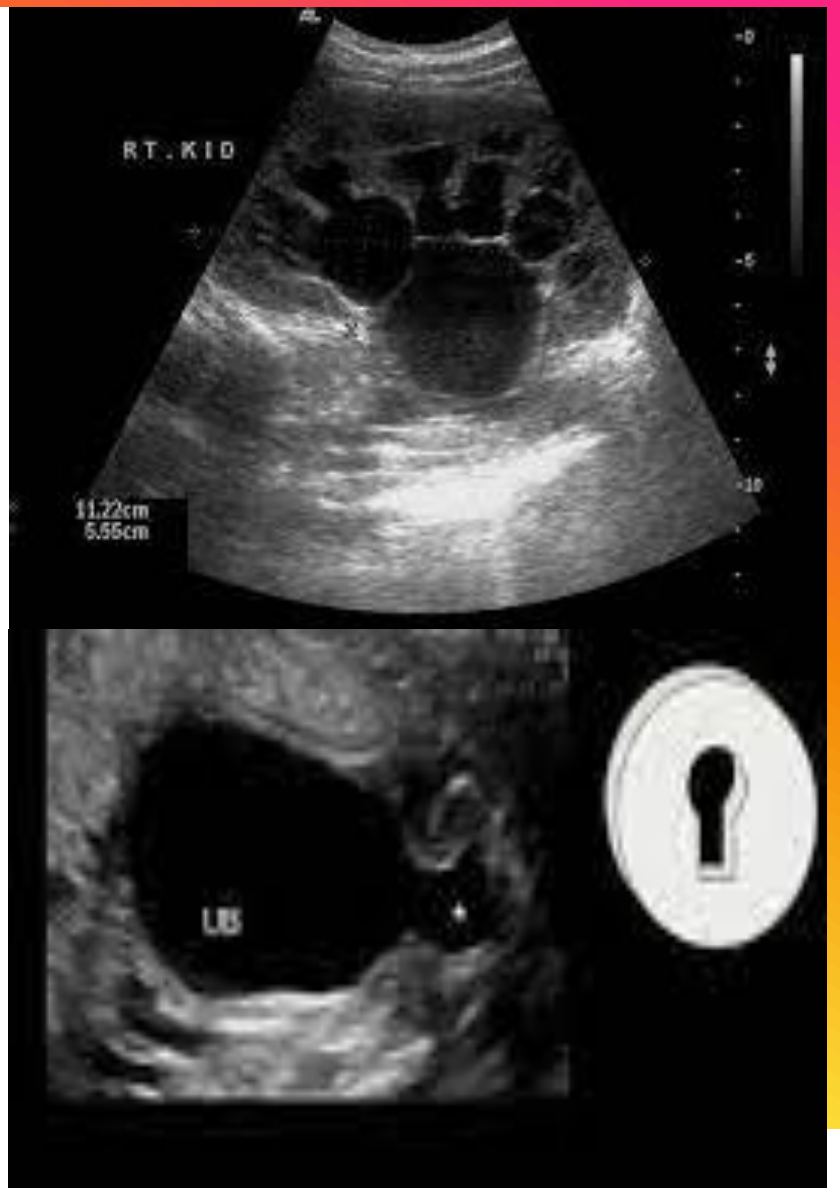
Type	Calcium	Phosphorus	25 (OH)D	1,25 $(OH)_2$ D	PTH
Calcipenic rickets					
Vitamin D deficiency	↓ or N	↓ or N	↓	Variable	↑
Vitamin D–dependent rickets type I	↓	↓ or N	N	↓	↑
Vitamin D–dependent rickets type II	↓	↓ or N	N	N or ↓	↑
Phosphenic rickets					
Nutritional phosphate deficiency	↑ or N	↓	N	↑	↓ or N
X-linked hypophosphatemic rickets	N	↓	N	N or ↓	or slightly ↑
Autosomal dominant hypophosphatemic rickets	N	↓	N	↓	N
Autosomal recessive hypophosphatemic rickets	N	↓	N	↓	N
Hereditary hypophosphatemic rickets with hypercalciuria	N	↓	N	↑	N or ↓


RICKETS
- Clinical signs
- Increased alkaline phosphatase
- X-ray changes
Measure serum bicarbonate and creatinine to exclude metabolic acidosis and chronic kidney disease
Low/normal serum levels of phosphate
Measure serum levels of PTH
Phosphopenic rickets
Normal/ low
High
Calcipenic rickets
Measure urine levels of phosphate
Measure serum levels of 25(OH)D
Low
High
Low
Normal/ high
Measure serum levels of FGF23
Measure serum levels of 1,25(OH2)D
Normal/ low
High
Low
Normal/ high
Low
Normal/ high
- Insufficient phosphate intake
- Decrease in gastrointestinal absorption of phosphate
- Internal redistribution
- Enhanced extra-renal removal of phosphate from the body
- Hereditary hypophospatemic rickets with hypercalciuria
- Fanconi syndrome
- Hereditary hypophospatemic rickets (including XLH)
- Aquired forms of hypophospatemic rickets due to high levels of FGF23
- VDDR1B
- VDDR3
- Nutritional vitamin D deficiency
- VDDR1A
- Dietary calcium deficiency
- VDDR2A
- VDDR2B
Genetic confirmation, unless a non-genetic cause can be proven, or in cases of a positive family history and clear clinical presentation

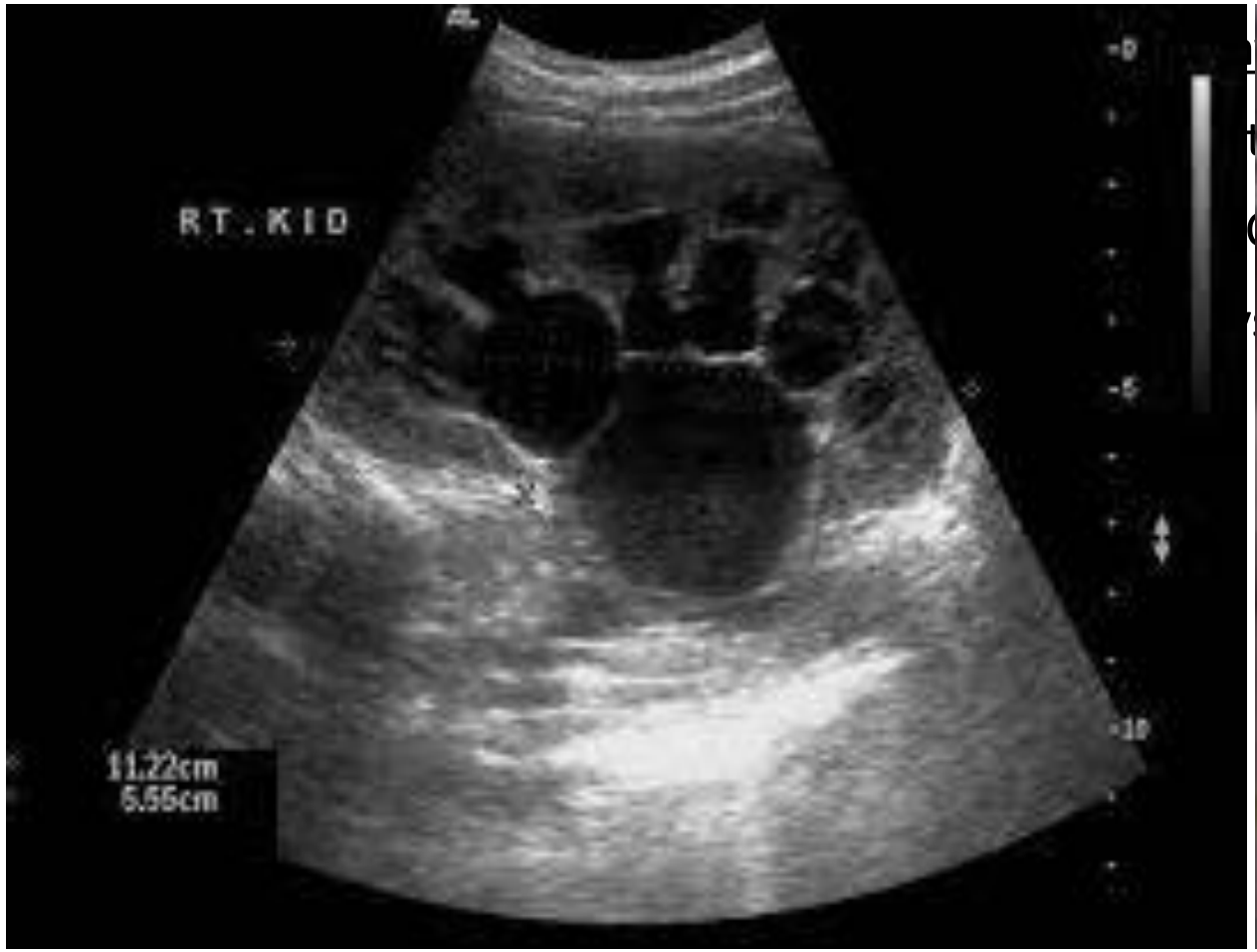
Case 6

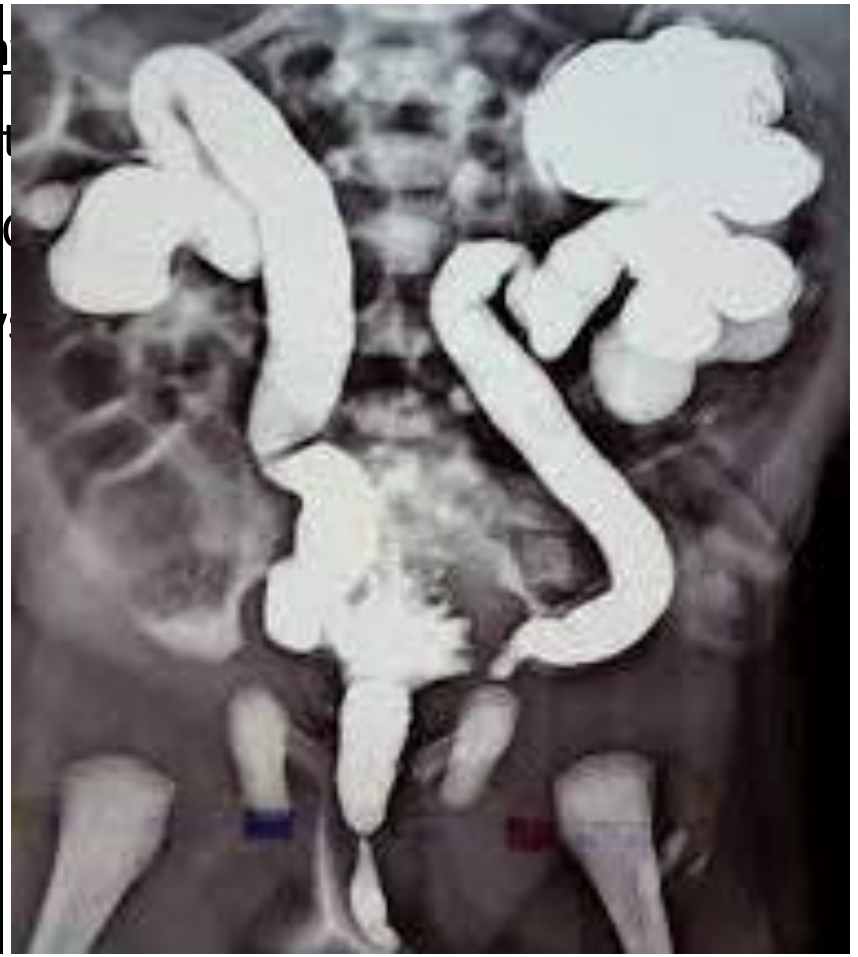
- 2 year old boy brought for evaluation of poor growth
- On probing, h/o of 3 episodes of UTI in the past
- Wt -4.2 z; Ht -3.9 z; BP 112/78 mm Hg
- Pallor +, Rickets +

Differentials?



Case 6: PUV





- Spine examination, LL tone, anal tone

Management

- Catheterize upon diagnosis; optimize metabolic parameters
- Fulguration at the earliest
- Follow-up evaluation to rule out residual valves
- Monitor renal functions; watch for UTI, valve-bladder syndrome
- If progression noted, optimize bladder before transplantation

PUV is a disease where fetal procedures have shown reasonable success

Take home messages

- Kidney diseases often encountered in the OPD but missed
- Detailed history and meticulous examination very helpful
- Tailor your investigations based on clinical suspicion
- Early & prompt diagnosis and timely referral improves survival

Thank you

SGLT2 Inhibitor- A Magic bullet in Nephrology! Pediatric Perspectives

Mahesh V

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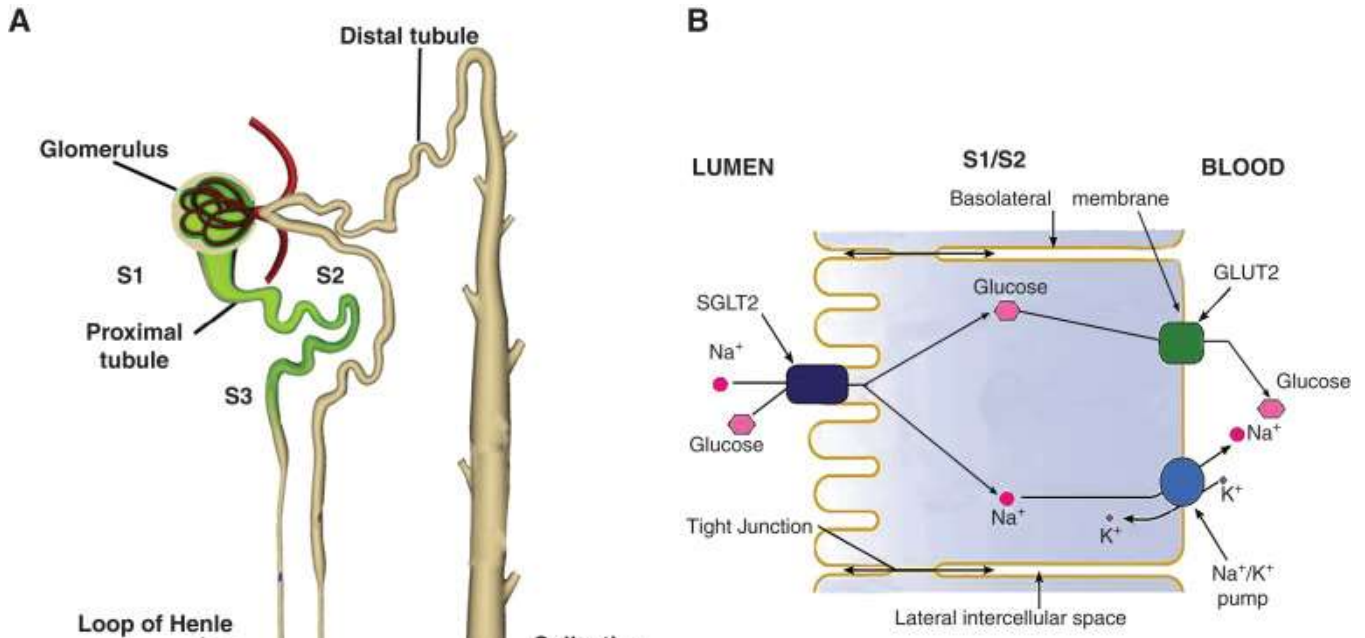
MD Pediatrics, DM Pediatric Nephrology (AIIMS, New Delhi)

Specific learning objectives

Drugs
Mechanism of action
Adverse effects
Trials in diabetic and non-diabetic nephropathy in adults
Guidelines for the use in CKD (KDIGO 2024)
Studies in children
Current stand for the use in children
Future directions

Sodium Glucose transporter 2 inhibitors

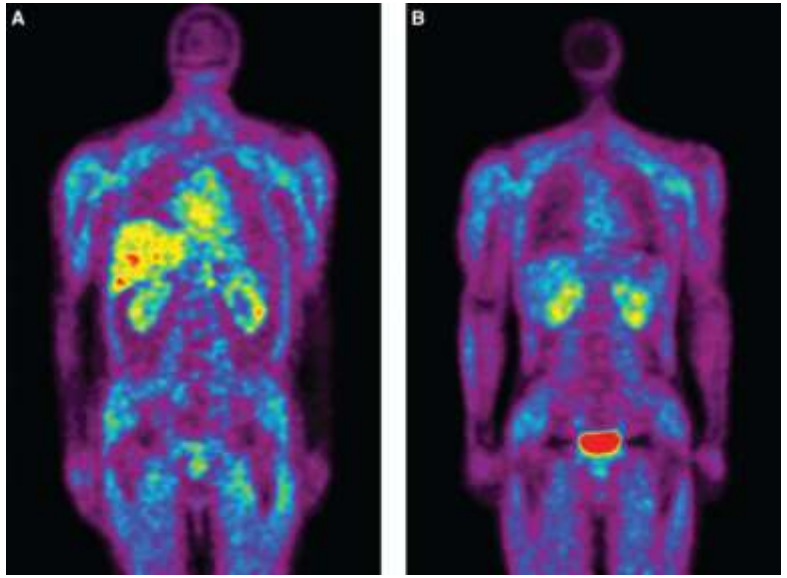
- SGLT2 is a channel: exclusive to PCT of kidney cortex
- SGLT inhibitors block this channel
- Glucosuria and increased natriuresis
- Glycemia control

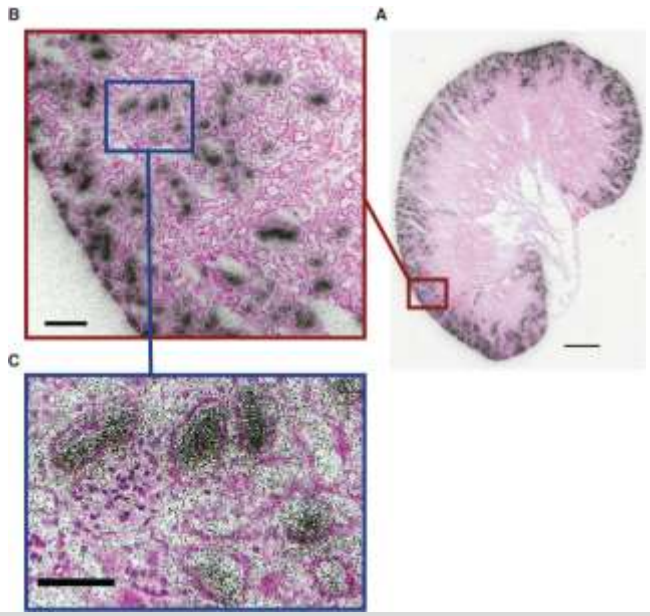


-Clin Pharmacokinet. 54, 691–708 (2015)

SGLT2 inhibitors: Pharmacokinetics

- Oral drugs, 95-99% bioavailability
- Metabolized in liver
- Filtered and excreted through kidney
- Act from the luminal side
- Half-life: ~24 hours
- Once daily administration





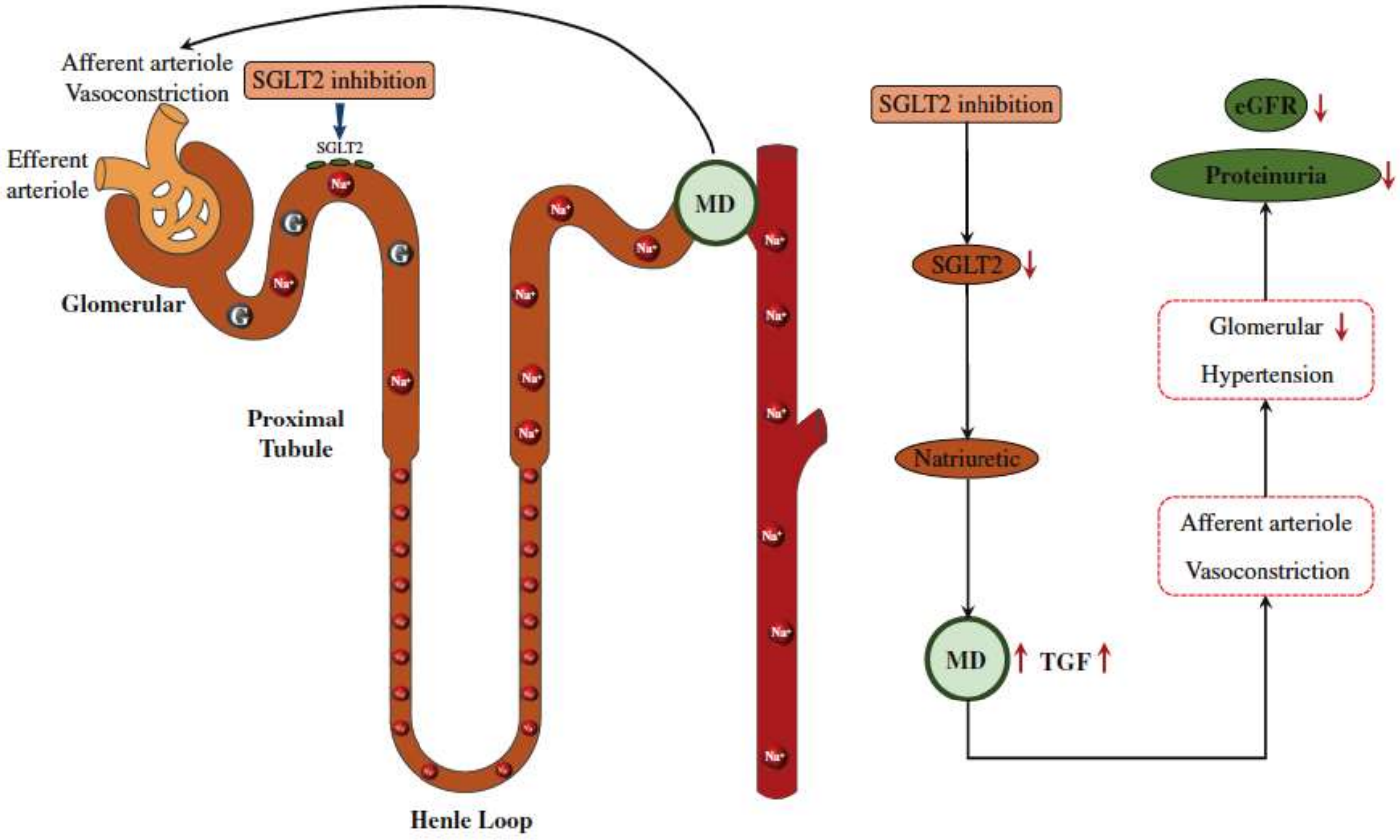
-KIDNEY360 2: 2027–2037, 2021

Drugs

Drugs	FDA approval in adults	FDA approval in children
Canagliflozin	March 2013	-
Dapagliflozin	January 2014	>10 years with T2DM- July 2024
Empagliflozin	August 2014	>10 years with T2DM- June 2023
Ertugliflozin	January 2017	-
Sotagliflozin	May 2023	-

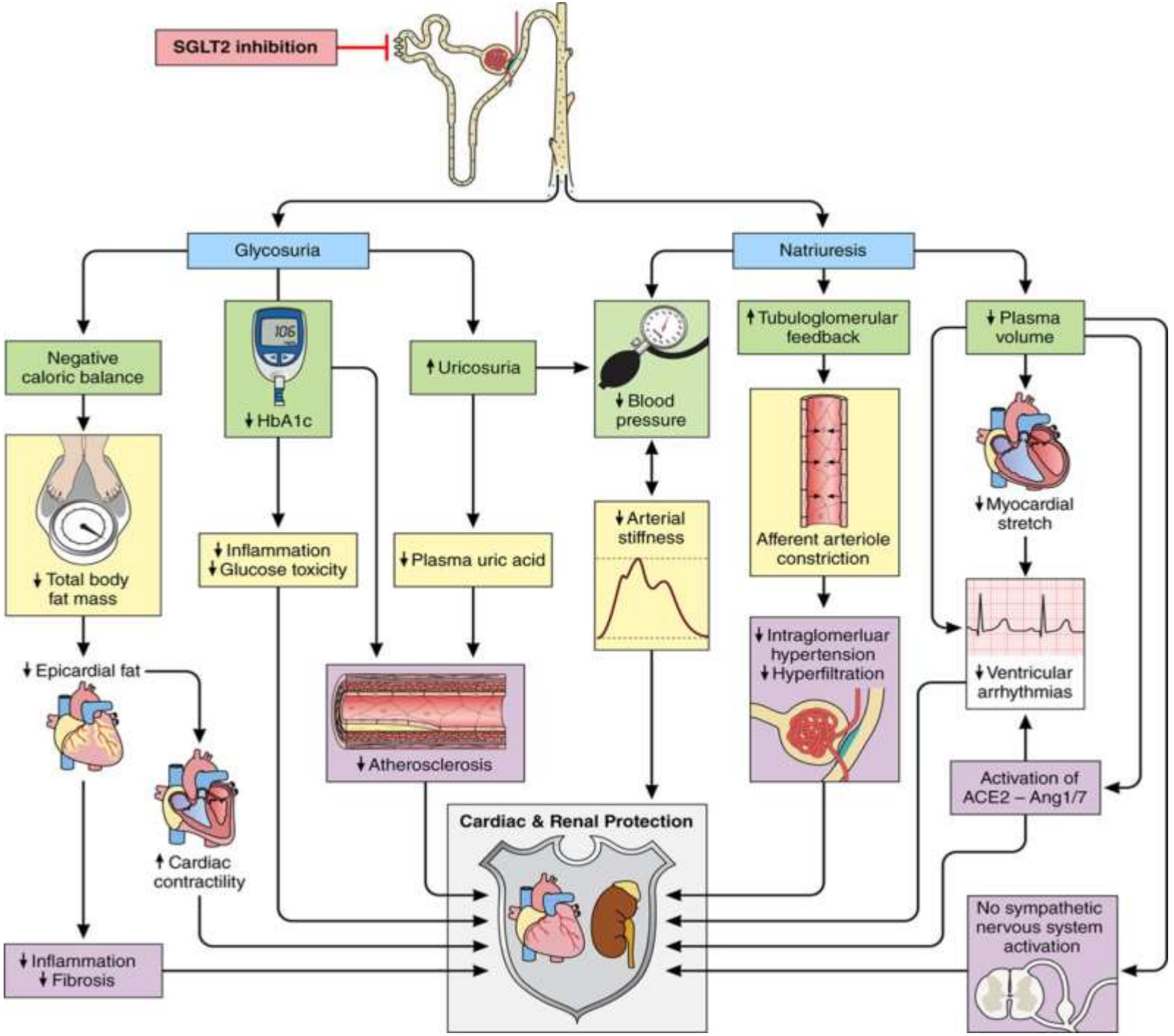
Mechanism of action: renoprotection

- Reduce workload on tubular cells
- Reduce direct glucose toxicity
- Reduce single nephron hyperfiltration
- Reduce BP modestly by decreasing fluid load
- Reduce pro-inflammatory cytokines and reduce fibrosis



-Nephrology. 2022;27:126–132.

Cardiac and renal protection



-Nephrology. 2022;27:126–132.

Adverse effects

Genital mycotic infections
Urinary tract infection
Euglycemic Diabetic ketoacidosis
Acute kidney injury
Hypotension
Fournier's gangrene
Lower limb amputation

SGLT2 inhibitor in patients with Primary Cardiovascular End Points (Adult)

	EMPA-REG OUTCOME	CANVAS	DECLARE TIMI 58
Population	7020, >18 years, T2DM with high CV risk and GFR >30	10,412, >18 years, T2DM with high CV risk and GFR >30 and <30	17,160 , >18 year, T2DM with high CV risk and GFR >60
Intervention	Empagliflozin 10 mg daily	Sotaligliflozin 200-400 mg daily	Dapagliflozin 10mg daily
Primary outcome **(HR, 95% CI)**	Composite of death due to CV events **0.62 (0.49-0.77)**	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke **0.86 (0.75 to 0.97)**	Rate of cardiovascular death or hospitalization for heart failure, MI or stroke **0.83(0.73 to 0.95)**
Renal outcomes **(HR, 95% CI)**	**0.51 [0.35–0.76]**	**0.61 [0.45–0.83]**	**0.55 [0.39–0.76]**

SGLT2 inhibitor in patients with Primary Renal End Points (Adult)

	CREDENCE	SCORED	DAPA-CKD	EMPA-KIDNEY
Population	4401, >18 years T2DM and CKD	10,584, >18 years, T2DM with CKD	4304, >18 year, CKD with or without T2DM	6609, >18 years, CKD with or without T2DM
Intervention	Canagliflozin 100 mg daily	Sotagliflozin 200-400 mg daily	Dapagliflozin 10mg daily	Empagliflozin 10 mg daily
Primary outcome **(HR, 95% CI)**	Composite of ESKD, doubling of creatinine, death due to renal or CV **0.70 (0.59-0.82)**	Composite of ESKD, doubling of creatinine, death due to renal or CV **0.71 [0.46–1.08]**	Composite of decline in eGFR, ESKD, death due to renal or CV **0.61 (0.51-0.72)**	Composite of hospitalization for HF, death from CV and death from any cause **0.72 (0.64-0.82)**
Adverse events	AKI, hypoglycemia	Diarrhoea, DKA, genital mycotic infections	Fournier's gangrene, hypoglycemia	DKA, lower limb amputation

SGLT2 inhibitors and IgA Nephropathy

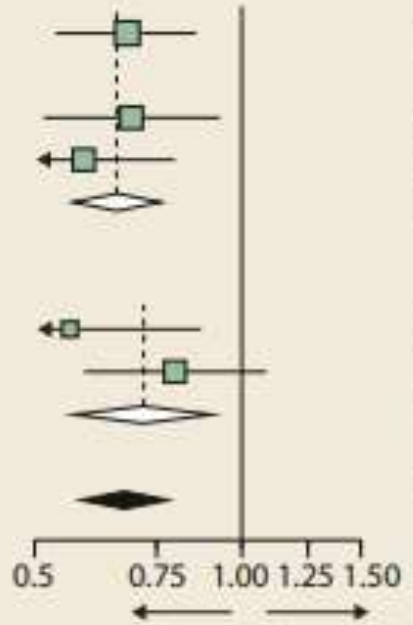
- DAPA-CKD had enrolled **270** patients with **IgAN** (Pre-specified)
- With GFR >45 and mean proteinuria of 900 mg/day
- Dapagliflozin significantly reduced the renal progression

  (HR: 0.23 [0.09–0.63])
- EMPA Kidney trial had 817 patients with IgAN (Post-hoc analysis)
- Combined DAPA CKD and EMPA Kidney trial data: 51% reduction in CKD progression (Meta-analysis)

-Biomedicines 2023, 11, 279.

SGLT inhibitors and renoprotection: Meta-analysis

	Mean baseline eGFR (ml/min/1.73 m²)	Events/participants		Rate per 1000 patient-years		Relative risk (95% CI)
		SGLT2i	Placebo	SGLT2i	Placebo	
Diabetes						
CREDENCE	56	116/2202	165/2199	20	29	0.68 (0.54, 0.86)
SCORED	44	NA/NA	NA/NA	26	37	
DAPA-CKD	44	77/1455	109/1451	24	39	0.69 (0.51, 0.92)
EMPA-KIDNEY	36	74/1525	116/1515			0.59 (0.44, 0.79)
Subtotal: DIABETES	**47**	**267/5182**	**390/5165**			0.66 (0.56, 0.77)
No diabetes						
DAPA-CKD	42	32/697	52/701	24	39	0.56 (0.36, 0.87)
EMPA-KIDNEY	39	83/1779	105/1790	25	31	0.80 (0.60, 1.07)
Subtotal: NO DIABETES	**40**	**115/2476**	**157/2491**			**0.72 (0.56, 0.91)**
TOTAL: OVERALL	**45**	**382/7658**	**547/7656**			**0.67 (0.59, 0.77)**



Heterogeneity by diabetes status: P=0.54

-Kidney International (2024) 105 (Suppl 4S), S117–S314

Current stand on use of SGLT2 inhibitors in adults: KDIGO 2024 guidelines

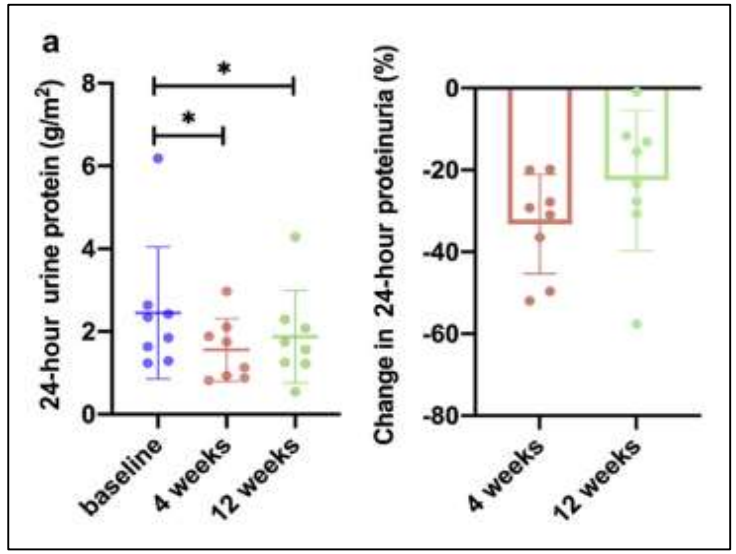
We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR >20 ml/min per 1.73 m2 with an SGLT2i (1A)

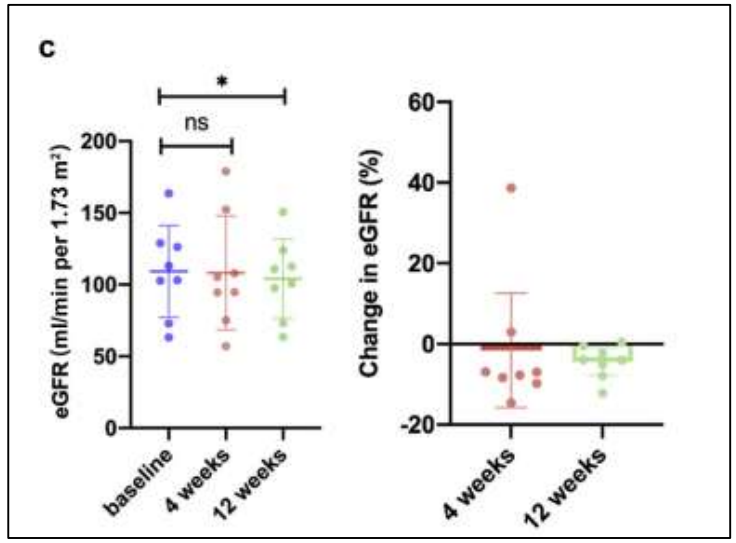
We recommend treating adults with CKD with an SGLT2i for the following (1A)

- eGFR >20 ml/min per 1.73 m2 with urine ACR >200 mg/g (>20 mg/mmol), or
- heart failure, irrespective of level of albuminuria

-Kidney International (2024) 105 (Suppl 4S), S117–S314

Studies in children





Single centre, China

N=9

CAKUT-2

Alport syndrome-5

Dent disease-1

FSGS-1

Mean age: 10.4 years

Males-5

Females-4

Intervention:

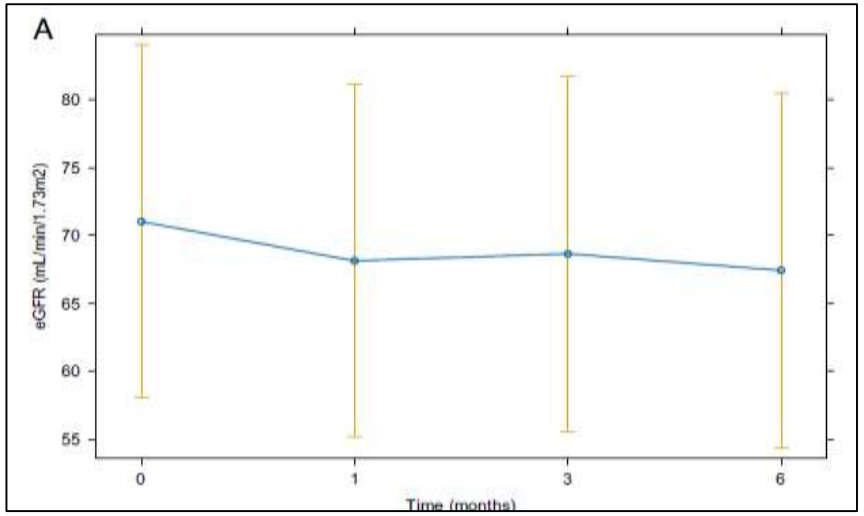
Dapagliflozin 5mg or 10mg once a day

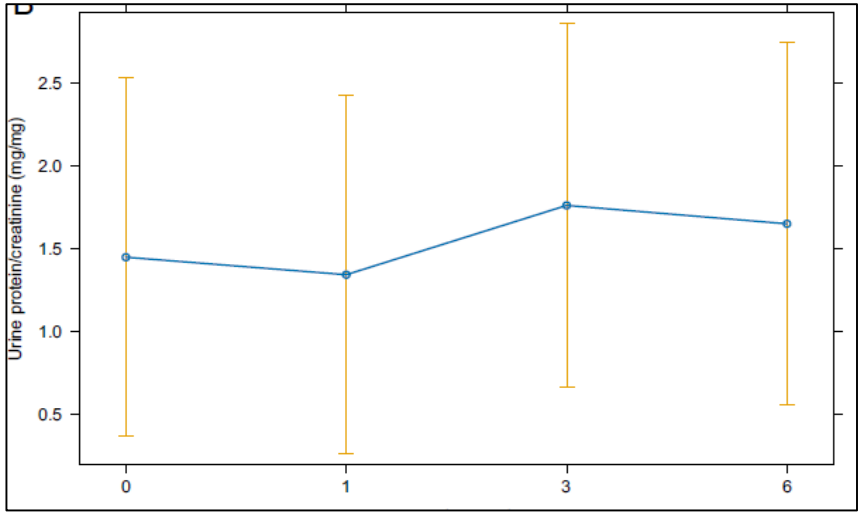
Adverse event:

asymptomatic bacteruria

-Kidney International Reports (2022) 7, 638–641

Studies in children





Single center, South Korea

N=22
Age- 15.6 (12.9-17.2 years)

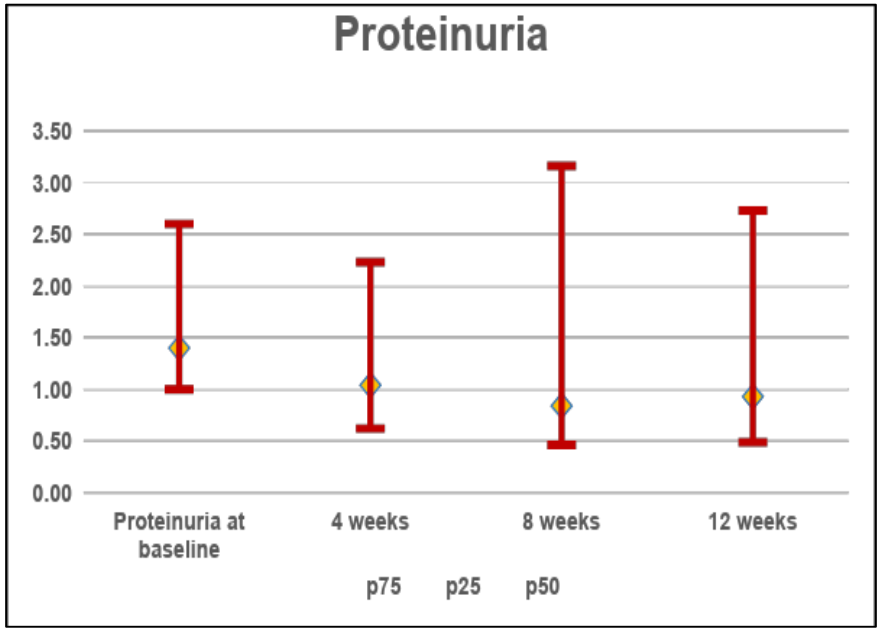
Alport syndrome-7
SRNS-7
IgAN-5
Atypical HUS-2
CAKUT-1

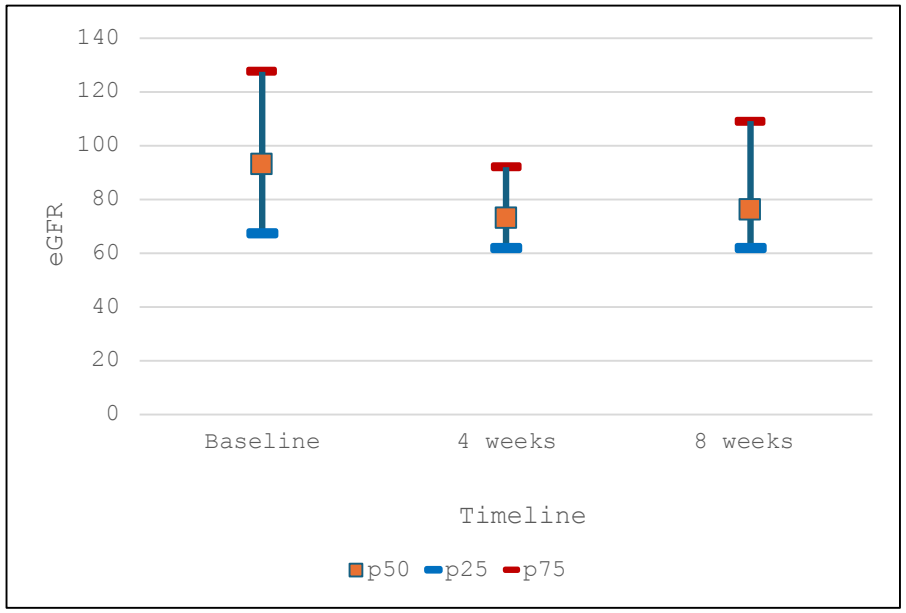
Characteristics	At baseline	At 6-month f/u
eGFR	71.1 (39.4-93.9)	65.5 (33.1-92.7)
UPCR	0.6 (0.4-1.5)	0.7 (0.3-1.7)
SBP	113 (104-121)	112 (107-123)
DBP	69 (63-74)	73 (71-80)

-Pediatric Nephrology (2024) 39:3551–3558

Studies in children: India (Unpublished data)

Single tertiary care center



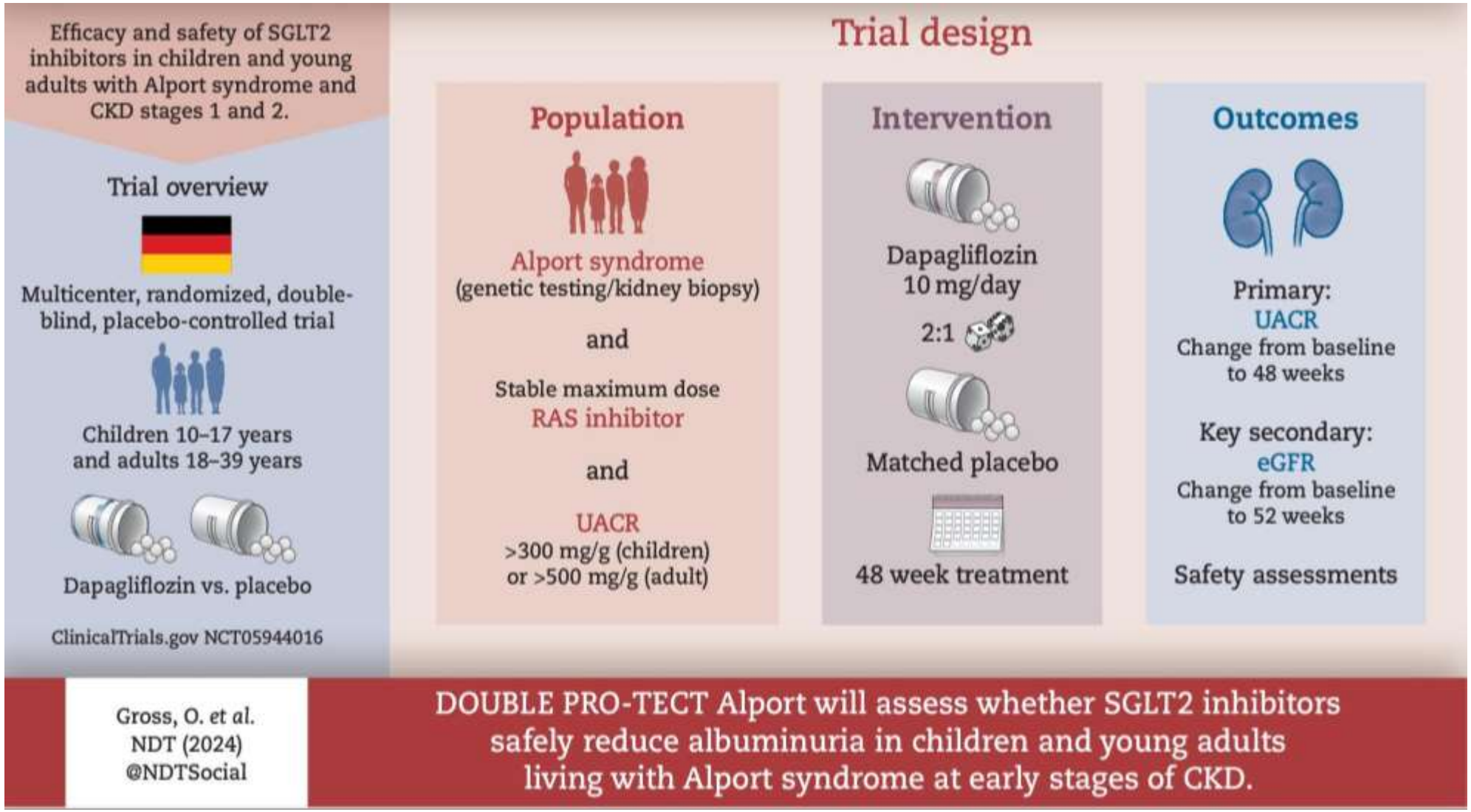


N=25
CNI resistant FSGS-11
Alport syndrome-7
GN-4
Others-3

Adverse effects
Rash, urticaria
Giddiness

-Courtesy: Dr Aditi Sinha, Addl Prof, AIIMS, New Delhi

Double PROTECT trial



-Nephrol Dial Transplant, 2024, Vol. 00, No. 0

Ongoing trials

Trial	Drug	Outcomes being tested	Trial Registration number
RENAL LIFECYCLES	Dapagliflozin	Renal outcomes in GFR <25, on dialysis and transplanted patients	NCT05374291
DAPA HD	Dapagliflozin	In hemodialysis patients	NCT05179668
NA	Empagliflozin	In hemodialysis patients	NCT05614115
PRESERVE	Dapagliflozin	In peritoneal dialysis patients	NCT05250752
CREST-KT	Dapagliflozin	In kidney transplant recipients	NCT04906213
INFINITI 2019	Dapagliflozin	In kidney transplant recipients	NCT04965935

-ClinicalTrials.gov

Future directions

The childhood kidney diseases which have less effective therapies like IgAN, Alport syndrome, CNI resistant nephrotic syndrome to be studied

Most of the childhood CKD is caused by CAKUT; fear of recurrent UTI due to SGLT2 inhibitors need to be studied

Children with CKD at high CV risk: obesity, metabolic syndrome and poorly controlled hypertension may benefit

Take home messages

Current data in children shows that the efficacy is inconclusive possibly because of small sample size and short follow up period

Data in children regarding efficacy and adverse events is lacking

Large multicentric trials with wide spectrum of children with CKD and/or proteinuria are required

Phase 2/3 trials in children <10 years and FDA approval are required

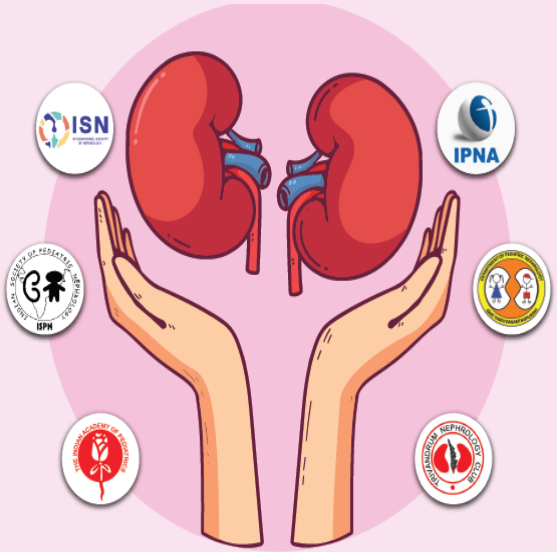
NATIONAL PEDIATRIC NEPHROLOGY CONCLAVE 2024

SAT-ISN SRC UPDATE 5 • IPNA TEACHING COURSE

Kidney Health for Every Kid Everywhere

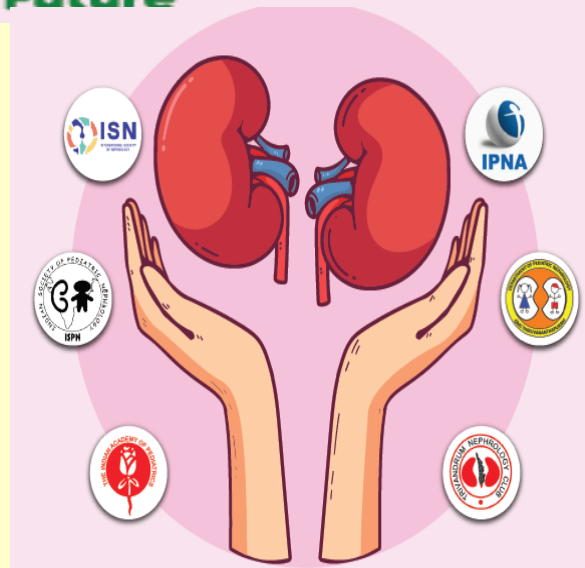
Kidney Diseases in Children

Optimizing Care & Preparing for Future



Organized by
Department of Pediatric Nephrology, SAT Hospital
Government Medical College, Thiruvananthapuram

MANAGEMENT STRATEGIES & OUTCOME



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Professor (Paed) & Head of Pediatric Nephrology, Institute of Child Health (Kolkata)
Consultant Paediatric Nephrologist, Apollo Gleneagles Hospital (Kolkata)

A STANDARD CASE SCENARIO

- 11 yrs girl
- Fever 2 week
- Myalgia and malaise
- Oral ulcer
- Rest of exam- normal

Investigation:

Hb 9.3, WCC 1800, N (56%),
Plt 1.1

Na 135, K 3.9, Cr 0.8, Alb 34

Urine: Protein 2+,
RBC: 10 -12 / HPF
24 hrs urine protein: 984mg
UP/UC=1.1

C3 66, C4 8.2, ANA & ds DNA +ve

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 71, No. 9, September 2019, pp 1400–1412
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SPECIAL ARTICLE

2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus

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Is it Lupus?

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR Anti-Smith antibody	6

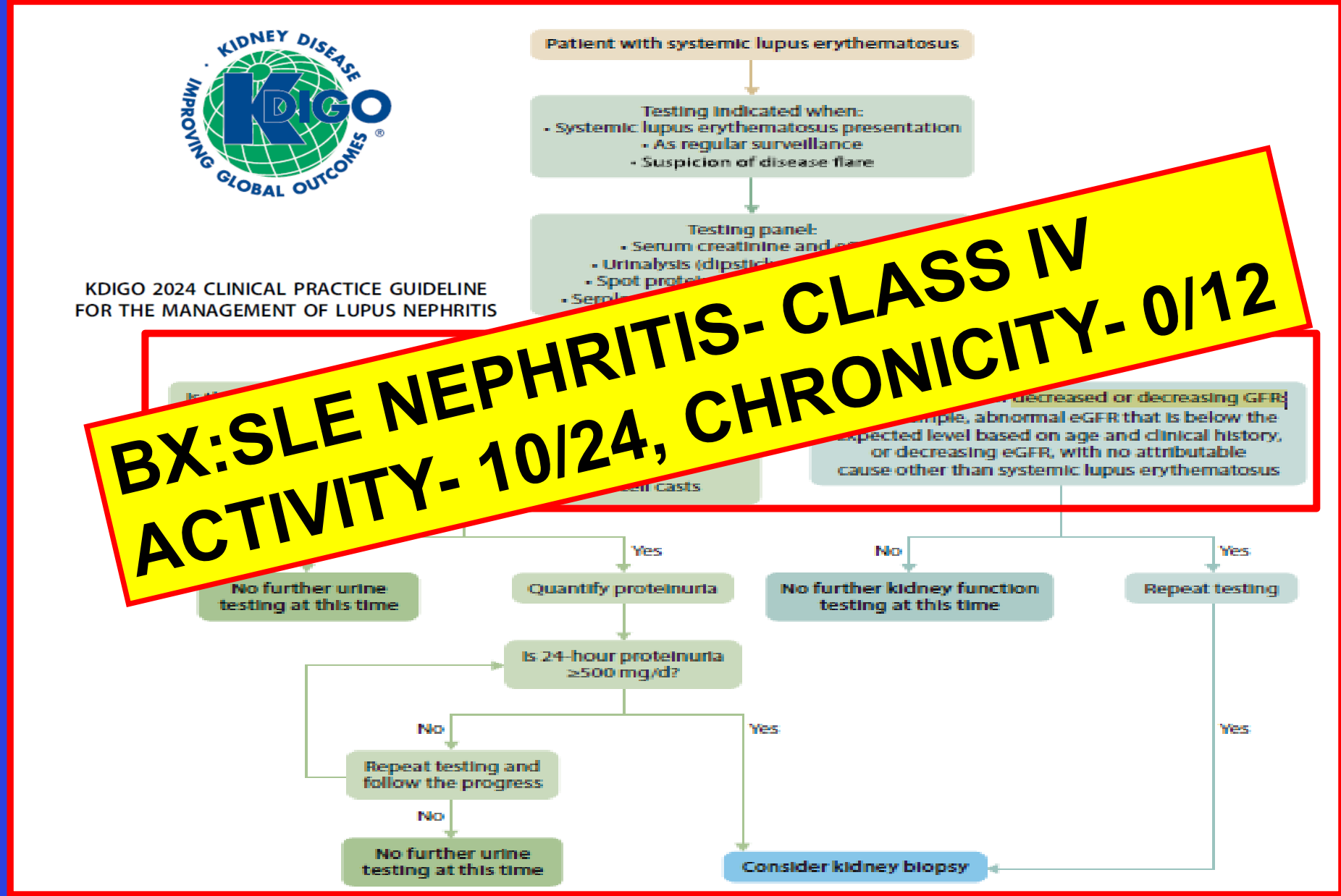
20 points

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Indications for Kidney Bx



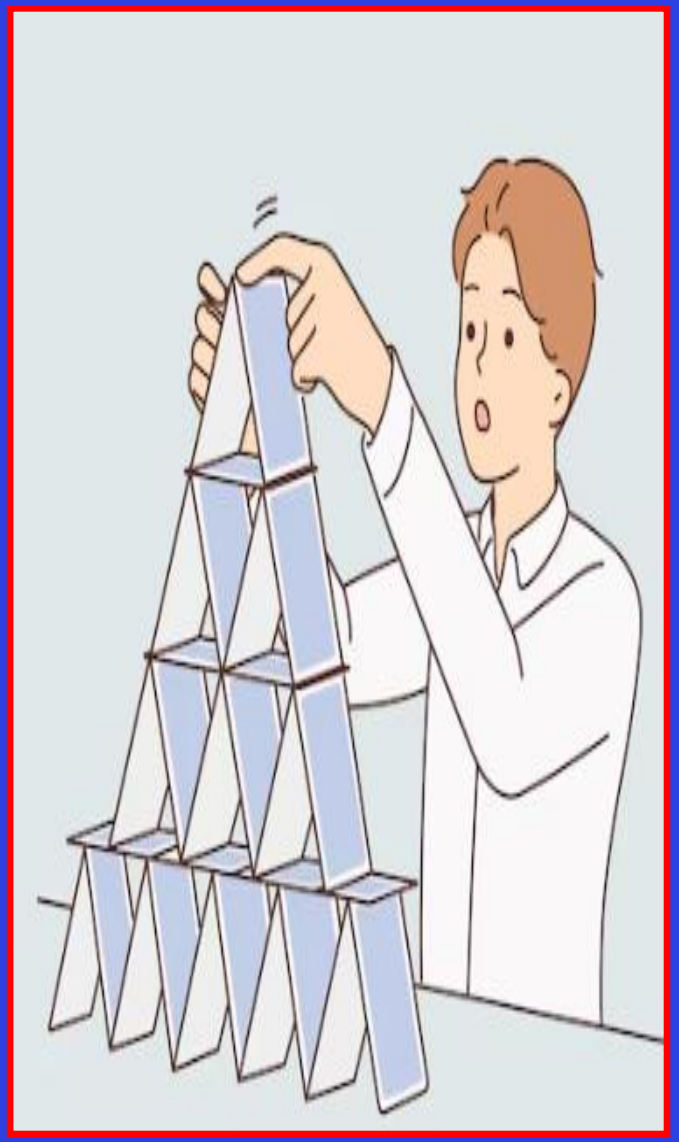
BX:SLE NEPHRITIS- CLASS IV
ACTIVITY- 10/24, CHRONICITY- 0/12

Objectives

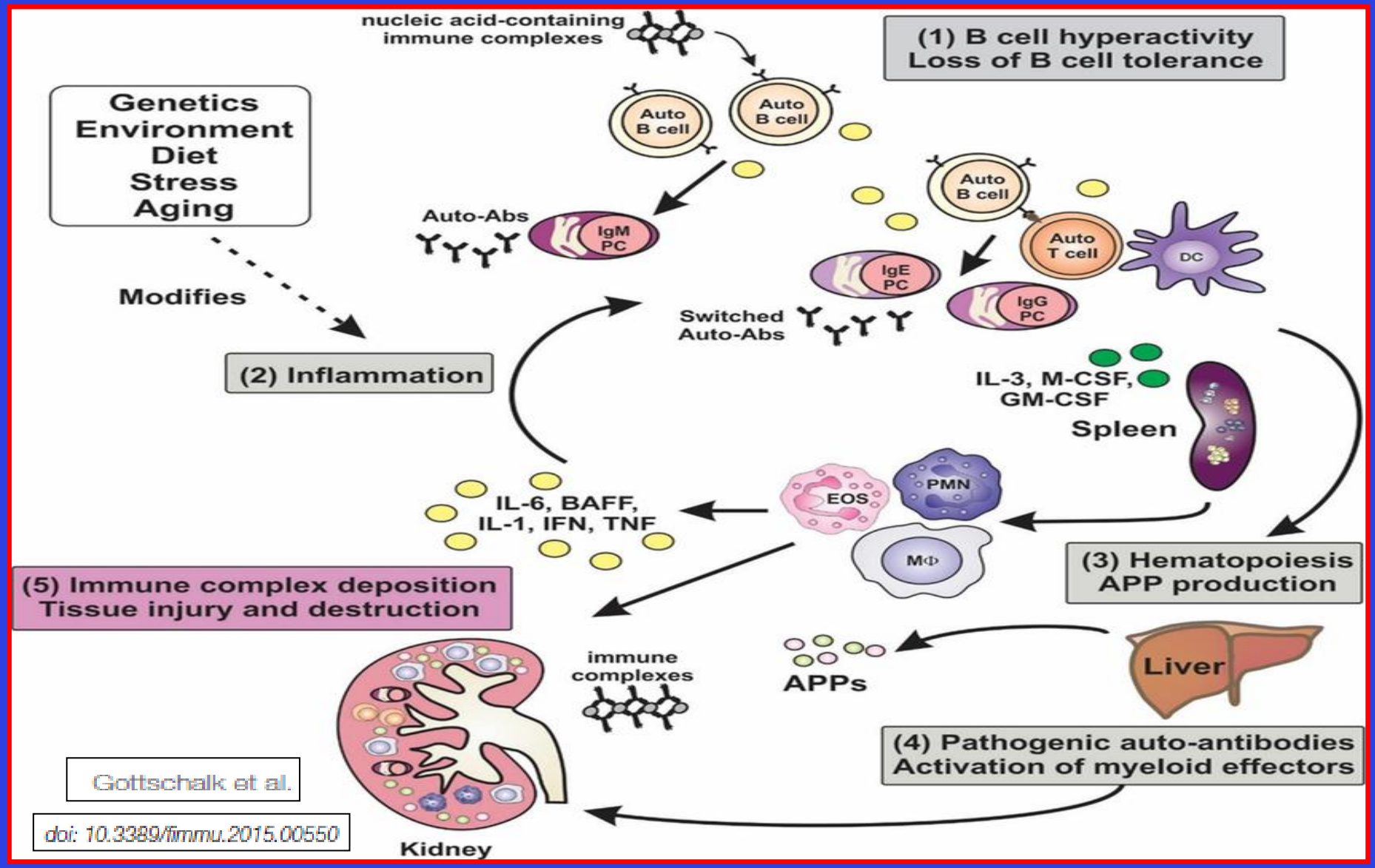
LUPUS NEPHRITIS:

- ***MANAGEMENT***
- ***OUTCOME***

How to manage?



Pathogenesis



Gottschalk et al.

doi: 10.3389/fimmu.2015.00550

LANDMARK TRIALS IN

LUPUS NEPHRITIS

1986

NIH

CYC or AZA + pred
vs
pred alone

Cytotoxic drugs group did better, specially IV CYC

1992

BOUPAS et al

IV Methylpred
vs
long or short course IV CYC

IV CYC was superior, long better than short course

1996

GOURLEY et al

IV Methylpred or IV CYC
vs
combination therapy

Combination therapy was superior

2000

CHAN et al

MMF + prednisolone
vs
CYC + prednisolone

MMF was as effective as CYC

2002

EUROLUPUS

Low dose CYC
vs
High dose CYC

Low dose group outcomes are comparable to high dose

2009

ALMS

MMF + pred
vs
IV CYC + pred

In post Hoc analysis, MMF was superior to CYC in hispanics and blacks

2011

ALMS Maintenace

MMF
vs
AZA

MMF was superior to AZA in maintaining remission

2012

LUNAR

MMF + pred + Ritux
vs
MMF + pred + placebo

Ritux did not improve outcomes

2015

Liu et al

Tacro + MMF + pred
vs
IV CYC + pred

No long term difference in outcomes

2018

AURA-LV

MMF + pred + Voclosporin
vs
MMF + pred + placebo

Voclosporin group had higher remission rates but also more serious adverse events

2020

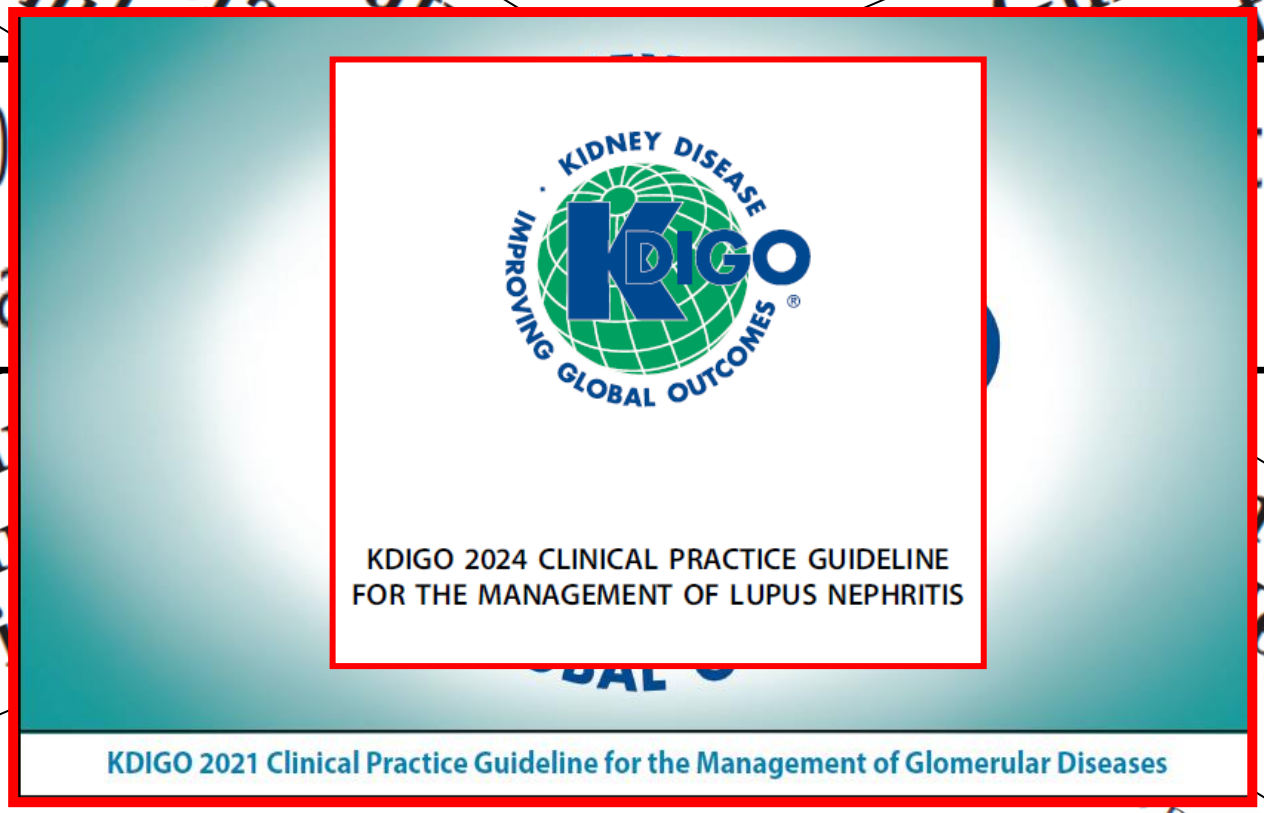
BLISS-LN

MMF + pred or IV CYC + pred
vs
MMF + pred or IV CYC + pred plus belimumab

Belimumab group had better renal outcomes

LANDMARK NEPHROLOGY

Guidelines


KDIGO 2024 CLINICAL PRACTICE GUIDELINE
FOR THE MANAGEMENT OF LUPUS NEPHRITIS
KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

STANDARD OF CARE

Non-immunosuppressant

10.2.1 General management of patients with lupus nephritis

Recommendation 10.2.1.1: We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contra-indicated *(1C)*.

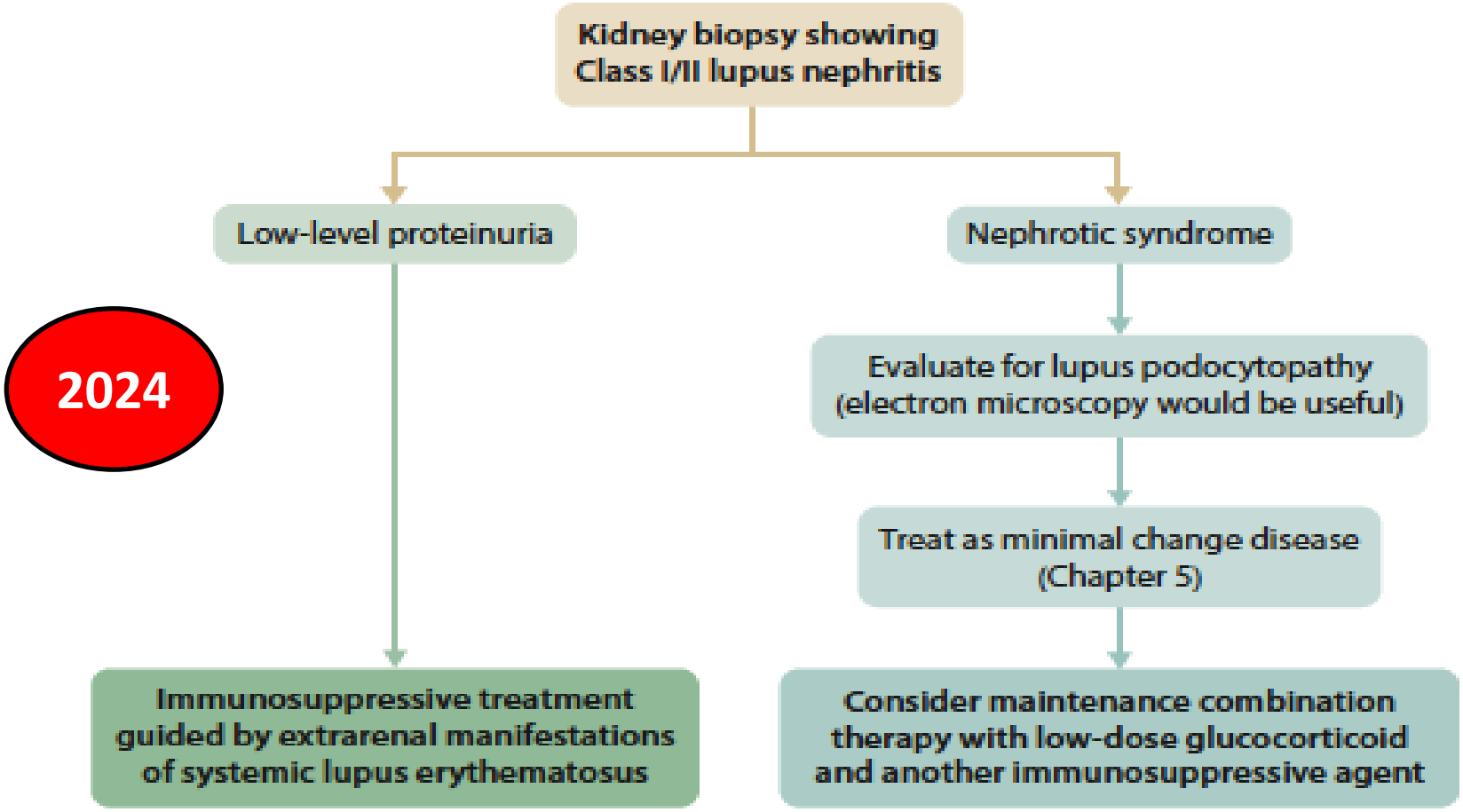
Risk	Risk attenuation
Cardiovascular risk	• Lifestyle modifications – smoking cessation, body weight optimization, exercise • Dyslipidemia management • Low-dose aspirin during pregnancy • Blood pressure control
Proteinuria and CKD progression (refer to Chapter 1)	• Avoid high-sodium diet • Optimize blood pressure • Renoprotective medications, such as RAAS blockade, SGLT2 inhibitor, etc., in stable patients without AKI • Avoid nephrotoxic insult • Prevent AKI
Infection risk	• Assess medical history of herpes zoster and tuberculosis • Screening for HBV, HCV, HIV, and HBV vaccination • *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below) • Influenza and pneumococcal vaccination • Individualized consideration for recombinant zoster vaccine • Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment
Bone injury	• Bone mineral density and fracture risk assessment • Calcium and vitamin D supplementation • Bisphosphonates when appropriate
Ultraviolet light exposure	• Broad-spectrum sunscreen • Limit ultraviolet light exposure
Premature ovarian failure	• Gonadotropin-releasing hormone agonists (i.e. leuprolide) • Sperm/oocyte cryopreservation
Unplanned pregnancy	• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)
Cancer	• Evaluate individual risk factors for malignancies • Age-specific malignancy screening • Minimize lifetime cyclophosphamide exposure to <36 g

2024

STANDARD OF CARE

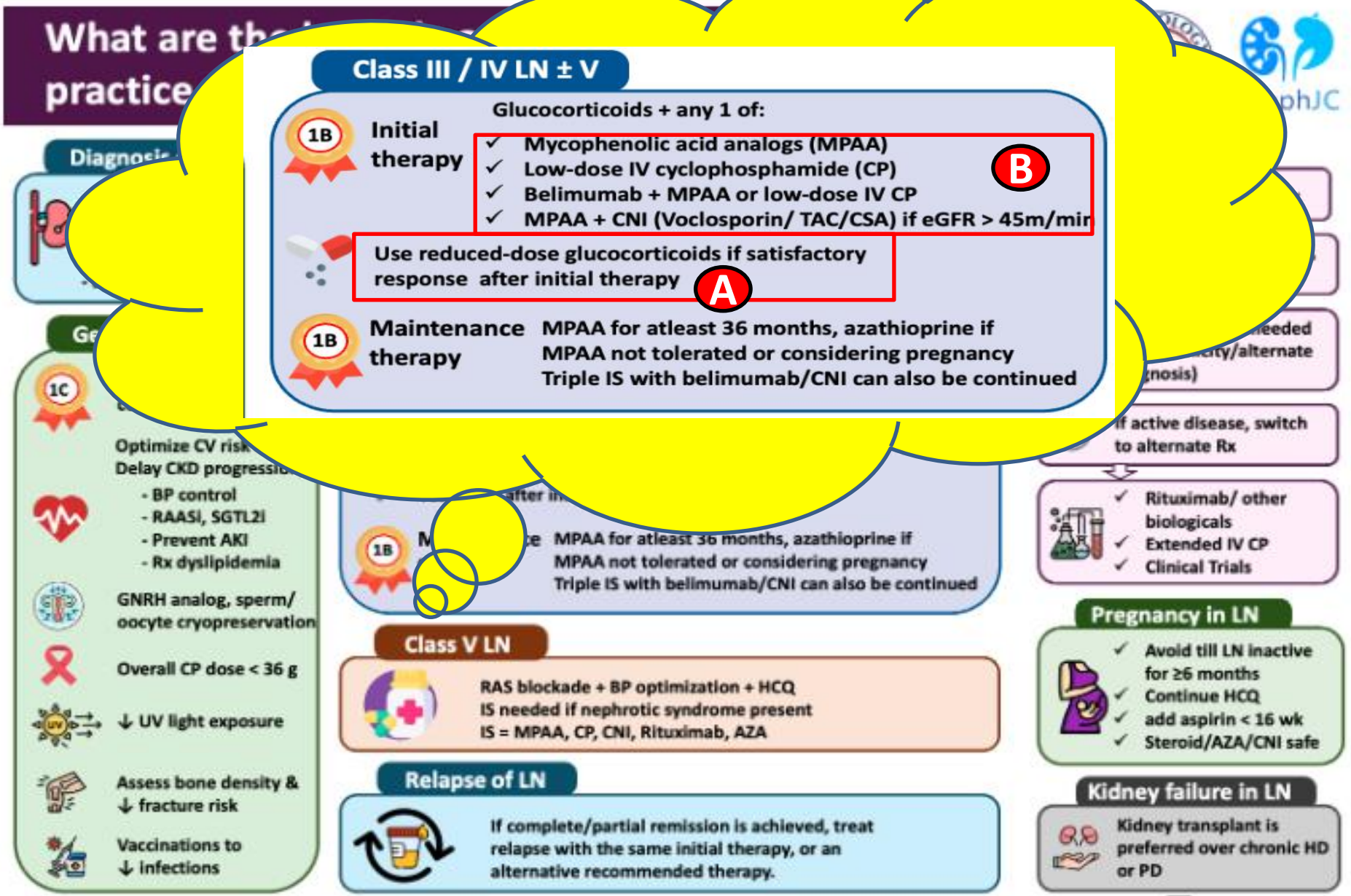
Immunosuppressant

10.2.2 Class I or Class II lupus nephritis



2024

Major changes in 2024 LN guideline update:



Rovin BH et al. Kidney International (2024) 105 (Suppl 1S), S1–S69

VA by Divya Bajpai @Divyaa24

Role of steroid

GENOMIC

NON-GENOMIC

Table 1. Current knowledge on the relationship between clinical dosing and cellular actions of glucocorticoids

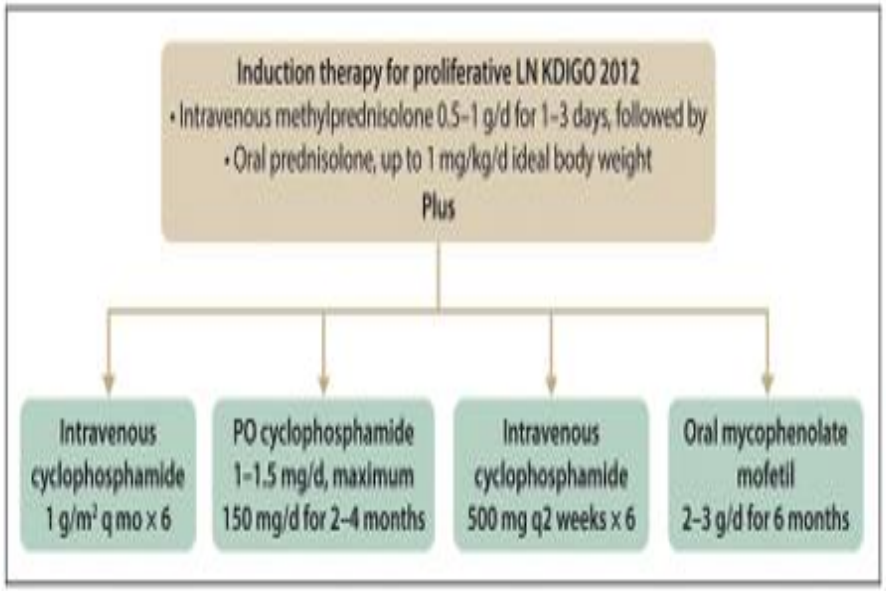
ARTHRITIS & RHEUMATISM
Vol. 50, No. 11, November 2004, pp 3408–3417
DOI 10.1002/art.20583

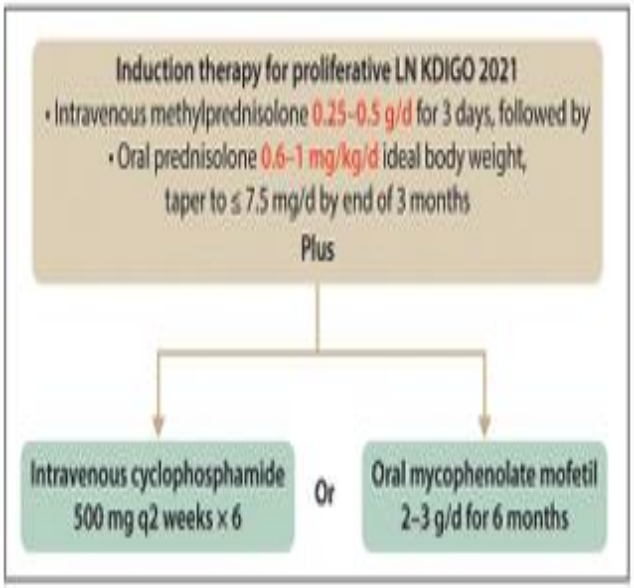
Terminology*	Clinical application†	Genomic actions (receptor saturation)‡§	Nongenomic actions§	
			Nonspecific	cGCR-mediated
Low dose (≤7.5 mg/day)	Maintenance therapy for many rheumatic diseases	+ (<50%)	–	?
Medium dose (>7.5 to ≤30 mg/day)	Initial treatment for primary chronic rheumatic diseases	++ (>50 to <100%)	(+)	(+)
High dose (>30 to ≤100 mg/day)	Initial treatment for subacute rheumatic diseases	++(+) (almost 100%)	+	+
Very high dose (>100 mg/day)	Initial treatment for acute and/or potentially life-threatening exacerbations of rheumatic diseases	+++ (almost 100%)	++	+(+?)
Pulse therapy (≥250 mg for 1 or a few days)	For particularly severe and/or potentially life-threatening forms of rheumatic diseases	+++ (100%)	+++	+(++?)

- **Genomic activity begins at low dose (<7.5 mg) and GCR fully saturated by 30 mg.**
- **Non –Genomic activity happens at high dose (100 mg of pred eq).**
- **Hence role of initial pulse methyl pred (500 mg x 3 days) to induce both Genomic & Non- Genomic activity followed by moderate dose GC (0.3-0.5 mg/Kg) for genomic activity.**

A

Reducing steroid dose…





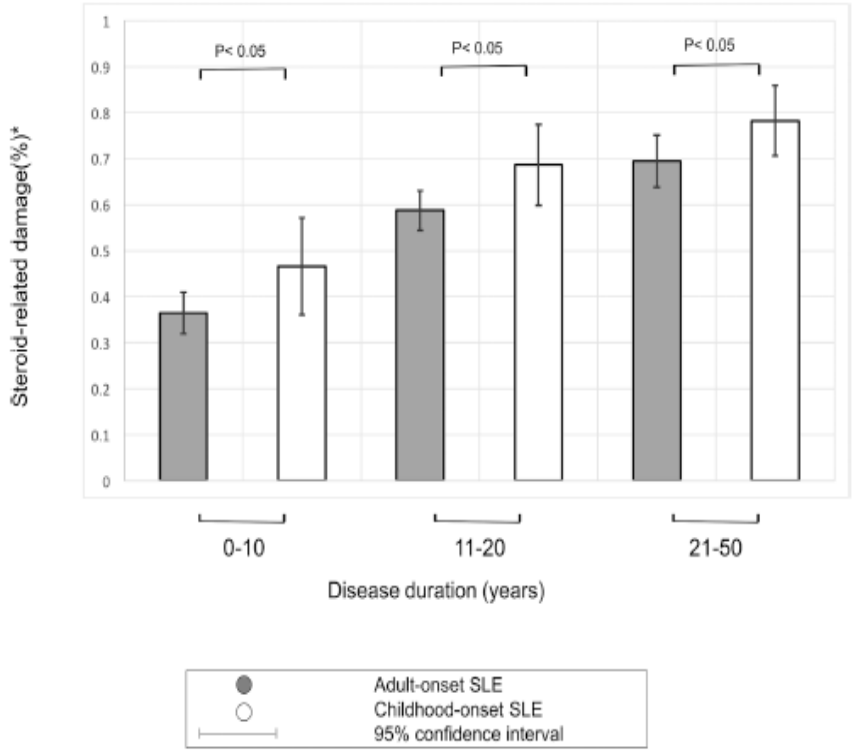
	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone Intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

2024

Why do we need to reduce steroid dose?

Semin Arthritis Rheum. 2019 October ; 49(2): 267–272. doi:10.1016/j.semarthrit.2019.05.010.

Longitudinal Disease- and Steroid-Related Damage Among Adults with Childhood-Onset Systemic Lupus Erythematosus



*Percentage of participants with steroid-related damage calculated from logistic regression results, adjusted for sex, ethnicity, age and disease duration category at time of base damage score, cyclophosphamide use ever and steroid use ever.

Figure 3: Adjusted frequency of steroid-related damage among adults with aSLE vs. cSLE by disease duration (N=1035)

Adjusted frequency of steroid-related damage is high in the entire cohort, but significantly higher in the childhood-onset group across all disease duration categories, with 78% of cSLE participants and 69% of aSLE participants reporting steroid-related damage after 20 years of disease duration (p=0.004).

Predictors of Steroid-related Damage^ in cSLE as compared to aSLE among 1035 participants in Lupus Outcomes Study

	Multivariate Analyses	
	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
cSLE	2.04 (1.30,3.30) *	1.70 (1.10,2.80) *
Demographics		
Age at baseline	1.08 (1.06,1.09) *	1.07 (1.06,1.09) *
Sex		
Male (reference)		
Female		1.10 (0.70,1.90)
Ethnicity		
Caucasian (reference)		
Hispanic		0.90 (0.60,1.40)
African American		1.80 (1.1,2.9) *
Asian		1.30 (0.80,2.00)
Other		1 (0.50,1.80)
SLE-related characteristics		
Disease duration category		
0–10 yrs (reference)		
10–20 years		1.70 (1.20,2.30) *
>20 years		1.80 (1.20, 2.70) *
Cyclophosphamide use		2.30 (1.50,3.40) *
Steroid use	3.62 (1.80,7.25) *	2.90 (1.40,5.80) *

^ Steroid-related damage is defined as one of the following: cataract, osteoporosis resulting fracture, avascular necrosis, diabetes.

OR=odds ratio

* P<0.05

Model 1: calculated from logistic regression results, adjusted for age at baseline BILD score and steroid use.

Model 2: calculated from logistic regression results, adjusted for baseline age, steroid use ever, demographics (sex, ethnicity) and SLE-related predictors (disease duration, cyclophosphamide use ever).

A

Why do we need to reduce steroid dose?

Comparison of standard of care treatment with a low steroid and mycophenolate mofetil regimen for lupus nephritis in the A IS and AURA studies

M Dall'Era[1], N Solomons[2], R Federico[2] and M Truman[2]

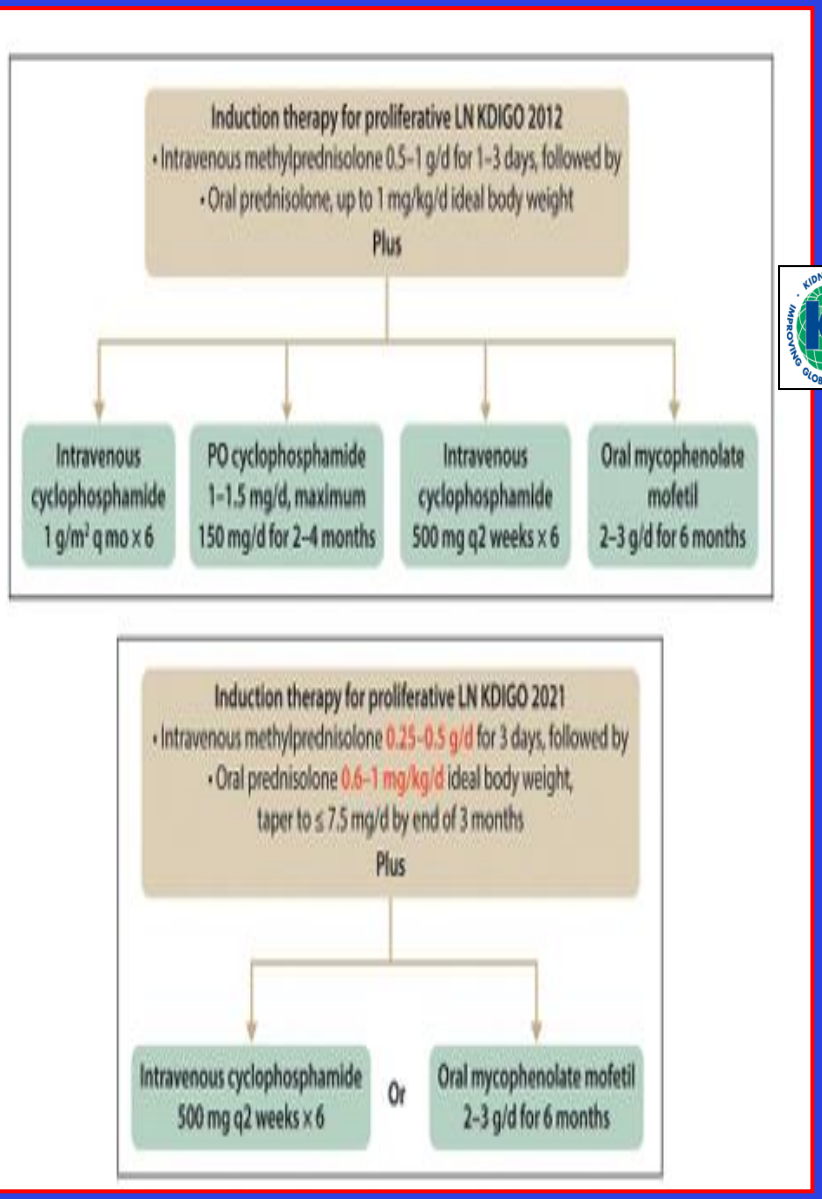
Table 5 Response to treatment in the 63 matched pairs of patients in ALMS and AU

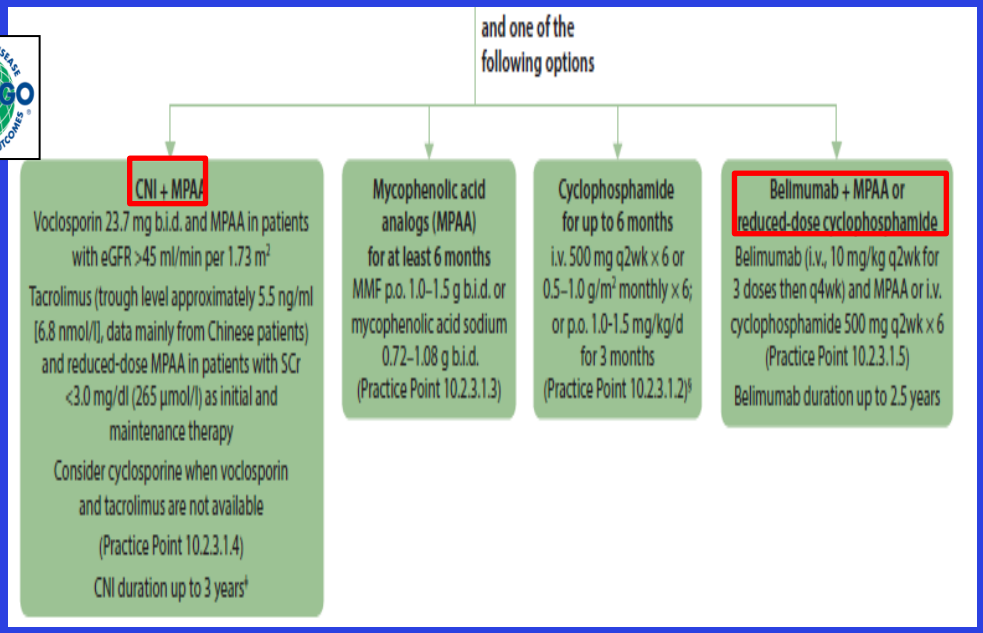
	ALMS			AURA					
	n	N	%				Odds ratio	(95% CI)	p-value
Week 24 response[a]	34					44.4	0.68	(0.34, 1.38)	0.2857
Week 24 remission[b]					63	14.3	0.88	(0.33, 2.35)	0.8035
Week 24 partial remission[c]				31	63	49.2	0.83	(0.41, 1.66)	0.5932
C3 normalization			27.3	13	56	23.2	0.81	(0.34, 1.90)	0.6628
C4 norm		55	45.5	18	56	32.1	0.57	(0.26, 1.23)	0.1516
	9	55	16.4	9	56	16.1	0.98	(0.36, 2.69)	0.9667
C3	31	55	56.4	22	56	39.3	0.50	(0.24, 1.07)	0.0731
C4 n week 24[f]	19	47	40.4	5	42	11.9	0.20	(0.07, 0.60)	0.0041
Anti-dsDNA pos, ≥30 IU/ml, week 24	26	48	52.4	25	51	49.0	0.81	(0.37, 1.79)	0.6087
>25% decrease proteinuria, week 24	28	52	53.8	33	60	55.0	1.05	(0.50, 2.21)	0.9027
UPCR ≤ 1 at week 24	32	48	66.7	24	53	45.3	0.41	(0.18, 0.93)	0.0323

Despite a total GC dose about 41% higher in ALMS than AURA, at 6 months the proportions of patients who achieved complete and partial renal responses were similar in both studies and not statistically different.

B

Expanding our IS basket…





Why do we need to expand our IS basket?

B

Treatment regimen	% with proteinuria >3 g/24 h at baseline[a]	Complete response rate (%) at 6 months[b]
ELNT, low dose ($n = 36$)	42	25
ELNT, high dose ($n = 38$)	45	24
ACCESS ($n = 66$)	52	23
ALMS, MMF ($n = 169$)	57	21
ALMS, CYC ($n = 171$)	60	22

ELNT, Euro-Lupus Nephritis Trial; ACCESS, Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study; ALMS, Aspreva Lupus Management Study; MMF, mycophenolate mofetil; CYC, cyclophosphamide.

[a]All subjects with proteinuria >1 g/24 h at baseline were included in the analysis.

[b]Complete response was defined as proteinuria ≤0.5 g/24 h and no worsening of the serum creatinine level, i.e. no more than 0.2 mg/dL increase from baseline.

May 2016 · Nephrology Dialysis Transplantation 31(7):gfw069
DOI: 10.1093/ndt/gfw069

Does addition of belimumab to standard therapy improve kidney outcomes in lupus nephritis?

#NephJC

Methods and

Multicentre, double blind RCT, n=448

Lupus Nephritis Class III to V

Mean age 33.4±10.6 yrs

Females: 88%

Conclusions: In act belimumab plus sta than those who rec

AURORA-1: Is voclosporin superior to placebo for treatment of lupus nephritis?

Methods

142 hospitals
27 countries
Double-blind

357 patients with active class III-V lupus

All received 2g/d MMF and tapere steroids

Conclusions: There in combination with MMF nephritis, with comparabl

Complete Renal Response

- ✓ UPCR <.5 mg/mg
- ✓ stable GFR
- ✓ no rescue Rx

Serious Adverse

B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial

Furie RA, *et al*. *Ann Rheum Dis* 2022;**81**:100–107.

ABSTRACT

Objective Randomised trials of type I anti-CD20 antibodies rituximab and ocrelizumab failed to show benefit in proliferative lupus nephritis (LN). We compared obinutuzumab, a humanised type II anti-CD20 monoclonal antibody that induces potent B-cell depletion, with placebo for the treatment of LN in combination with standard therapies.

Methods Patients with LN receiving mycophenolate and corticosteroids were randomised to obinutuzumab 1000 mg or placebo on day 1 and weeks 2, 24 and 26, and followed through week 104. The primary endpoint was complete renal response (CRR) at week 52. Exploratory analyses through week 104 were conducted. The prespecified alpha level was 0.2.

Results A total of 125 patients were randomised and received blinded infusions. Achievement of CRR was greater with obinutuzumab at week 52 (primary endpoint, 22 (35%) vs 14 (23%) with placebo; percentage difference, 12% (95% CI −3.4% to 28%), p=0.115) and at week 104 (26 (41%) vs 14 (23%); percentage difference, 19% (95% CI 2.7% to 35%), p=0.026). Improvements in other renal response measures, serologies, estimated glomerular filtration rate and proteinuria were greater with obinutuzumab. Obinutuzumab was not associated with increases in serious adverse events, serious infections or deaths. Non-serious infusion-related reactions occurred more frequently with obinutuzumab.

Conclusions Improved renal responses through week 104 were observed in patients with LN who received obinutuzumab plus standard therapies compared with standard therapies alone. Obinutuzumab was well tolerated and no new safety signals were identified.

B

Expanding our IS basket…

and one of the following options

CNI + MPAA

Voclosporin 23.7 mg b.i.d. and MPAA in patients with eGFR >45 ml/min per 1.73 m^2

Tacrolimus (trough level approximately 5.5 ng/ml [6.8 nmol/l], data mainly from Chinese patients) and reduced-dose MPAA in patients with SCr <3.0 mg/dl (265 µmol/l) as initial and maintenance therapy

Consider cyclosporine when voclosporin and tacrolimus are not available

(Practice Point 10.2.3.1.4)

CNI duration up to 3 years‡

Mycophenolic acid analogs (MPAA) for at least 6 months

MMF p.o. 1.0–1.5 g b.i.d. or mycophenolic acid sodium 0.72–1.08 g b.i.d.

(Practice Point 10.2.3.1.3)

Cyclophosphamide for up to 6 months

i.v. 500 mg q2wk × 6 or 0.5–1.0 g/m^2 monthly × 6; or p.o. 1.0-1.5 mg/kg/d for 3 months

(Practice Point 10.2.3.1.2)§

Belimumab + MPAA or reduced-dose cyclophosphamide

Belimumab (i.v., 10 mg/kg q2wk for 3 doses then q4wk) and MPAA or i.v. cyclophosphamide 500 mg q2wk × 6

(Practice Point 10.2.3.1.5)

Belimumab duration up to 2.5 years

NOT AVAILABLE IN INDIA & UNLIKELY TO BE WIDELY AVAILABLE IN INDIA IN NEAR FUTURE

Calcineurine inhibitors

Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials

Table 1. Network Treatment Estimates for Efficacy of Induction Therapies for Disease Remission in Proliferative Lupus Nephritis

Treatment Strategy	Complete Remission[a]	All-Cause Mortality[b]	ESKD[b]	Doubling Scr[b]	Treatment Failure[b]
MMF + calcineurin inhibitor	2.69 (1.74-4.16)[c]	1.00 (0.02-52.8)	—	3.02 (0.12-74.5)	—
Calcineurin inhibitor	1.74 (1.09-2.79)[c]	0.83 (0.27-2.56)	2.08 (0.23-18.9)	3.26 (0.25-42.0)	0.28 (0.12-0.65)[c]
IV cyclophosphamide + MMF	1.48 (0.62-3.53)	0.92 (0.06-15.3)	—	—	—
MMF	1.44 (1.00-2.06)[c]	1.20 (0.59-2.44)	2.60 (0.36-18.7)	1.51 (0.12-19.3)	0.51 (0.29-0.90)[c]
Oral cyclophosphamide	0.57 (0.23-1.40)	2.86 (0.82-10.0)	1.34 (0.31-5.88)	1.85 (0.48-7.22)	1.70 (0.24-12.5)
Prednisone	0.57 (0.23-1.40)	2.03 (0.72-5.77)	2.40 (1.05-5.48)	2.95 (1.45-6.01)[c]	4.03 (1.30-12.6)[c]
Mizoribine	0.29 (0.08-1.11)	—	—	—	—
Azathioprine	—	1.52 (0.52-4.46)	1.79 (0.56-5.70)	3.39 (1.18-9.71)[c]	4.15 (0.16-105)
Plasma exchange	—	8.21 (0.22-304)	2.92 (0.31-27.8)	—	—
Rituximab	—	—	—	—	—
No. of studies; no. of participants in network	19; 1,862	21; 1,694	12; 819	9; 984	10; 753

Am J Kidney Dis. 2017;70(3):324-336

Calcineurine inhibitors in children

Good outcomes with mycophenolate–cyclosporine-based induction protocol in children with severe proliferative lupus nephritis

Lupus (2010) 19, 965–973
http://lup.sagepub.com

E Aragon[1], YH Chan[2], KH Ng[1,3], YW Lau[1], PH Tan[4] and HK Yap[1,3]

Table 3 Comparison of parameters at pre-induction, 6 months and 12 months with MMF–CSA-based protocol ($n = 16$)

	Pre-induction	*6 months*		*12 months*	
		Descriptive	p-*value*[b]	*Descriptive*	p-*value*[c]
C3 (mg/dl)	47 ± 21	107 ± 27	<0.001	111 ± 38	<0.001
C4 (mg/dl)	12 ± 14	23 ± 14	0.04	22 ± 11	0.03
Anti-dsDNA[a]	15 (93.8%)	4 (25%)	<0.05	4 (25%)	<0.05
Haematuria (>5 red cells/high power field)	41 ± 57	4 ± 12	0.16	3 ± 6	0.13
24-h urine total protein (g/day/1.73 m^2)	6.97 ± 7.09	0.98 ± 1.56	0.02	0.21 ± 0.13	0.01
Creatinine					
(mg/dl)	3.3 ± 4.2	0.8 ± 0.3	0.05	0.7 ± 0.2	0.05
(μmol/l)	296 ± 371	69 ± 29		65 ± 21	
eGFR[d](ml/min/1.73 m^2)	72 ± 57	110 ± 34	0.04	117 ± 28	0.04
SLEDAI[e]	25.4 ± 8.7	3.8 ± 2.7	<0.001	2.9 ± 2.8	<0.001

Long-term outcomes with multi-targeted immunosuppressive protocol in children with severe proliferative lupus nephritis

E Aragon[1], LP Resontoc[1], YH Chan[2], YW Lau[1], PH Tan[4], HL Loh[4], KH Ng[1,3] and HK Yap[1,3]

Table 2 Comparison of parameters pre-induction and at last follow-up with multi-targeted immunosuppressive protocol ($n = 16$)

Descriptive	*Pre-induction*	*Last follow-up*	p *value (unadjusted)*	p *value (adjusted)*
C3 (mg/dL)	47 ± 21	107 ± 27	<0.001	<0.001
C4 (mg/dL)	12 ± 14	23 ± 14	0.011	0.043
Haematuria (red blood cell/high power field)	40.5 ± 56.8	3.9 ± 12.3	0.022	0.019
Urine protein (g/day/1.73m^2)	6.97 ± 7.09	0.20 ± 0.02	0.002	0.001
Creatinine (mg/dL)	3.3 ± 4.2	0.8 ± 0.3	0.022	0.023
(μmol/L)	(296 ± 371)	(69 ± 29)		
eGFR (ml/min/1.73m^2)	72 ± 57	109.7 ± 34	0.009	0.034
SLEDAI	25.4 ± 8.7	0.4 ± 0.8	<0.001	<0.001

Lupus (2015) 0, 1–8
http://lup.sagepub.com

p values refer to the comparisons between the values of the clinical and laboratory parameters pre-induction and at last follow-up. Mixed model analysis was performed adjusting for age at induction, gender, duration of disease prior to induction, prior treatment with CYC and/or AZA and duration of follow-up/therapy.

CNI use in pSLE Nephritis
@ ICH, Kolkata

- **8** children (5 girls) with **median age 10.2 years** (IQR 8.5-12 years) having SLE Nephritis received CNI for induction
- All of them had **Nephrotic range** proteinuria at presentation
- Extra-renal manifestations were also present in all of them
- Histopathological, 3 had **Class V**, 2 patients had Class **IV+V**, 1 had **class III+V** and another 2 had only **class IV** Lupus nephritis
- CNI (Tacrolimus) was used in these children as **second line** induction agent after Cyclophosphamide or MMF
- All the children achieved **Complete Remission** within median period of 6 months (IQR 4 - 7.5 months) of initiation of CNI
- **No** renal flare have been recorded in these children till date.

Rituximab…

THE JOURNAL OF PEDIATRICS • www.jpeds.com (J Pediatr 2017;187:213-9) ORIGINAL ARTICLES

Efficacy and Safety of Rituximab in the Management of Pediatric Systemic Lupus Erythematosus: A Systematic Review

Table IV. Effectiveness data

Studies	Follow-up	Corticosteroid dose	C3, mg/L	C4, mg/L	Hemoglobin, g/dL	Albumin, g/dL	dsDNA, IU/L	SLEDAI
Willems et al (2006)[20]	2-9 mo	NR	I	I	NR	NR	D, n = 5; increase, n = 1; remain high, (n = 1)	-
Nwobi et al (2008)[17]	1-3 mo	D (P< .0001)	I (P< .01)	NI	-	I (P= .001)	I (P< .01)	D (P= .0004)
Podolskaya et al (2008)[19]	6 mo	NR	I (P< .005)	I (P< .05)	I (P< .05)	I (P< .005)	I (P< .005)	-
	12 mo		I (P< .05)	I (P< .05)	I (P< .05)	I (P< .05)	I (P< .05)	-
Jansson et al (2011)[14]	6 mo	NR	I (P= .006)	NR	NR	NR	NR	NR
Su et al[10] (2012)*	12 mo	D (P< .001)	NR	NR	NR	NR	NR	NR, score obviously reduced
Pavon-Sanchez and Sánchez-Sánchez (2013)[16]	4 wk	NR	I (P= .048)	I (P= .032)	NI (P= .53)	NR	NR	D (P= .03)
Alexeeva et al (2013)[18]*	6 mo	D (P< .01)	NR	I (P= .04)	NR	NR	I (P= .04)	D (P= .002)
	12 mo	D (P< .01)		I (P< .01)			I (P< .01)	D (P< .001)
Lehman et al (2014)[13]	12 mo	D (P< .05)	I (P< .001)	NR	I (P< .05)	I (P< .025)	NR	D (P< .005)
Ale'ed et al (2014)[12]	6 mo	D (P= .005)	I (P= .003)	I (P= .01)	NR	NR	NI (P= .5)	D (P= .0002)
Olfat et al (2015)[11]	1 mo	NR	NR	NR	I	NR	NR	NR
Tambralli et al (2015)[9]	12 mo	D (P< .001)	I (P< .001)	I (P< .001)	I (P< .001)	I (P< .001)	NI (P= .128)	NR
Watson et al (2015)[15]	2.5 mo	D (P= .01)	I (P< .001)	I (P= .001)	I (P= .02)	I (P= .026)	I (P< .001)	NR

MAINTENANCE immunosuppressant

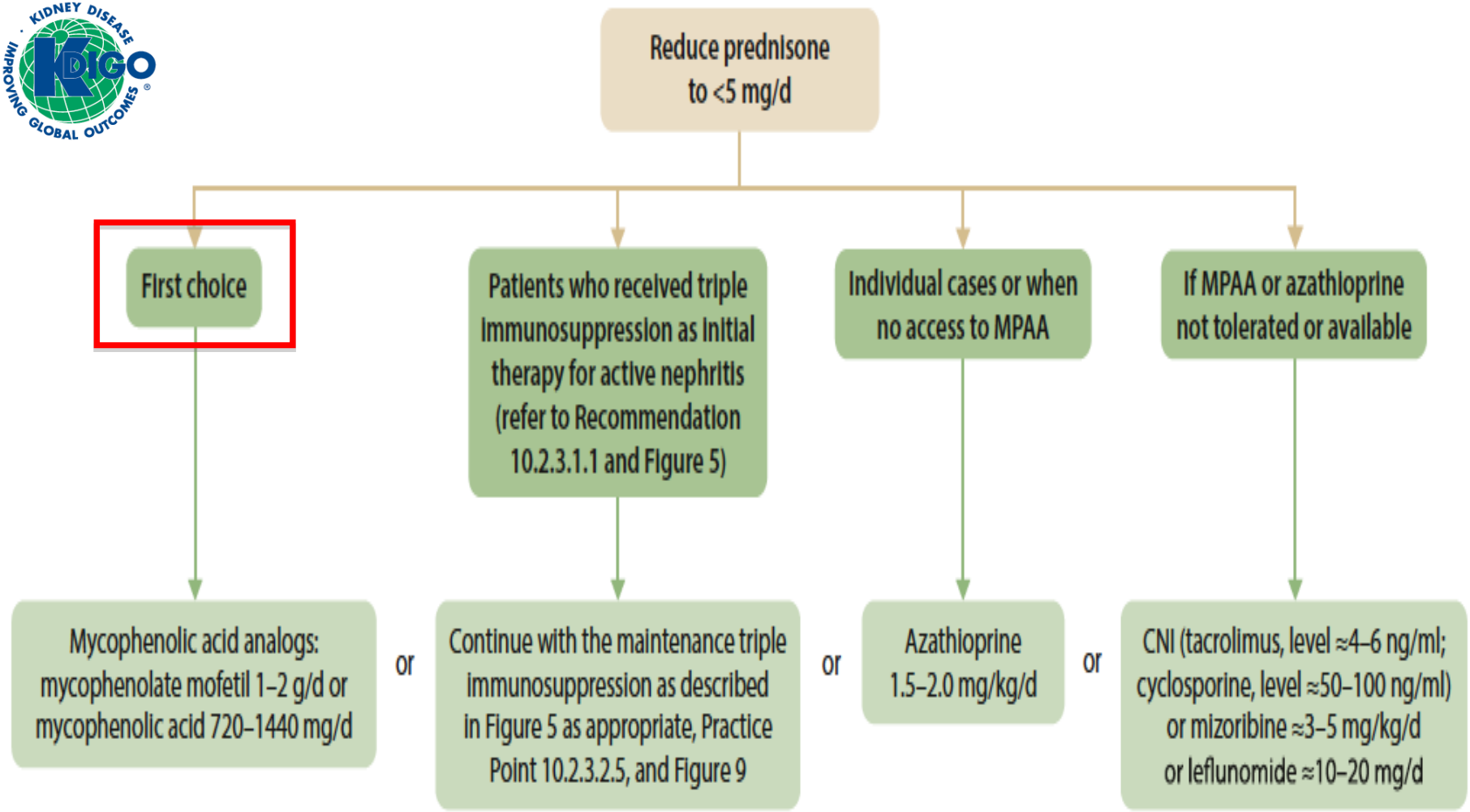
Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials

Table 4. Summary Network Estimates of Drug Regimens as Maintenance Treatment on Disease Relapse Compared to Azathioprine

Drug(s) Comparison for Relapse	Network Meta-analysis Estimate vs Azathioprine
MMF	0.53 (0.31-0.90)[a]
Calcineurin inhibitor	0.64 (0.22-1.88)
Azathioprine	1.00 (reference)
IV cyclophosphamide	1.68 (0.51-5.51)

Note: Based on 6 studies (570 participants) in network. Values are given as odds ratio (95% confidence interval) derived from network meta-analysis. Odds ratio $<$ 1 favors active drug class. The heterogeneity tau (τ) value in the network analysis for treatment relapse was $\tau < 0.001$ (low heterogeneity), consistent with the possibility there was insufficient statistical power in the network to detect heterogeneity. Treatment estimates are shown in order of efficacy per the surface under the cumulative ranking (SUCRA) curve.

Maintenance immunosuppressant



Choice of Induction Agents

MMF
96 (61%)

CYC
55 (35%)

RTX
2 (1%)
Due to AIHA

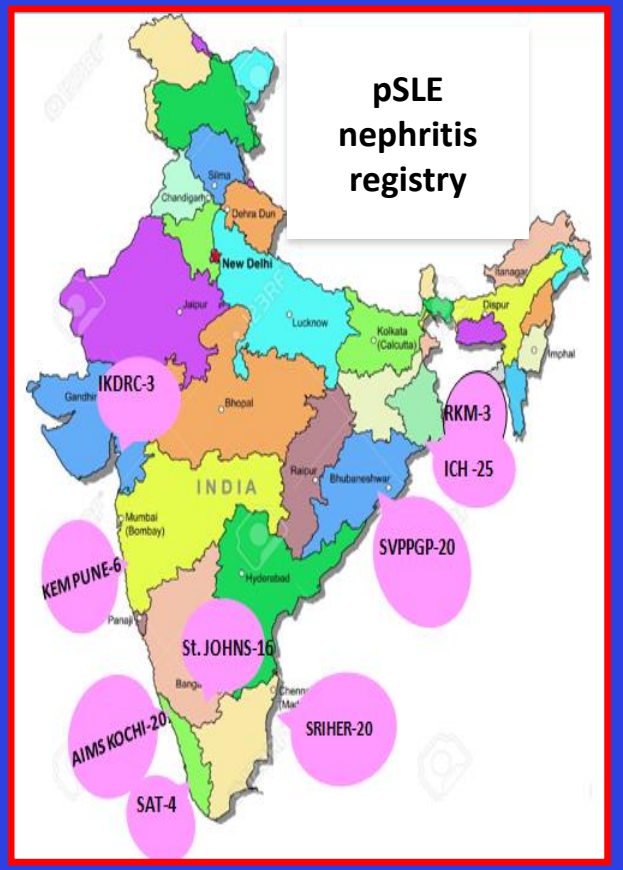
None
(2 deaths, 2 class 2, 1 class 1

2nd line 11 (11%):
- CYC – 1
- RTX – 3
- CNI - 7

2nd line 10 (18%):
- MMF – 6
- RTX – 3
- CNI - 1

3rd line 1 (1%):
- CNI – 1 (RTX 2nd line)

3rd line 2 (4%):
- CNI – 1 (MMF 2nd line)
- MMF – (RTX 2nd line)



A STANDARD CASE SCENARIO

- **11 yrs girl**
- **Wt: 38 kg, Ht 138 cm, BSA:**
- **Fever 2 week**
- **Myalgia and malaise**
- **Oral ulcer**
- **ANA+VE, C3⬇**
- **Cr 0.8 mg/dl**
- **UP/UC =1.1**

✓ **SLE NEPHRITIS TYPE IV**

Activity score:10

Chronicity score:0

✓ **T/t with pulse CH3pred, Pred & MMF**

✓ **HCQ, Enalapril, Vit D and Sun screen**

At 6 months (Pred 10 mg / MMF 500 mg BD):

- ✓ Afebrile, normal activity
- ✓ 24 hrs urine protein: 380 mg i.e. 0.54mg/1.73 m^2/24 hrs. (UP/UC: 0.4)
- ✓ Cr 0.6, C3 / C4 Normal
- ✓ Urine R/E: Pr 1+, RBC 10-15/Hpf

Measuring outcome

You have a right to perform your prescribed duty, but you are not entitled to the fruits of action. Never consider yourself the cause of the results of your activities, and never be attached to not doing your duty.
(Bhagavad-gītā 2.47)

Measuring outcome

Practice Point 10.2.5.1.1: Definitions of response to therapy in LN used in clinical trials are provided in Figure 11.

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but no later than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 • eGFR ≥ the pre-flare value or ≥60 ml/min • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

PARTIAL REMISSION

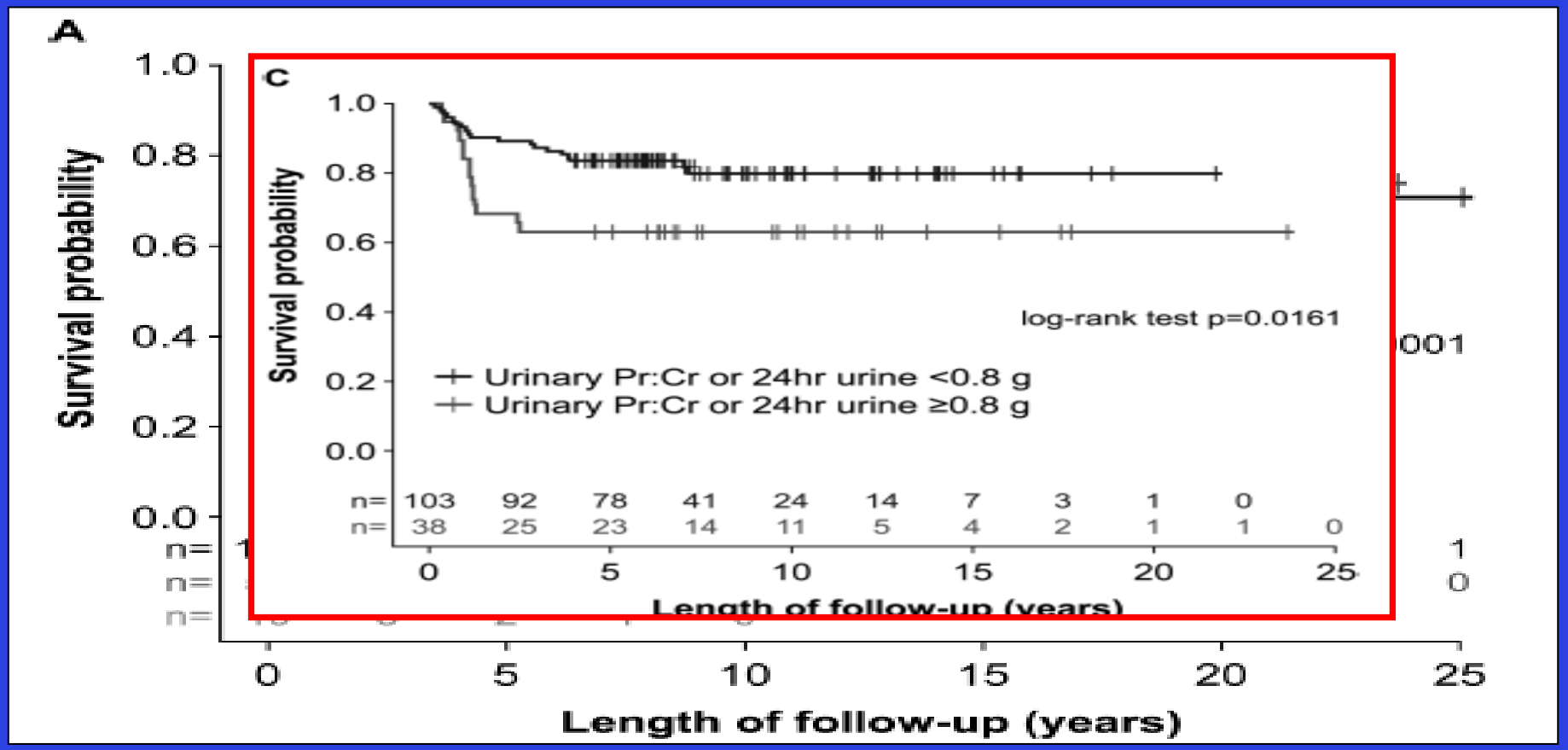
Figure 11 | Definitions of response commonly used in clinical trials of lupus nephritis. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m^2 per day or <300 mg/m^2 per day based on a 24-hour urine specimen. eGFR, estimated glomerular filtration rate; PCR, protein–creatinine ratio.

IMPORTANCE OF REMISSION

Renal Remission Status and Longterm Renal Survival in Patients with Lupus Nephritis: A Retrospective Cohort Analysis

J Rheumatol 2018;45:671–7; doi:10.3899/jrheum.161554

Julie E. Davidson, Qinggong Fu, Beulah Ji, Sapna Rao, David Roth, Laurence S. Magder, and Michelle Petri



Outcome

› Lupus. 2009 Apr;18(4):348-54. doi: 10.1177/0961203308097570.

n=54

Outcome of lupus nephritis in Indian children

› Saudi J Kidney Dis Transpl. 2012 Jul;23(4):871-5. doi: 10.4103/1319-2442.98194.

n=13

Renal involvement in childhood lupus: a study from Kolkata, India

› Lupus. 2015 May;24(6):641-7. doi: 10.1177/0961203315570166. Epub 2015 Feb 22.

n=53

Childhood lupus nephritis in a developing country-24 years' single-center experience from North India

› Lupus. 2016 Apr;25(5):547-57. doi: 10.1177/0961203315619031. Epub 2015 Dec 3.

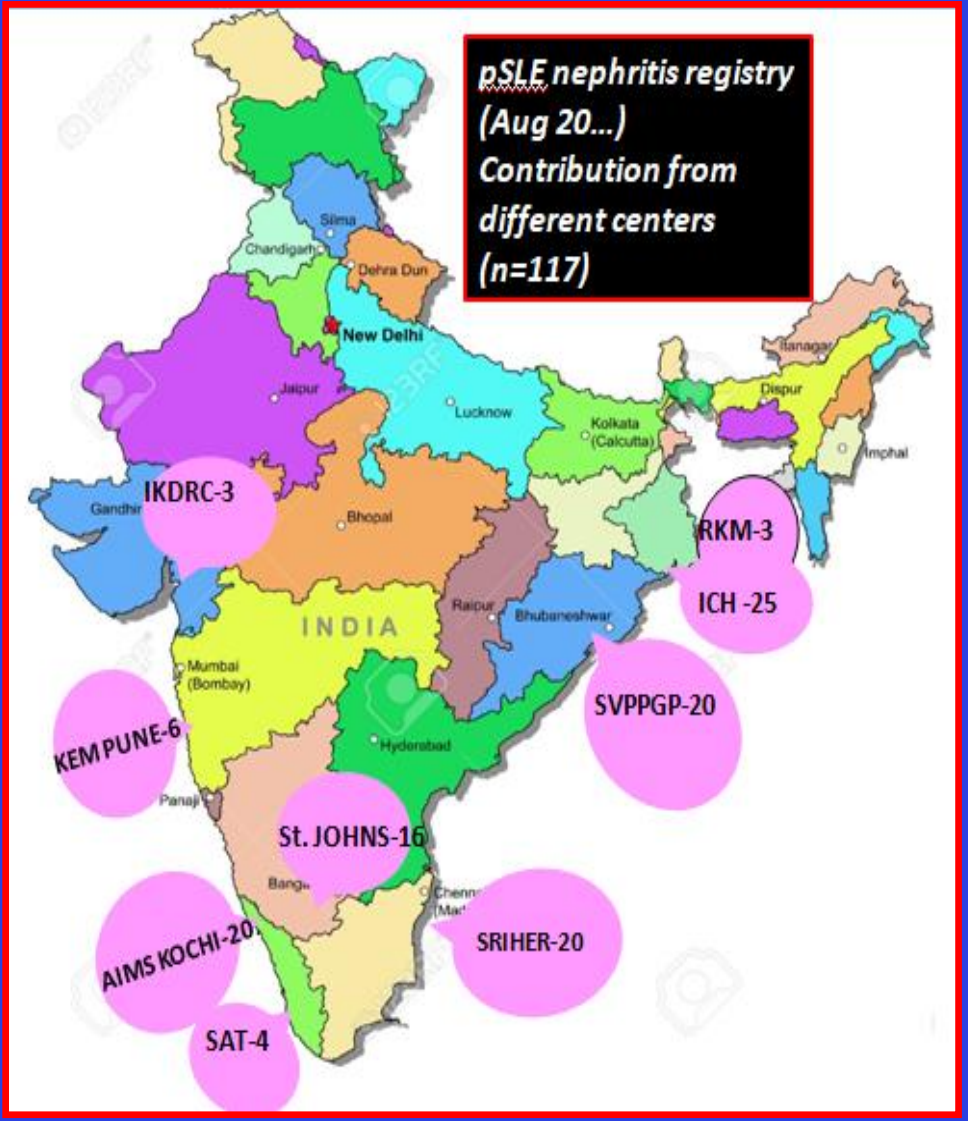
n=92

Outcome of lupus nephritis in childhood onset SLE in North and Central India: single-centre experience over 25 years

› Lupus. 2021 Oct;30(12):2008-2016. doi: 10.1177/09612033211045069. Epub 2021 Sep 24.

Pediatric onset lupus nephritis in western India-is it different from the rest of the country?

n=19



Presentation and outcome of pediatric lupus nephritis from a large single centre contemporary cohort in Eastern India

n=60

Lupus
2023, Vol. 0(0) 1–7

DOI: 10.1177/09612033231202843
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Debopoma Biswas[1,*], Deblina Dasgupta[2,*], Priyankar Pal[1] and Rajiv Sinha[2]

OUTCOME

Presentation and outcome of pediatric lupus nephritis from a large single centre contemporary cohort in Eastern India

Lupus
2023, Vol. 0(0) 1–7
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DOI: 10.1177/09612033231202843
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Debopoma Biswas[1,*], Deblina Dasgupta[2,*], [illegible]al[1] and Rajiv Sinha[2]

Mortality: n= 6 (10%)

Outcome as p[illegible] analyzed only among 52 children who [illegible]ed up for at least 24 months (Median: 57; IQR [illegible]83.7; range 24–132 months).

Of these 52 children, 88% ($n = 46$) were in CR, 6% ($n = 3$) PR, and 6% ($n = 3$) showed no response.

SYSTEMATIC REVIEW/META-ANALYSIS

Management and outcomes in children with lupus nephritis in the developing countries

Priyanka Khandelwal[1] · Srinivasavaradan Govindarajan[1] · Arvind Bagga[1]

Table 1 Pooled proportion of patients with complete (CR), partial remission (PR), and disease flare

	Middle-income countries		High-income countries		Overall	
					Patients; studies (*N*)	Pooled proportion (95% CI)
CR at 1 year					1654; 24[c]	59% (51–67%)
PR at 1 year					1257; 18[c]	27% (19–37%)
CR at 2 year					626; 9[c]	69% (51–85%)
PR at 2 year					389; 6[c]	14% (4–27%)
CR at last follo					3686; 61[c]	57% (49–64%)
PR at last follo					2479; 36[c]	22% (16–28%)
Flare (renal or non-renal)[b]	1053; 20	27% (20–35%)	745; 18	35% (27–44%)	1798; 38	31% (25–37%)

(CKD5) was lower in MICs, especially in lower MICs compared to HICs (83% vs. 93%; $P = 0.002$). The pooled 5-year patient survival was significantly lower in MICs than HICs (85% vs. 94%; $P < 0.001$). In patients with class IV LN, the 5-and 10-year respective risk of CKD5 was 14% and 30% in MICs; corresponding risks in HICs were 8% and 17%. Long-term data from developing countries was limited. Sepsis (48.8%), kidney failure (14%), lupus activity (18.1%), and intracranial hemorrhage/infarct (5.4%) were chief causes of death; mortality due to complications of kidney failure was more common in lower MICs (25.6%) than HICs (6.4%).

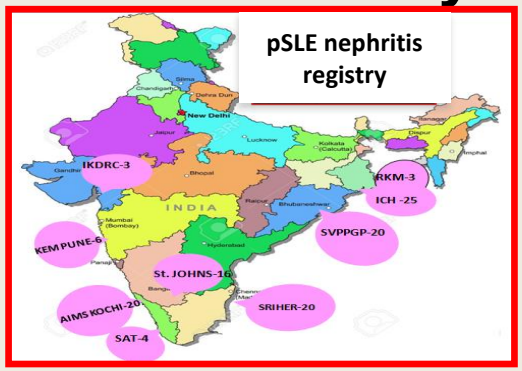
$P > 0.05$ for all comparisons between lower or upper middle-income countries and high-income countries. Mean time to remission 8.0 (95% CI 4.3–11.8) months ($n = 310$, 7 studies). Mean time to flare 27.2 (95% CI 18.6–35.8) months ($n = 314$, 10 studies)

Outcome of Indian Childhood LN registry (1 year follow up)

158 enrolled; analysed 60 who completed 1 year follow up

CR	PR	NR
42 (70%)	13 (22%)	5 (8%)

- **No of serious infections requiring hospitalisation: 5**
- **No of renal flares: 9 children each had one flare in first yrs**
- **No of deaths: 9**
- **Lost to follow ups in one year: 7**



A STANDARD CASE SCENARIO

- 11 yrs girl
- Fever 2 week
- Myalgia and malaise
- Oral ulcer
- ANA+VE, C3⬇
- Cr 0.8 mg/dl
- UP/UC =1.1

✓ **SLE NEPHRITIS TYPE IV**
Activity score:8
Chronicity score:0

✓ **T/t with pulse CH3pred, Pred & MMF**
✓ **HCQ, Enalapril, Vit D and Sun screen**

At 6 months:
✓ Afebrile, normal activity
✓ 24 hrs urine protein: 340 mg (UP/UC: 0.4), Cr 0.6
✓ Urine R/E: Pr 1+, RBC 10-15/Hpf
✓ Normal C3/ C4

At 14 months:
✓ Prednisolone 5 mg OD, MMF 500 mg BD, HCQ, & Enalapril
✓ Febrile, Joint ache and generalized unwell
✓ 24 hrs urine protein: 1020 mg (UP/UC: 0.1.6), Cr 0.9
✓ C3 78, C4 10
✓ Urine R/E: Pr 2+, RBC 30-35/Hpf

LUPUS FLARES

Lupus Nephritis Relapses

The rate of renal flares due to SLE is 25% to 50% on therapy.[48–52] Three types have been defined[37]:

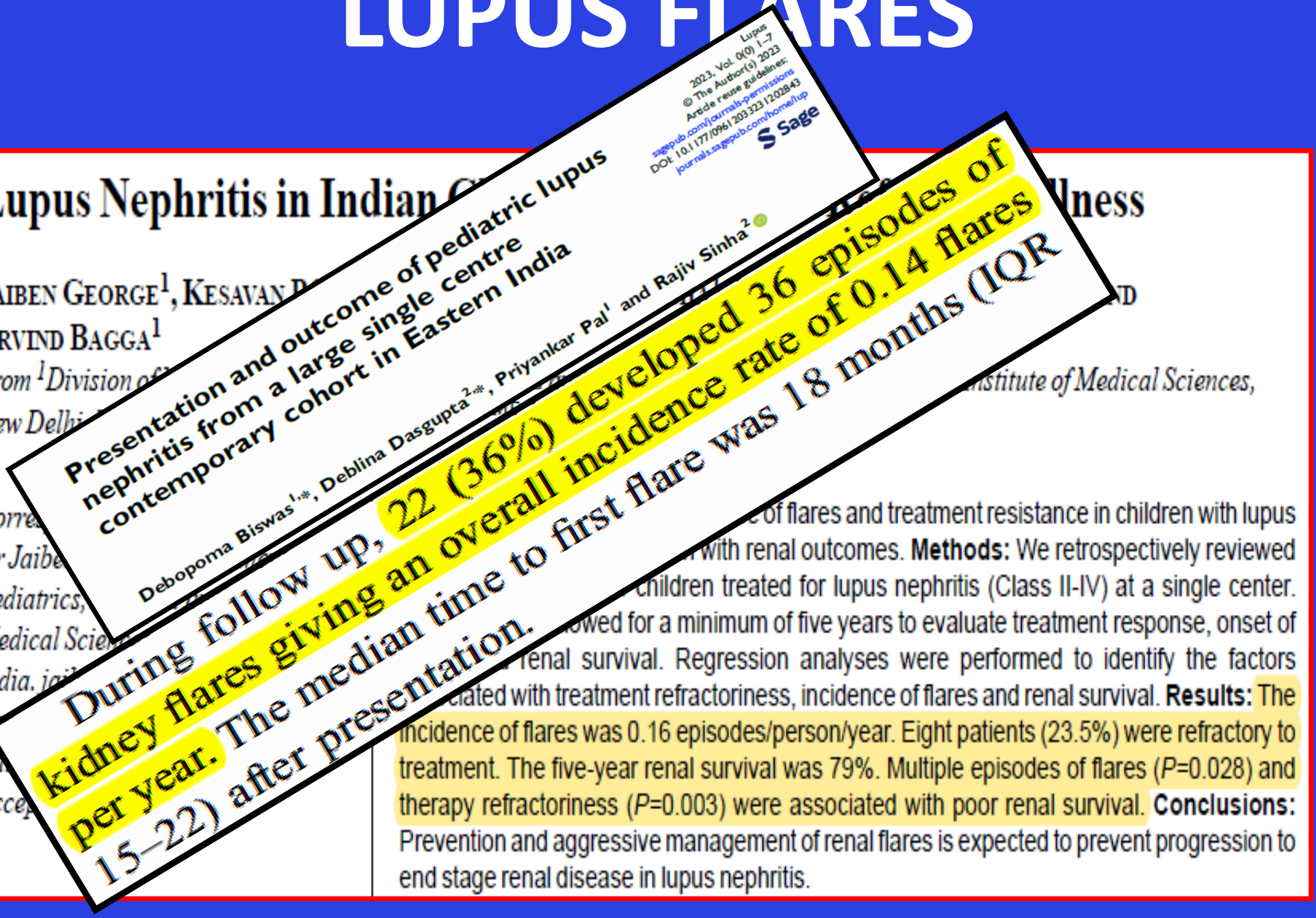
- Proteinuric flare: abnormal prote… complete remission or doubling of proteinuria after mild…
- Nephritic flare: incre… …currence of active urinary sediment (increased hematuria ± reappearance of cellular casts) ± increased proteinuria
- Acute kidney injury (AKI) with worsening serologies

Nephritic flare

LN relapses	
Proteinuric flares	• Encourage medication adherence • Restart or increase steroid ± maintenance immunosuppression
Nephritic flares	• Encourage medication adherence • Consider repeat biopsy • Restart initial therapy, based on prior responsiveness
AKI	• Encourage medication adherence • Consider repeat biopsy, consider nonclassifiable causes • Restart initial therapy, including IV steroids
End-stage LN (class VI)	
Conservative therapy	• Avoid additional immunosuppression • Low-dose oral steroids and hydroxychloroquine • Consider renin angiotensin blockade

Pediatr Clin N Am 66 (2019) 87–99

LUPUS FLARES



Lupus Nephritis in Indian C… …lness

Jaiben George[1], Kesavan R… …nd
Arvind Bagga[1]

From [1]Division of… …nstitute of Medical Sciences, New Delhi…

Corre… Dr Jaibe… Pediatrics, Medical Scie… India. jai… Acce…

…e of flares and treatment resistance in children with lupus …with renal outcomes. **Methods:** We retrospectively reviewed …children treated for lupus nephritis (Class II-IV) at a single center. …owed for a minimum of five years to evaluate treatment response, onset of …renal survival. Regression analyses were performed to identify the factors …ciated with treatment refractoriness, incidence of flares and renal survival. **Results:** The incidence of flares was 0.16 episodes/person/year. Eight patients (23.5%) were refractory to treatment. The five-year renal survival was 79%. Multiple episodes of flares (P=0.028) and therapy refractoriness (P=0.003) were associated with poor renal survival. **Conclusions:** Prevention and aggressive management of renal flares is expected to prevent progression to end stage renal disease in lupus nephritis.

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Presentation and outcome of pediatric lupus nephritis from a large single centre contemporary cohort in Eastern India

Debopoma Biswas[1,*], Deblina Dasgupta[2,*], Priyankar Pal[1] and Rajiv Sinha[2]

During follow up, 22 (36%) developed 36 episodes of kidney flares giving an overall incidence rate of 0.14 flares per year. The median time to first flare was 18 months (IQR 15–22) after presentation.

RESISTANT / REFRACTORY LUPUS NEPHRITIS

Refractory lupus nephritis: When, why and how to treat.

Autoimmunity Reviews, https://doi.org/10.1016/j.autrev.2019.03.004

Andreas Kronbichler, Biljana Brezina, Philipp Gauckler, Luis F. Quintana, David R.W. Jayne

Definitions
#1 Failure of at least one immunosuppressive drug [7-9]
#2 Failure of at least two immunosuppressive drugs [10]
#3 Poor response to at least one immunosuppressive drug [11]
#4 Failure to respond to immunosuppressive therapy including cyclophosphamide [12]
#5 Failure to respond to the combination of any immunosuppressive drug and corticosteroid therapy for at least 6 months [13, 14]
#6 Failure to respond following treatment with mycophenolate mofetil or cyclophosphamide [15]
#7 Refractory to 'standard' treatment [16]
#8 No response to 'standard' treatment [17]
#9 Refractory to established therapy including high-dose corticosteroids and immunosuppressants [18]

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative first-line regimen when there is persistent disease activity (mycophenolic acid analogs to cyclophosphamide-based regimen or vice versa)
5	Consider the following in patients refractory to first-line treatment regimens: • Combined mycophenolic acid analogs and calcineurin inhibitor therapy, or • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide

CORRESPONDENCE · Volume 403, Issue 10437, P1627-1630, April 27, 2024 THE LANCET

CAR T-cell therapy rescues adolescent with rapidly progressive lupus nephritis from haemodialysis

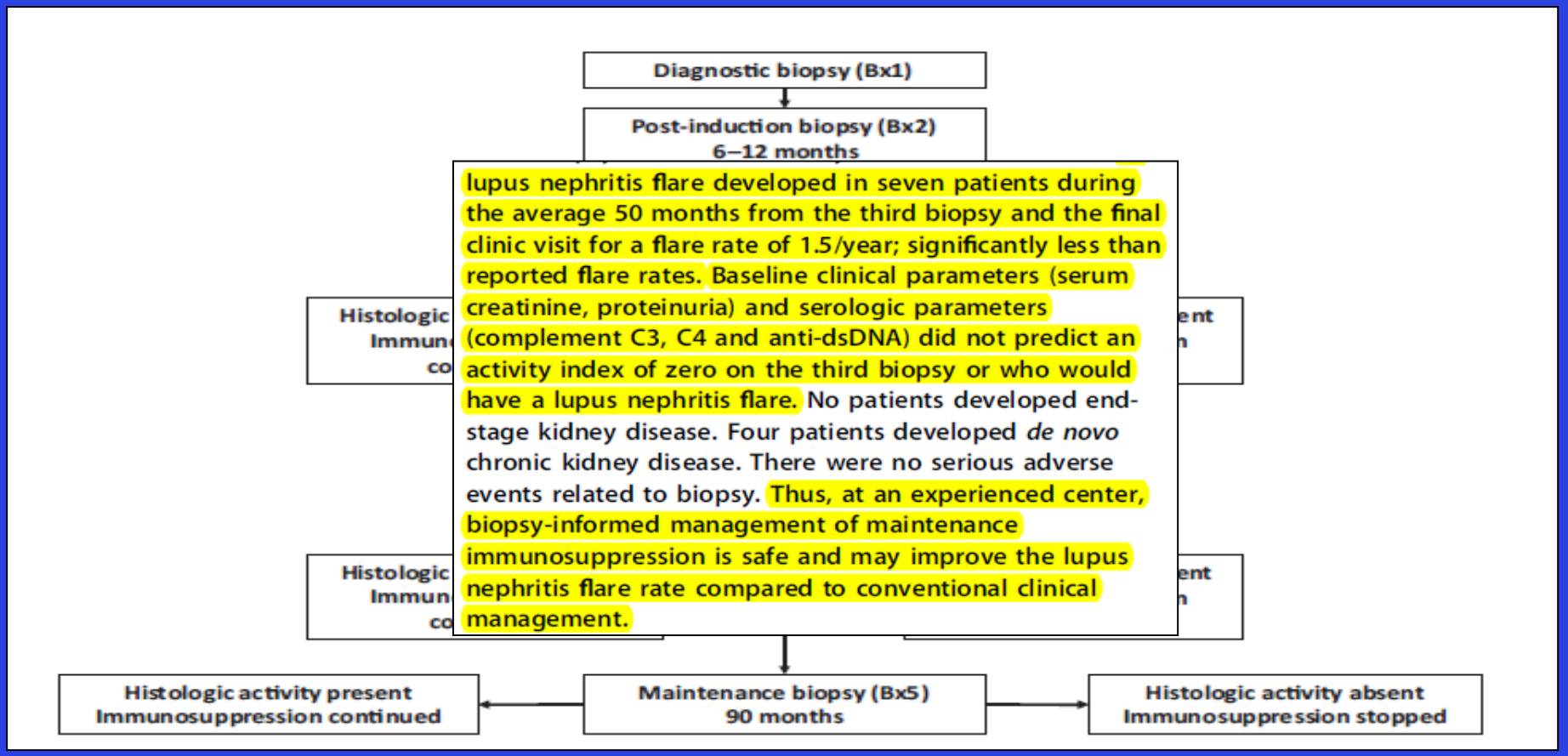
Tobias Krickau [a,b] · Nora Naumann-Bartsch [a,b,e] · Michael Aigner [b] · Soraya Kharboutli [b,c,e] · Sascha Kretschmann [c,e] · Silvia Spoerl [b,e,c] · et al. Show more

WHEN TO STOP TREATMENT?

The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be ≥36 months.

Kidney biopsy–based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis

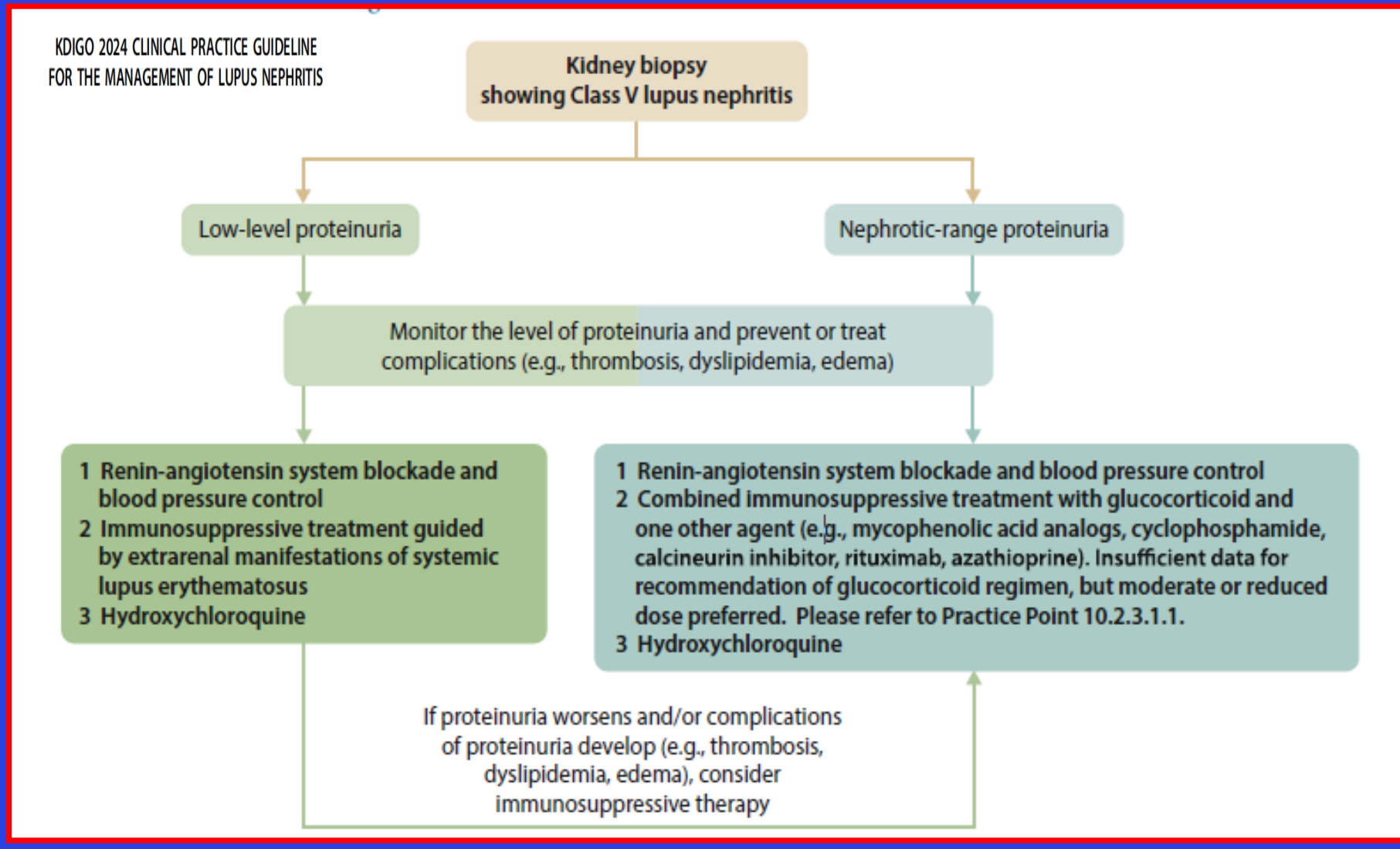
Ana Malvar[1], Valeria Alberton[2], Bruno Lococo[1], Matias Ferrari[1], Pamela Delgado[1], Haikady N. Nagaraja[3] and Brad H. Rovin[4]

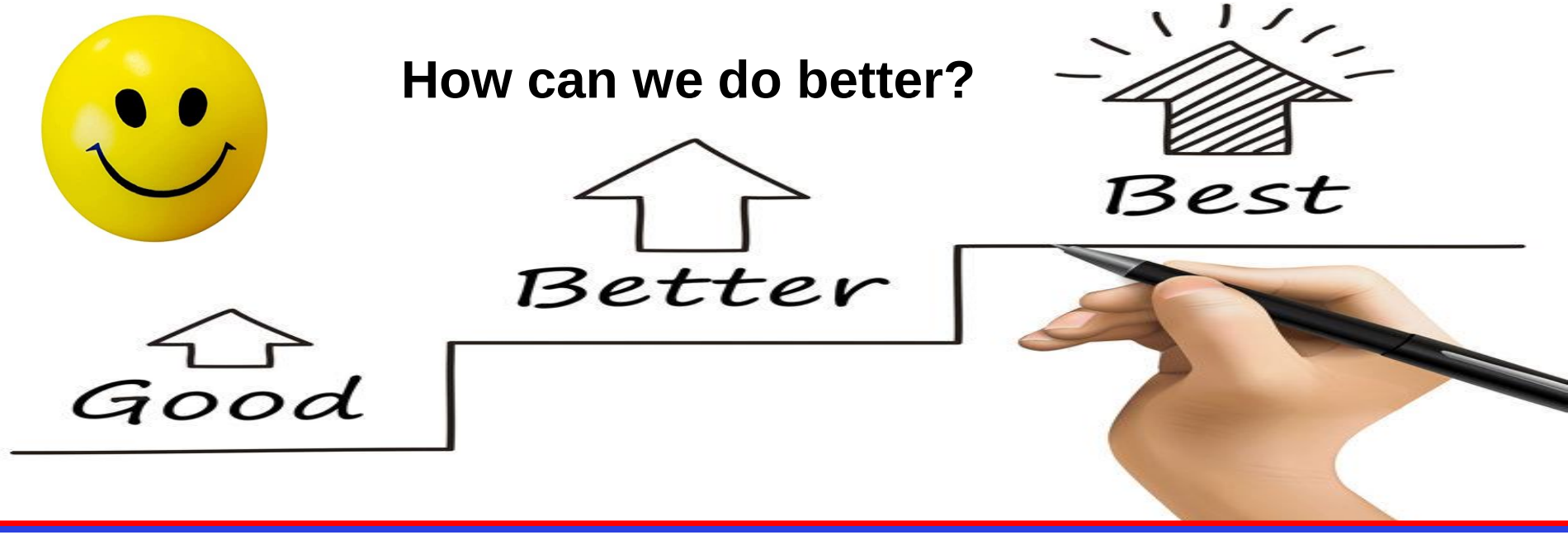


lupus nephritis flare developed in seven patients during the average 50 months from the third biopsy and the final clinic visit for a flare rate of 1.5/year; significantly less than reported flare rates. Baseline clinical parameters (serum creatinine, proteinuria) and serologic parameters (complement C3, C4 and anti-dsDNA) did not predict an activity index of zero on the third biopsy or who would have a lupus nephritis flare. No patients developed end-stage kidney disease. Four patients developed *de novo* chronic kidney disease. There were no serious adverse events related to biopsy. Thus, at an experienced center, biopsy-informed management of maintenance immunosuppression is safe and may improve the lupus nephritis flare rate compared to conventional clinical management.

Kidney International (2019) ■, ■–■; https://doi.org/10.1016/j.kint.2019.07.018

Class V Lupus Nephritis





Trial	Definition of kidney response	52-wk Results, % achieving kidney response				104-wk Results, % achieving kidney response			
		PBO	EXP	DIFF	*P* value	PBO	EXP	DIFF	*P* value
AURORA[a]	• uPCR <0.5 g/g • eGFR >60 ml/min per 1.73 m^2 or no worse than 20% below baseline value • No rescue medications	23	41	18	<0.0001	N/A	N/A	N/A	N/A
BLISS-LN[b]	• uPCR ≤0.7 g/g • eGFR ≥60 ml/min per 1.73 m^2 or no worse than 20% below preflare value • No rescue medications	35	47	11	0.02	32	43	11	0.03
NOBILITY[c]	• uPCR <0.5 g/g • SCr ≤ upper limit of the clinical laboratory normal and no worse than 15% below baseline • Inactive urine sediment: <10 RBCs/HPF and no RBC casts	23	35	12	0.12	23	41	18	0.026

ROLE FOR REPEAT BX

How can we do better?

Need for innovative strategies

Lupus nephritis: When and how often to biopsy and what does it mean?

Gabriella Moroni [a,*], Federica Depetri [a], Claudio Ponticelli [b]

Transformation of histological classes and change in activity and chronicity index from baseline and second renal biopsy.

Author (reference number)	N° repeat renal biopsies (N° pts)	Interval from first to second renal biopsy Months	Indication to repeat renal biopsy	Transformation of histological classes %			Activity index at renal biopsy			Chronicity Index at renal biopsy		
				Total	From proliferative (III,IV) to non-proliferative (II,V	From non-proliferative (II,V to Proliferative (III,IV)	First renal biopsy	Repeat renal biopsy	p	First renal biopsy	Repeat renal biopsy	p
Bajaj [79]	57 (57)	52.8	Clinical	40	22	24	5.01	3.96	0.064	1.3	3.37	0.0001
Wang [81]	50 (44)	≥6	Clinical	64	19	100	6 ± 3	4.7 ± 2.6	NS	1.8 ± 1.2	3.4 ± 2	0.0001
Daleboudt [80]	49 (35)	49.2	Clinical	49	16	83	6.18	5.27	NS	2.62	4.2	<0.001
Pagni [83]	142 (142)	58.8	Clinical/ Protocol	40.8	18	42	4.5	3.3	NA	1.5	3.6	NA
Esdaile [52]	87 (42)	25	Clinical	36	45	28	7	2	0.0001	1.6	2.7	0.003
Moroni [78]	38 (31)	42	Clinical	55	18	100	7.3 ± 4.4	5.2 ± 4.4	0.051	1.5 ± 1.5	4.9 ± 2.7	0.0001
Gunnarsson [69]	18 (18, class III/IV)	6	Protocol	66	66	NA	8	4	<0.0001	1	2	NS
Grootscholten[a] [77]	39 (39)	>24	Protocol	64	38	NA	8	2.7	<0.01	2.7	3.3	<0.001
Alsuwaida [75]	77 (77)	12–18	Protocol	58.4	15	20	3	2	<0.001	3	5	NS
Zickert [48]	67 (67)	8	Protocol	64	64	0	5	2	<0.001	1	1.5	<0.001
Malvar [73]	69 (69, class III/IV)	6	Protocol	NA	NA	NA	8.5 ± 3.1	3.5 ± 2.4	<0.0001	2.6 ± 1.7	4 ± 1.5	<0.0001
Gao[b] [135]	47 IV-S:14 IV-G:33	>6[b]	Protocol	58	57 (IV-S) 27 (IV-G)	NA	8.6 ± 5.0 6.6 ± 4.2	NA	NA	2.2 ± 1.8 1.8 ± 1.9	NA	NA
Alvarado [71]	25 (25)	≥6	Protocol	NA	NA	NA	8.9	4.3	<0.0001	2.8	4.2	0.012
Greloni[c] [82]	71 (45)	40.8	Protocol	54.9	24.4	58.3	NA	NA	NA	6.6 ± 1.6[c]	2.9 ± 1.7[c]	<0.0001
Stoenoiu[d] [76]	30 (30) AZA:16 MMF:14	24	Protocol	60	40	100	10	2	0.002	1	2.5	0.006
							8.5	3.5	0.003	1	2.5	0.02

ROLE FOR REPEAT BX

How can we do better?

Need for innovative strategies

Lupus nephritis: When and how often to biopsy and what does it mean?

Gabriella Moroni [a,*], Federica Depetri [a], Claudio Ponticelli [b]

Table 4
Value of repeat renal biopsy in lupus nephritis for the therapeutical management of patients and for predicting long-term renal outcome.

Author (reference number)	N° repeat renal biopsies (N° pts)	Indication for repeat renal biopsy	Follow-up		Changing immunosuppresive therapy after repeat RB			Predictors of doubling serum creatinine/ESRD at repeat RB		
			From I° to II° RB Months	AfterII° RB Months	Total (%)	Increase therapy (%)	Reduction therapy (%)	Clinical features	Active histological lesions	Chronic histological lesions
Bajaj [79]	57 (57)	Clinical	52.8	NA	77	47	30	NA	NA	NA
Wang [81]	50 (44)	Clinical	≥6	NA	44	30	14	NA	NA	NA
Daleboudt [80]	49 (35)	Clinical	49.2	NA	59	43	16	NA	NA	NA
Esdaile [52]	87 (42)	Clinical	25	84	NA	NA	NA	None	Sub-endothelial deposits	None
Moroni [78]	38 (31)	Clinical	42	126	79	60.5	18.5	S. creat, hematocrit sex	Crescents >30% of glomeruli	CI > 5
Greloni [82]	71 (45)	Clinical	40.8	63.6	87.3	NA	NA	S. creat	None	CI ≥ 6.5
Grootscholten [77]	87 (39)	Protocol	>24	77	NA	NA	NA	S. creat	none	none
Hill[a] [68]	71 (71)	Protocol	6	84.6	NA	NA	NA	None	GAI, IFI. BxInfl[a]	none
Alsuwaida[b] [75]	77 (77)	Protocol	12–18	104	NA	NA	NA	None	AI[b]	none
Zickert [48]	67 (67)	Protocol	8	120	60	18	42	S.creat. C4, anti- DNA	None	CI
Malvar [73]	69 (69)	Protocol	6	73	10.1	10.1	NA	Log (S.creat)	None	CI ≥ 4
Stoeniou [76]	30 (30)	Protocol	24	51.5	NA	NA	NA	None	None	CI > 4

ROLE FOR REPEAT BX

How can we do better?

Need for innovative strategies

Table 1: Repeat biopsy studies in clinically quiescent disease

	Population	Timing of repeat biopsy	Clinical status at repeat biopsy	Serological status at repeat biopsy	Biopsy findings	Follow-up	N (%) with flares	Predictors of flares
Lledo 2022 [15]	56 LN class II-V, mixed	Median 41m after diagnosis	Complete remission in 51 (91%), partial remission in 5 (9%)	30 (55%) anti-dsDNA 21 (37%) low complement	11 (20%) AI ≥2	67m	18 (32%)	No concomitant HCQ
Das 2015[45]	29 LN class III, IV, mixed	≥36m immunosuppression, ≥24m clinical remission	sCreat normal or 50% reduced from baseline, proteinuria <0.5 g/24 h, inactive urine sediment, serum albumin >3.5 g/dl	2 (7%) anti-dsDNA	27 (93%) AI=0	NA	NA	NA
Malvar 2020 [16]	76 LN class III, IV, mixed	≥42m immunosuppression, ≥12m clinical remission	sCreat normal or stable, proteinuria <1 g/24 h, no extrarenal activity	10 (13%) anti-dsDNA 17 (22%) low C3 10 (13%) low C4	55 (72%) AI=0 21 (28%) AI=1-5	50m	7 (9%)	None
Parodis 2020 [17]	42 LN class III, IV, mixed	Median 24m after diagnosis	Median sCreat=0.8, median proteinuria 0.2 g/24 h	NA	Median AI=3	108m	11 (26%)	AI>2, glomerular lesions
De Rosa 2018 [18]	36 LN class III, IV, mixed	≥36m immunosuppression, ≥12m clinical remission	sCreat normal, proteinuria <0.5 g/24 h, inactive urine sediment	8 (22%) anti-dsDNA 5 (14%) low C3 13 (36%) low C4	20 (56%) AI=0 9 (25%) AI=1-2 7 (19%) AI=3-5	24m	11 (31%)	Decline C3 6m before biopsy, AI, endocapillary proliferation, subendothelial deposits, duration of SLE

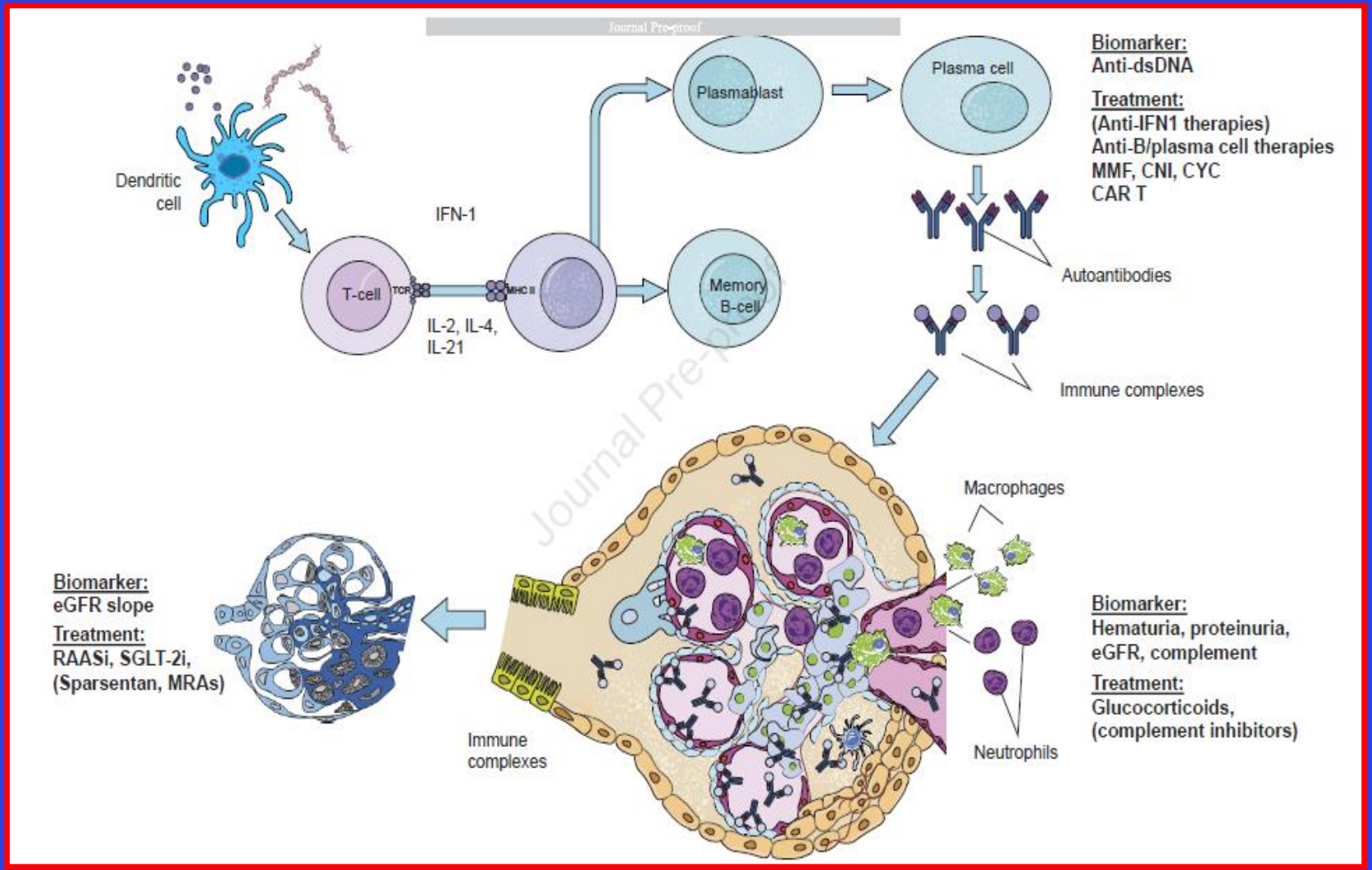
sCreat, serum creatinine; NA, not available; AI, activity index; SLE, systemic lupus erythematosus; LN, lupus nephritis; HCQ, hydroxychloroquine

De Vriese AS, Sethi S, Fervenza FC, Lupus Nephritis: Redefining the treatment goals, *Kidney International (2024), doi: https://doi.org/10.1016/j.kint.2024.10.018*.

ROLE FOR BIOMARKER

How can we do better?

Need for innovative strategies

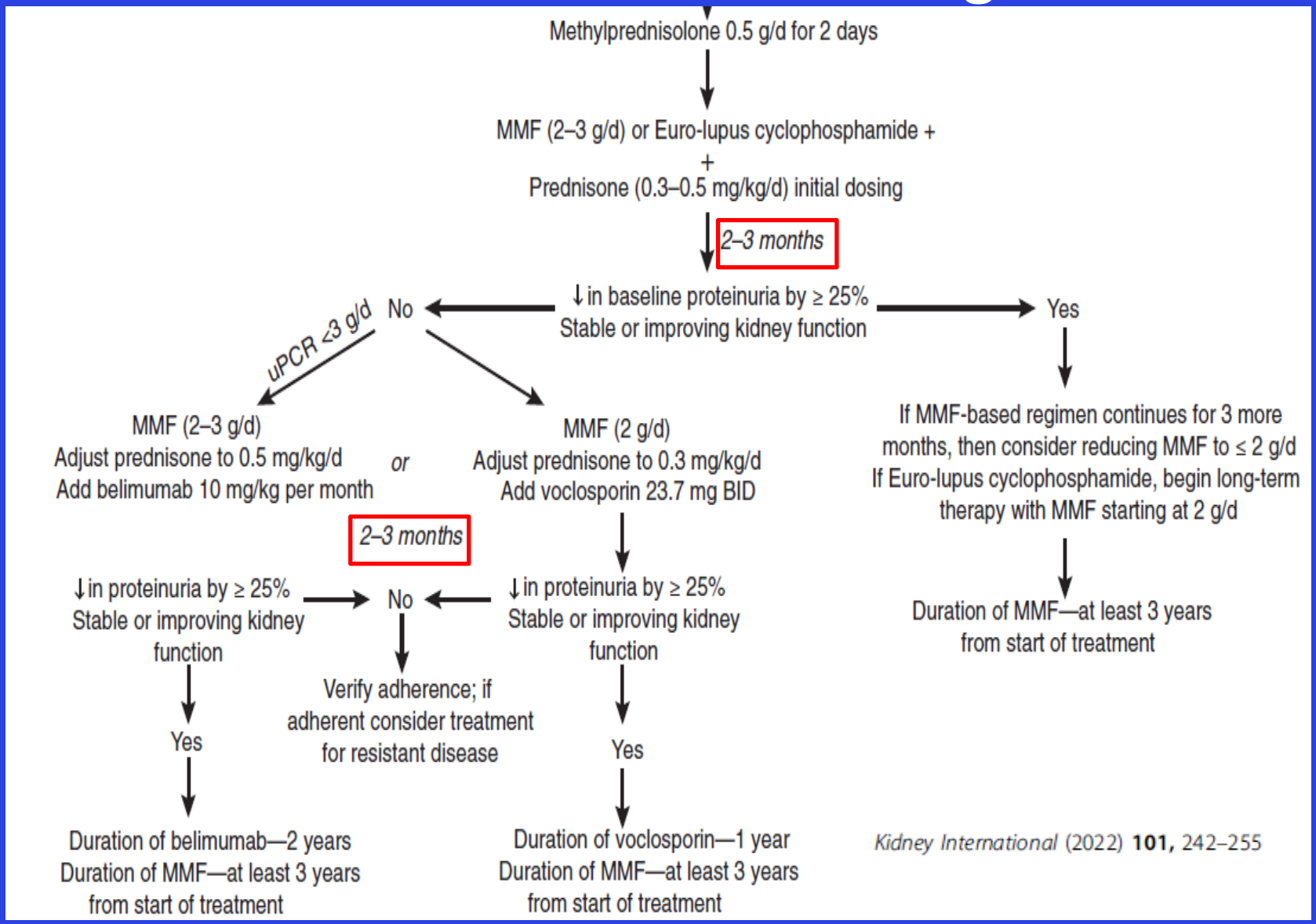


De Vriese AS, Sethi S, Fervenza FC, Lupus Nephritis: Redefining the treatment goals, *Kidney International (2024), doi: https://doi.org/10.1016/j.kint.2024.10.018*.

ROLE FOR PROTOCOL REVISION

How can we do better?

Need for innovative strategies

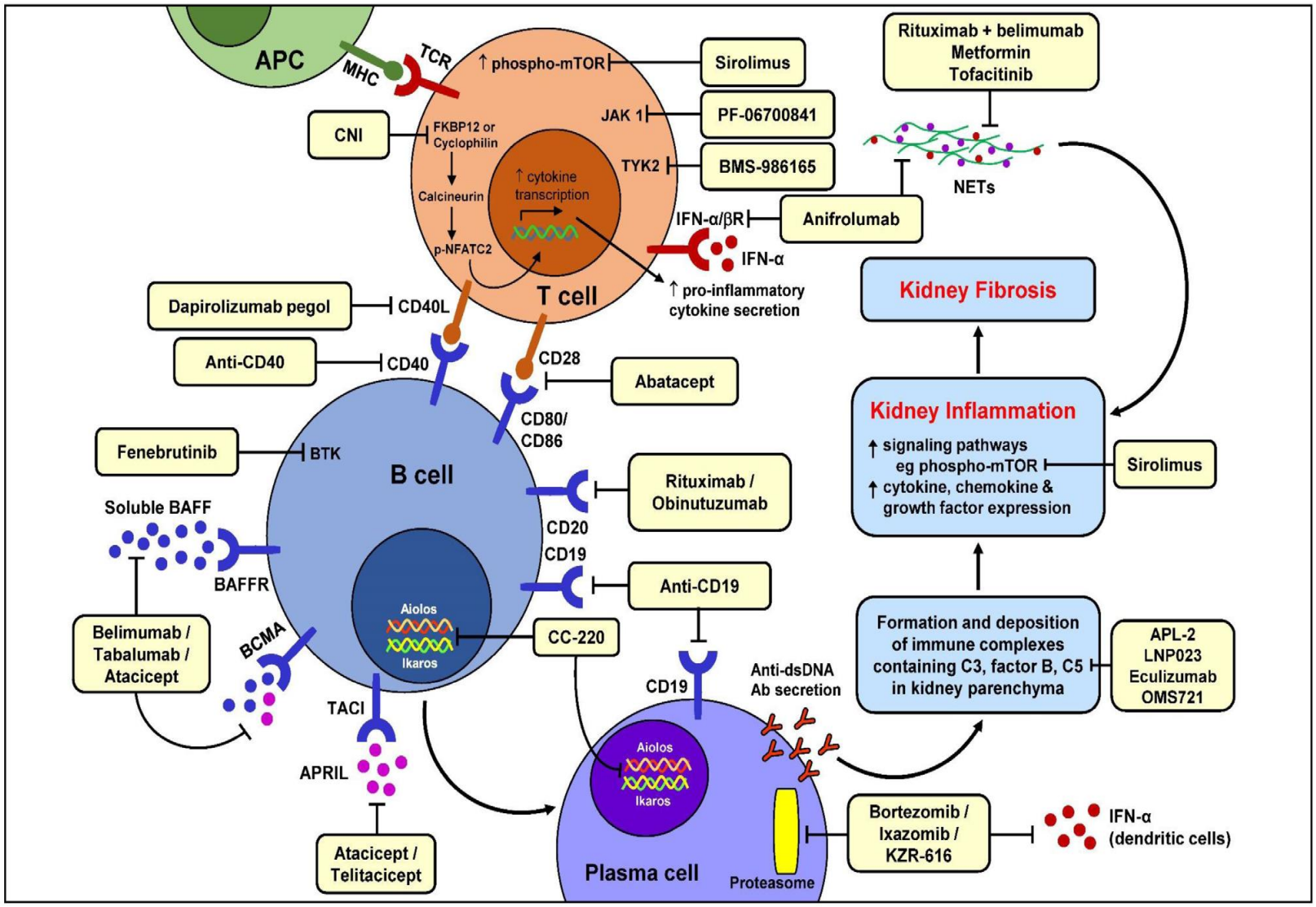


Kidney International (2022) **101,** 242–255

NEWER DRUGS

How can we do better?

Need for innovative strategies



F1000Research 2020, 9(Faculty Rev):905 Last updated: 31 MAR 2022

STEROID AVOIDANCE

How can we do better?

Need for innovative strategies

Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

Marie B Condon,[1] Damien Ashby,[1] Ruth J Pepper,[1] H Terence Cook,[1,2] Jeremy B Levy,[1] Megan Griffith,[1] Tom D Cairns,[1] Liz Lightstone[1,2,3]

ABSTRACT

Objectives Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE). All current treatment regimens include oral steroids, which are associated with severe adverse events and long-term damage. We have piloted a steroid-avoiding protocol (rituxilup) for the treatment of biopsy-proven active International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, or class V LN.

Methods We report the findings from the first 50 consecutive patients, treated with 2 doses of rituximab (1 g) and methyl prednisolone (500 mg) on days 1 and 15, and maintenance treatment of mycophenolate mofetil. Patients on maintenance steroids or with life-threatening SLE or requiring dialysis were excluded. Renal remission was defined as serum creatinine no greater than 15% above baseline; complete biochemical remission (CR) was defined as urine protein : creatinine ratio (PCR)<50 mg/mmol or partial remission (PR) if PCR>50 mg/mmol but non-nephrotic and >50% reduction.

Results A total of 45 (90%) patients achieved CR or PR by a median time of 37 weeks (range 4–200). Overall, 72% (n=36) achieved CR (median time 36 weeks (11–58)) and a further 18% (n=9) achieved persistent PR (median time 32 weeks (19–58)). By 52 weeks, CR and PR had been achieved in 52% (n=26) and 34% (n=17) respectively. In all, 12 relapses occurred in 11 patients, at a median time of 65.1 weeks (20–112) from remission. A total of 6/50 patients had systemic flares. Of the 45 responders, only 2 required >2 weeks of oral steroids. Adverse events were infrequent; 18% were admitted, 10% for an infective episode.

Conclusions The rituxilup cohort demonstrates that oral steroids can be safely avoided in the treatment of LN. If findings are confirmed, it could mark a step change in the approach to the treatment of LN.

Ann Rheum Dis 2013;**72**:1280–1286. doi:10.1136/annrheumdis-2012-202844

SUMMARY

Tit - Bits

Ten Common Mistakes in the Management of Lupus Nephritis

Bhadran Bose, MBBS, FRACP, Earl D. Silverman, MD, FRCPC, Joanne M. Bargman, MD, FRCPC

Am J Kidney Dis. 2014;63(4):667-676.

AJKD

Box 1. Ten Common Mistakes in the Management of Lupus Nephritis

1. Assuming that intravenous cyclophosphamide is the gold-standard induction agent for lupus nephritis
2. Improper dosing of corticosteroids
3. Not using antimalarial agents routinely
4. Using urinary sediment for response criteria
5. Not scaling the intensity of immunosuppression to the different classes of lupus nephritis, especially class V membranous lupus
6. Missing nonadherence to therapy as a cause of "treatment failure"
7. Not reducing or minimizing immunosuppressive exposure in patients with advanced kidney disease
8. Forgetting to monitor side effects of immuno-suppression and to use prophylaxis
9. Performing a biopsy on the kidney, especially in a high-risk patient, when it will not affect therapy
10. Neglecting to address pregnancy

SUMMARY
Tit - Bits

Lupus Nephritis: Redefining the treatment goals

An S. De Vriese, M.D., Ph.D, Sanjeev Sethi, M.D., Ph.D, Fernando C. Fervenza, M.D., Ph.D

Persistent low C3 levels, proteinuria, and persistent microscopic hematuria (from glomerular origin) suggests active glomerular inflammation.

Elevated anti-dsDNA signifies ongoing immunological activity.

Negative anti-dsDNA needs to be confirmed by a second assay.

Immunological remission generally implies clinical remission and ensuing histological remission.

Persistent proteinuria in the presence of immunological remission may be explained by chronic damage without active inflammation or delayed restoration of the glomerular filtration barrier.

Persistent low-grade histologic activity (AI 1 or 2) in patients with clinical and immunological remission may be explained by delayed clearance of deposited immune complexes and not signify ongoing disease activity.

The treatment goal in proliferative LN is the achievement and maintenance of immunological remission.

De Vriese AS, Sethi S, Fervenza FC, Lupus Nephritis: Redefining the treatment goals, *Kidney Internationaln(2024), doi: https://doi.org/10.1016/j.kint.2024.10.018*

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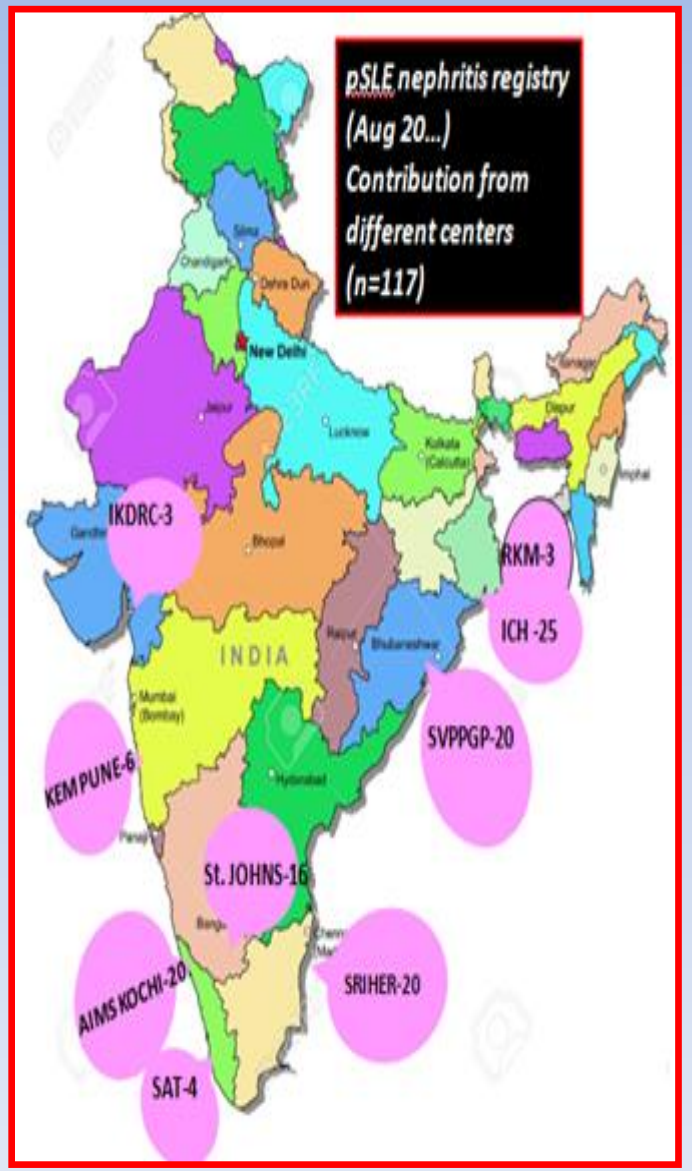
PROF PRIYANKAR PAL

DR JIGNA BHATIA

DR RAVALI PRATIMA

DR ANINDITA PAL

DIVISION OF PAEDIATRIC RHEUMATOLOGY



THANK YOU

NATIONAL PEDIATRIC NEPHROLOGY CONCLAVE 2024

SAT-ISN SRC UPDATE 5 • IPNA TEACHING COURSE

Kidney Health for Every Kid Everywhere

Kidney Diseases in Children
Optimizing Care & Preparing for Future

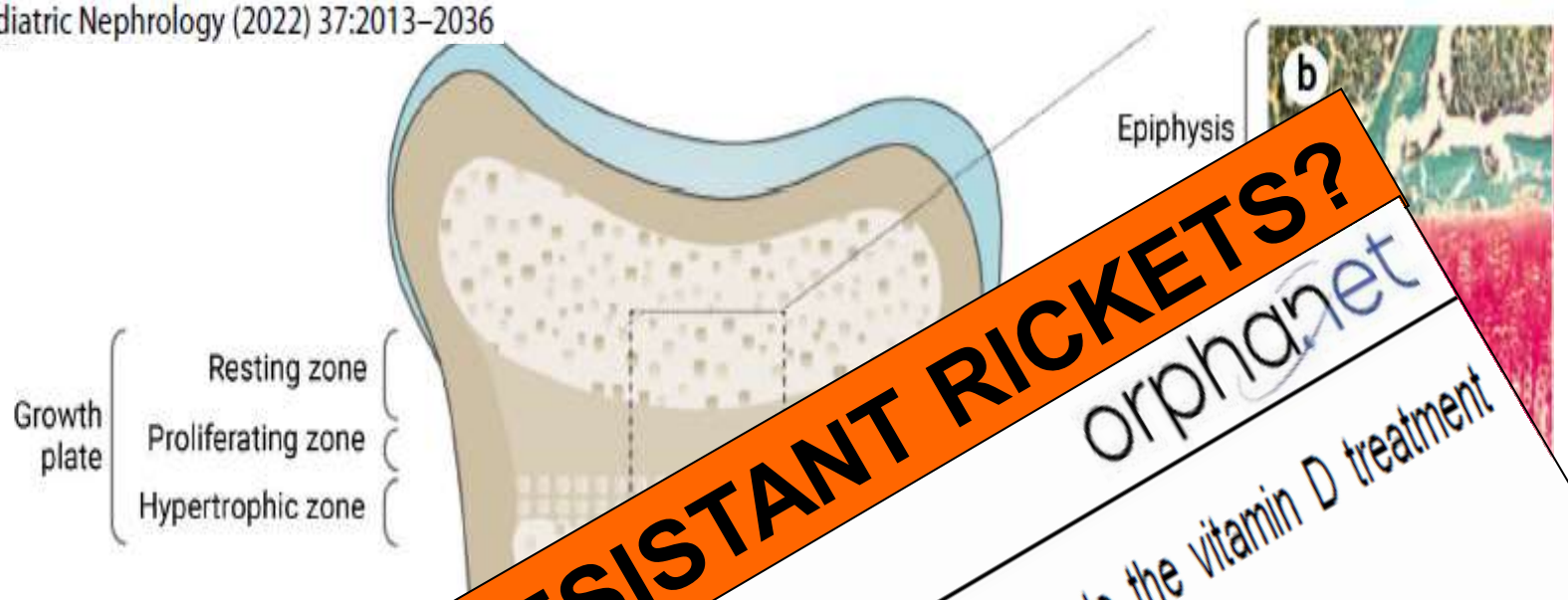
Organized by
Department of Pediatric Nephrology, SAT Hospital
Government Medical College, Thiruvananthapuram

Resistant Rickets
"A simplified approach"

Rajiv Sinha

MD (Cal), FRCPCH (UK), CCT- Paed Neph (UK)
Fellowship -Paed Neph (Canada)
Prof & HOD Paed Nephrology, ICH, Kolkata
Consultant Paediatric Nephrologist: Apollo Hospitals, Kolkata

Pediatric Nephrology (2022) 37:2013–2036



WHAT IS RESISTANT RICKETS?

orphanet

Vitamin D resistant rickets is defined by its resistance to the vitamin D treatment

Vitamin D resistant rickets

Author: Doctor Michèle Garabédian[1]

Fig. 1
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What is Rickets?

CALCIPENIC / PHOSPHOPENIC RICKETS

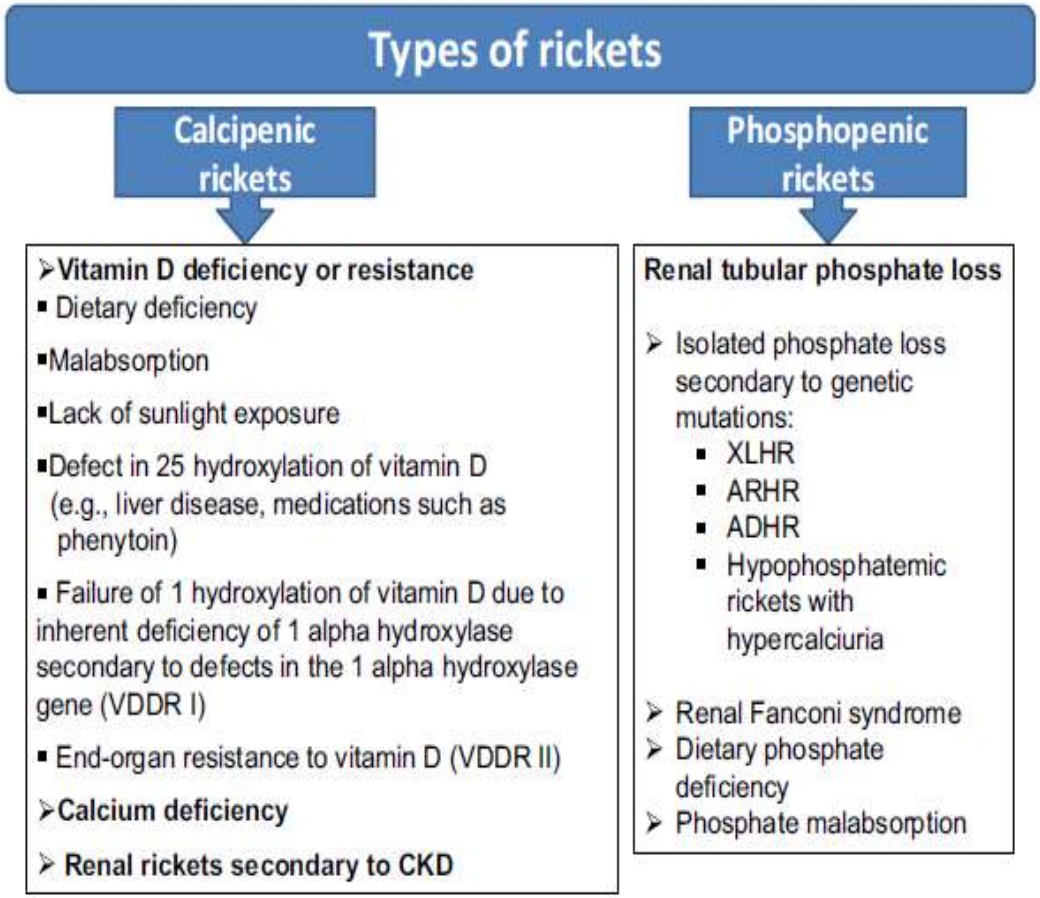


Figure 1. Different types of rickets. ADHR, autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; CKD, chronic kidney disease; VDDR, vitamin D–dependent type 1 rickets; XLHR, X-linked hypophosphatemic rickets.

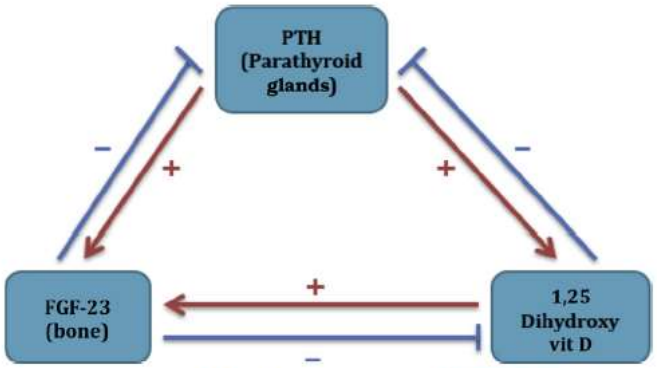
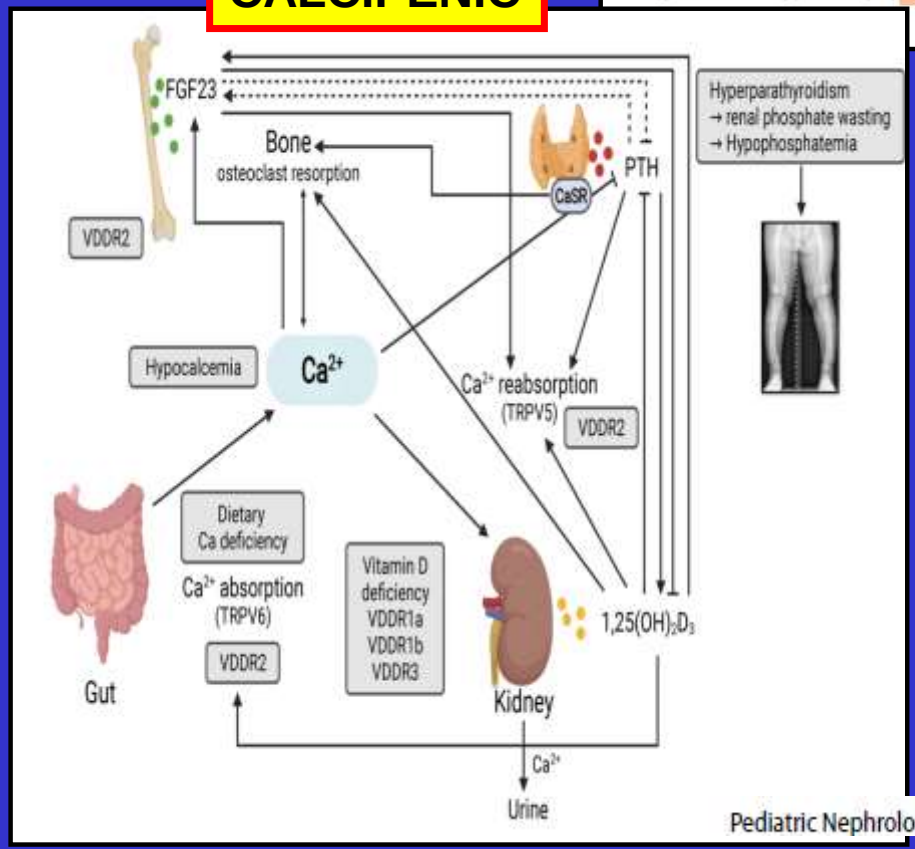
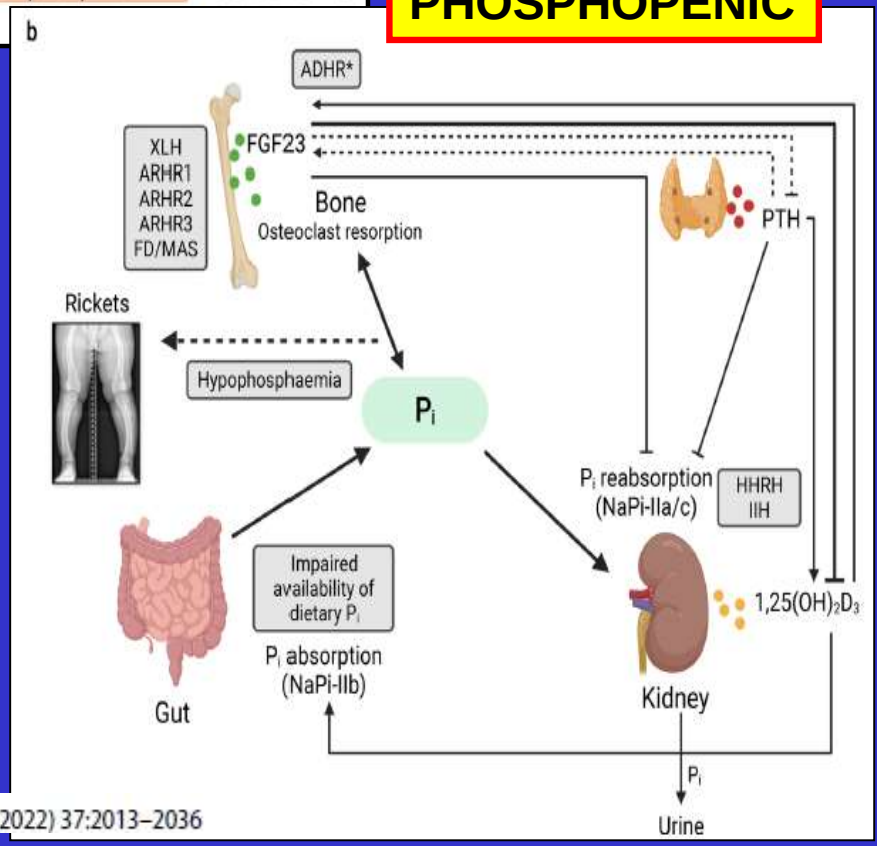


Figure 3. Parathyroid/bone/kidney axis. 1. Parathyroid hormone (PTH) increases 1,25 dihydroxy vitamin (vit) D synthesis in the kidney. 2. Fibroblast growth factor 23 (FGF-23) is produced by bone and it acts on the kidney. 3. FGF-23 decreases PTH and 1,25 dihydroxy vitamin D. 4. Both PTH and 1,25 dihydroxy vitamin D increase FGF-23

CALCIPENIC

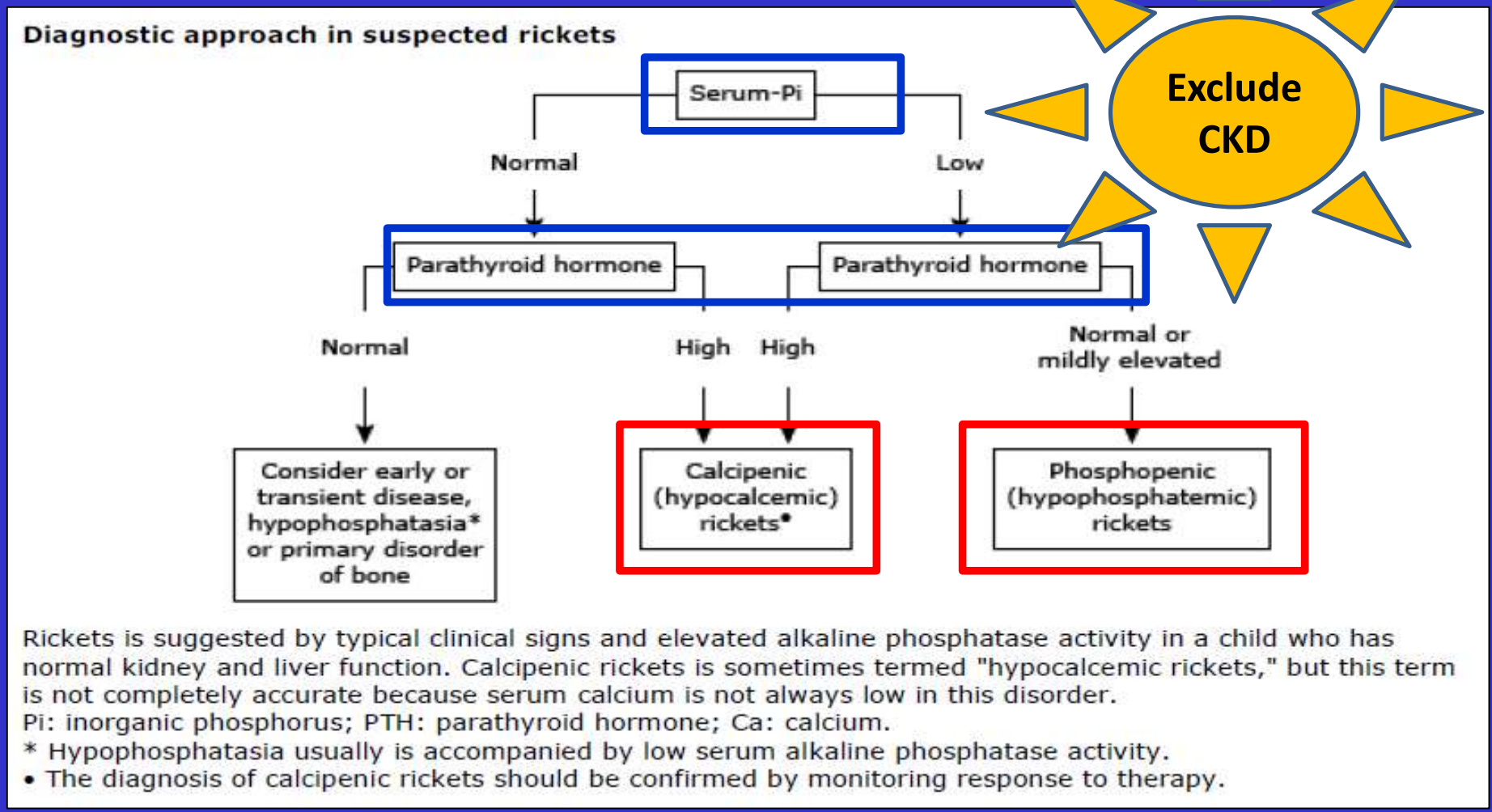


PHOSPHOPENIC



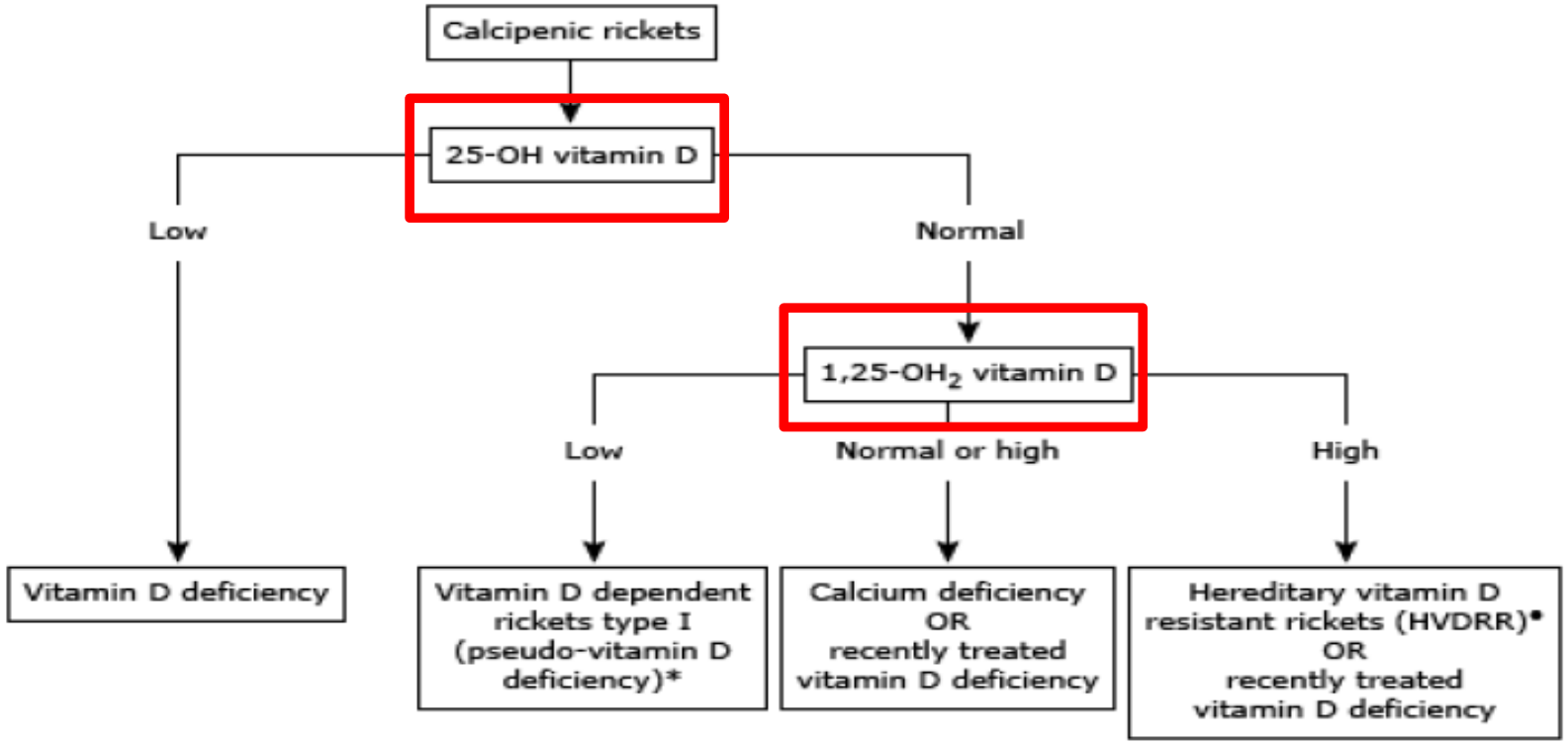
Pediatric Nephrology (2022) 37:2013–2036

APPROACH TO RICKETS



Adapted from www.uptodate.com

APPROACH TO HYPOCALCEMIC RICKETS



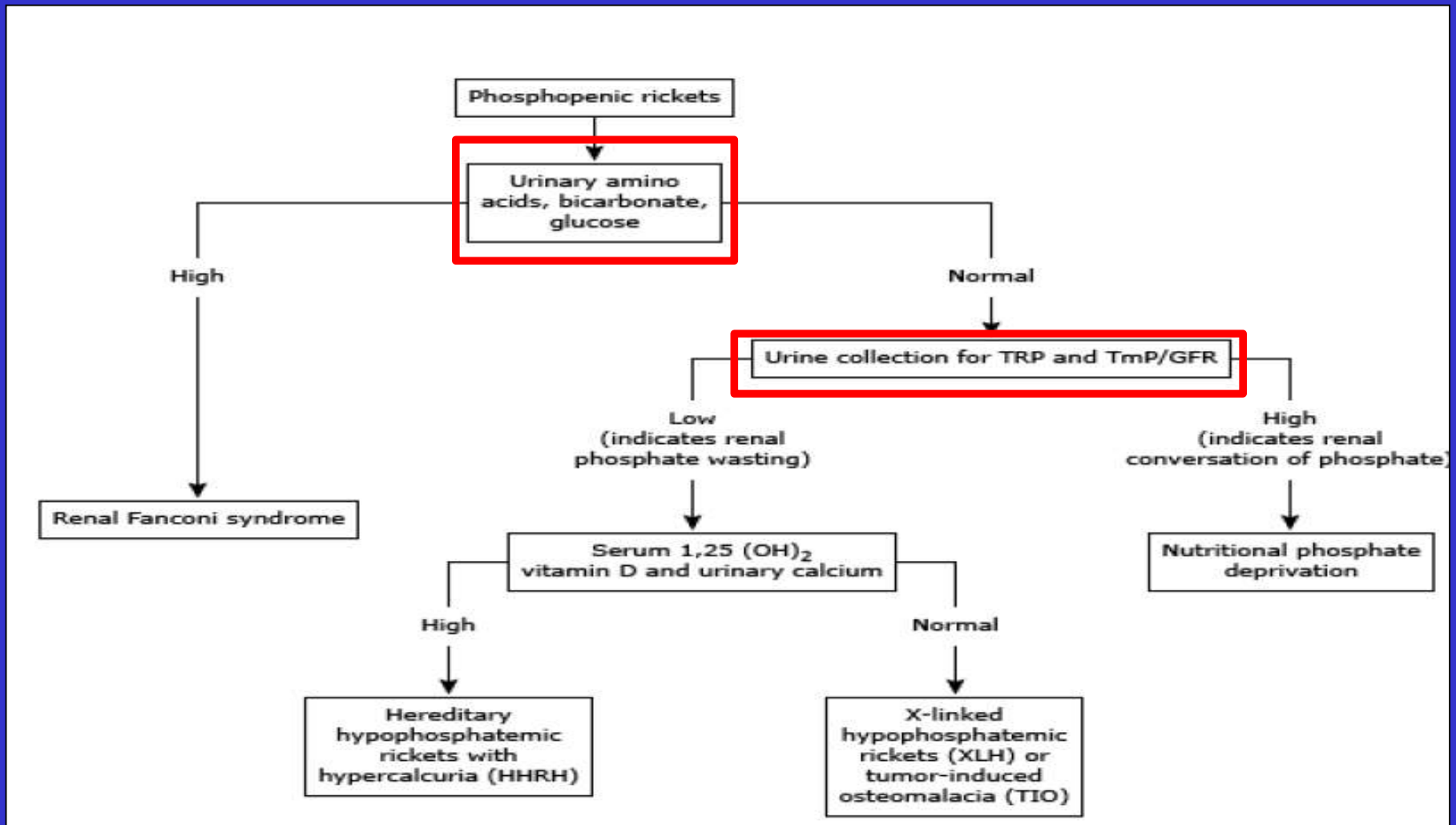
Calcipenic rickets is sometimes termed "hypocalcemic rickets," but this term is not completely accurate because serum calcium is not always low in this disorder. Calcipenic rickets is most commonly caused by vitamin D deficiency. Calcipenic rickets also may be caused by a mixed deficiency of vitamin D and calcium.

* Vitamin D dependent rickets type I (VDDR-I), also called pseudo-vitamin D deficiency, is caused by defective conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D.

• Hereditary vitamin D resistant rickets (HVDRR) has also been called vitamin D dependent rickets type II. It is a rare disorder characterized by end-organ resistance to vitamin D, usually caused by a defect in the vitamin D receptor.

Adapted from www.uptodate.com

APPROACH TO HYPOPHOSPHATEMIC RICKETS



TRP: total reabsorption of phosphorus; TmP/GFR: maximal tubular reabsorption of phosphorus per glomerular filtration rate; 1,25 $(OH)_2$ vitamin D: 1,25 dihydroxyvitamin D (calcitriol).

Adapted from www.uptodate.com

OBJECTIVE

KEEP IT SIMPLE AND STRAIGHTFORWARD

With aid of case based discussion to be able to

a) Develop a diagnostic approach to a child with resistant rickets

b) Find diagnostic clues of non-nutritional aetiology in a child with rickets

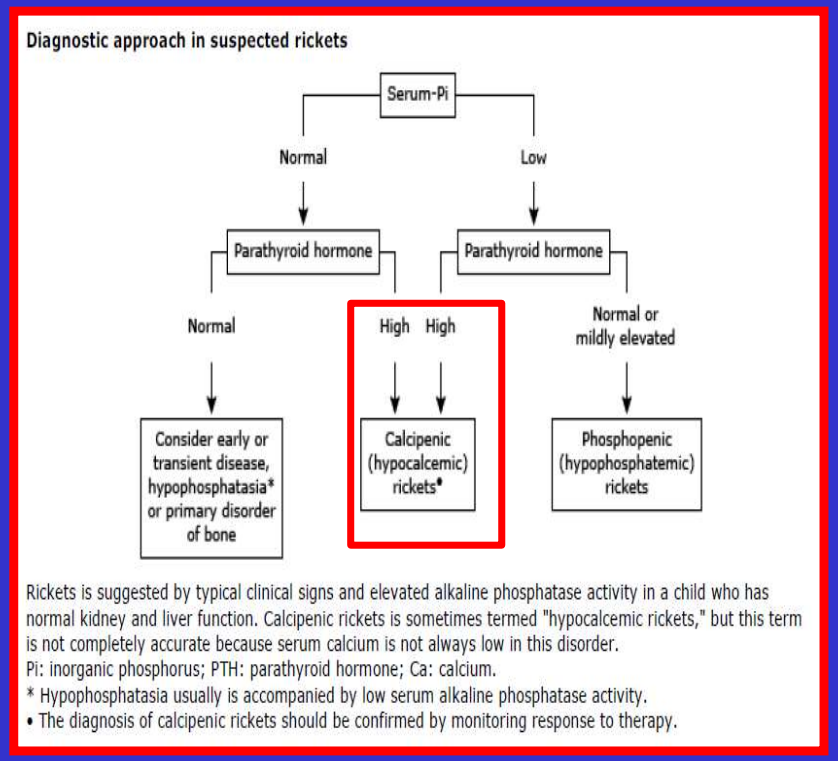
THE STORIES

STORY NO: 1a

- 3 yrs old girl
- Prolonged H/O rickets
- Multiple courses of Vit D
- Delayed dentition & motor development

STORY NO: 1a

Biochemistries	Plasma mg/dl
Calcium	7.8 (↓)
Phosphate	4.5
Creatinine	0.4
Sodium (mmol/L)	138
Potassium (mmol/L)	3.9

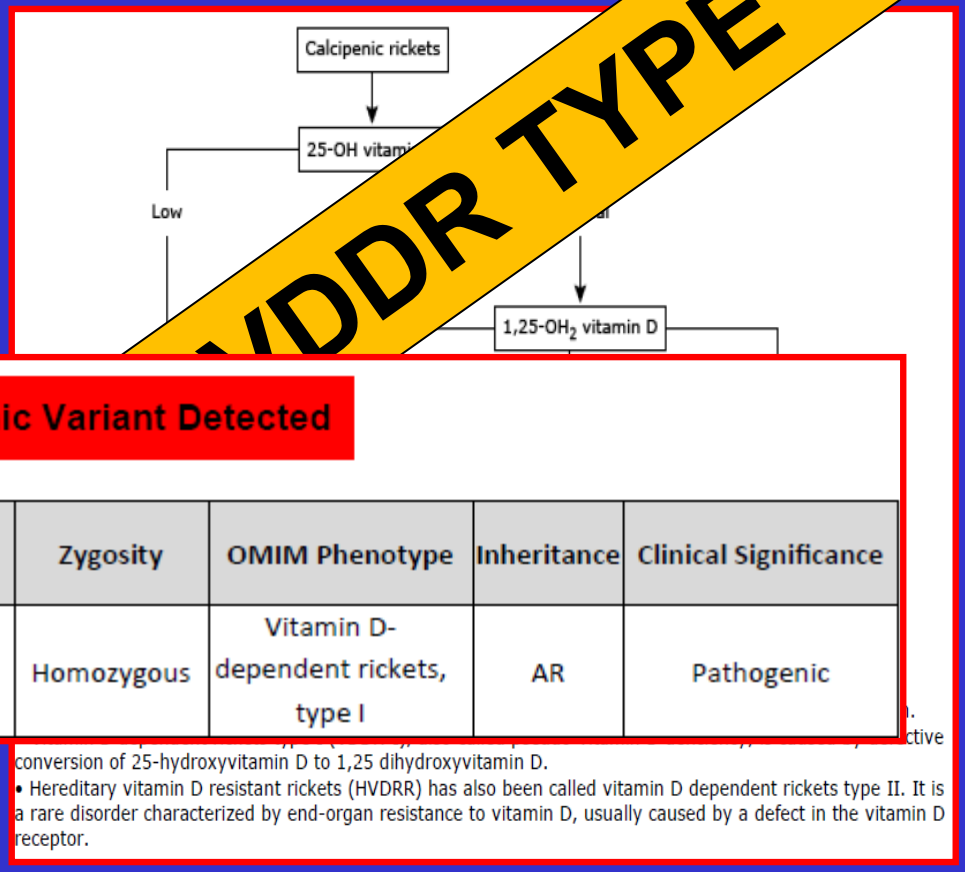


Rest of electrolytes: NAD, Urine R/E: NAD

PTH: 127 pmol/L (↑)

STORY NO: 1a

Biochem	Plasma mg/dl
Calcium	7.8 (↓)
Pho	
Cre	
Sod (mr	
Potassium (mmol/L)	3.9



Pathogenic Variant Detected

Gene (Transcript ID)	Chromosome position	Variant	Zygosity	OMIM Phenotype	Inheritance	Clinical Significance
CYP27B1 (NM_000785)	chr12:58158315-58158317	c.980_982delinsT p.Ser327Leufs*5	Homozygous	Vitamin D-dependent rickets, type I	AR	Pathogenic

Rest of ytes: NAD, Urine R/E: NAD

PT mol/L (↑)

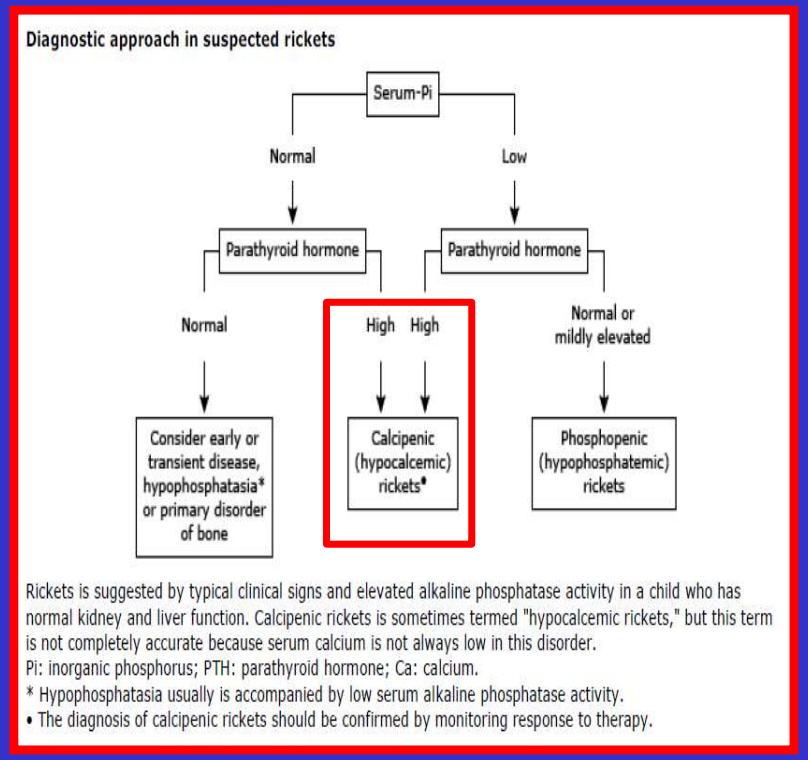
VDDR TYPE 1

NON-NUTT

STORY NO:1b

- 2.6 yrs old male with FTT
- Delayed eruption of teeth
- Widened wrist & rickety rossary
- Multiple courses of Vit D
- Current inv:

  Ca 7.3 mg/dl (↓), PO4 3.2 mg/dl (↓),
  ALP 4028 IU/L (↑), PTH 489 pg/ml (↑),



STORY NO:1b

- 2.6 yrs old male with FTT
- Delayed eruption of teeth
- Widened wrist & rickety rossary
- Multiple courses of Vit D
- Current inv:

  Ca 7.3 mg/dl (↓),

  PO4 3.2 mg/dl (↓), ALP 4028 IU/L (↑),
  PTH 489 pg/ml (↑),

  25(OH) D 35 ng/ml, 1,25(OH)2D 108 pg/ml (↑)

Calcipenic rickets is sometimes termed "hypocalcemic rickets," but this term is not completely accurate because serum calcium is not always low in this disorder. Calcipenic rickets is most commonly caused by vitamin D deficiency. Calcipenic rickets also may be caused by a mixed deficiency of vitamin D and calcium.

* Vitamin D dependent rickets type I (VDDR-I), also called pseudo-vitamin D deficiency, is caused by defective conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D.

• Hereditary vitamin D resistant rickets (HVDRR) has also been called vitamin D dependent rickets type II. It is a rare disorder characterized by end-organ resistance to vitamin D, usually caused by a defect in the vitamin D receptor.

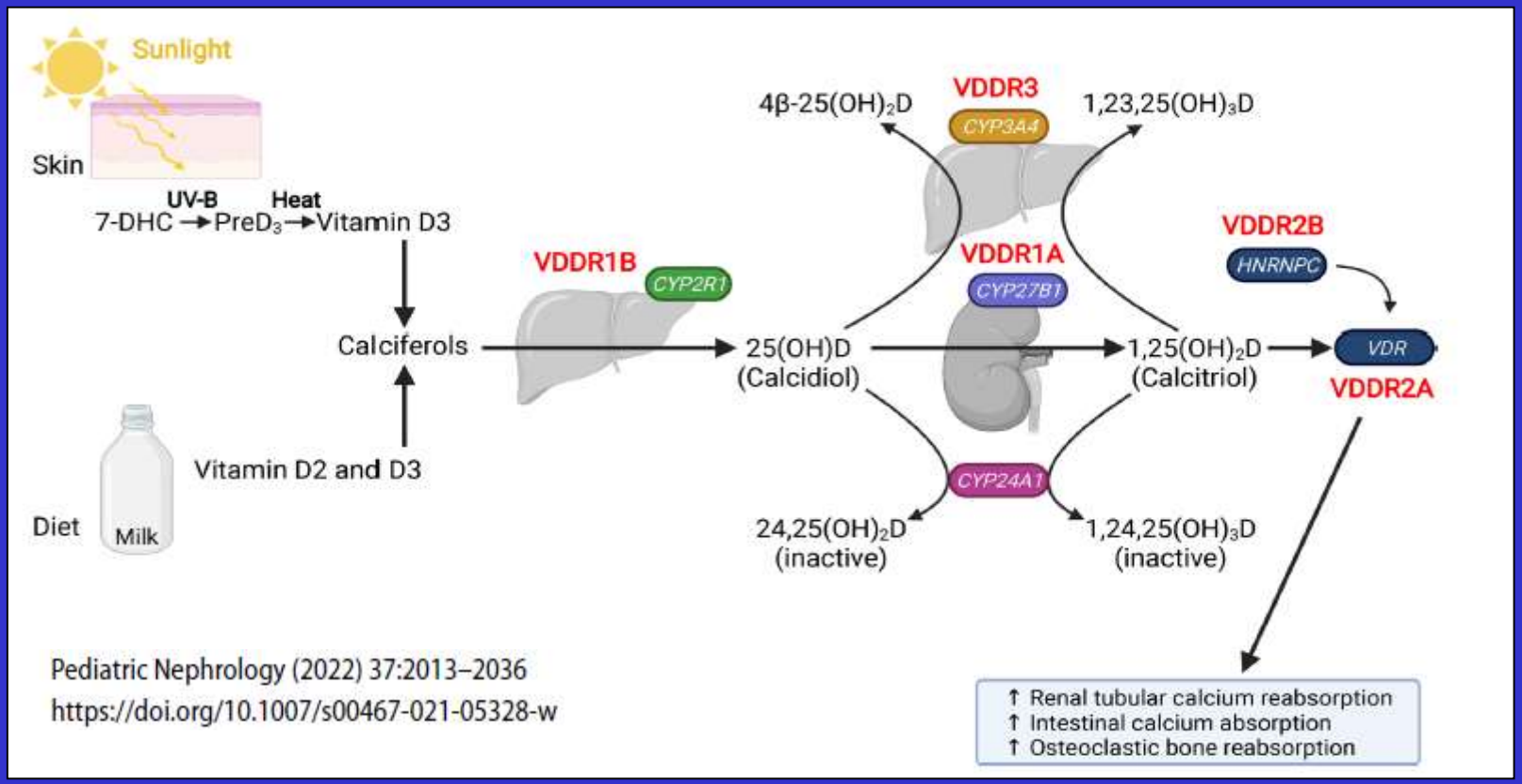


Table 3 Suggested vitamin D dose for maintenance treatment of patients with VDDR

	VDDR1A (μg per day)	VDDR1B (μg per day)	VDDR2 (μg per day)	VDDR3 (μg per day)
Vitamin D_3 or D_2	NI	100–200	125–1,000?[a]	**1000 to?**
Calcidiol	NI	**20–50**	20–200[a]	50 to?
Calcitriol	**0.3–2**	0.3–2	**5–60**[b]	1 to?
Alphacalcidiol	**0.5–3**	0.5–3	**5–60**[b]	2 to?

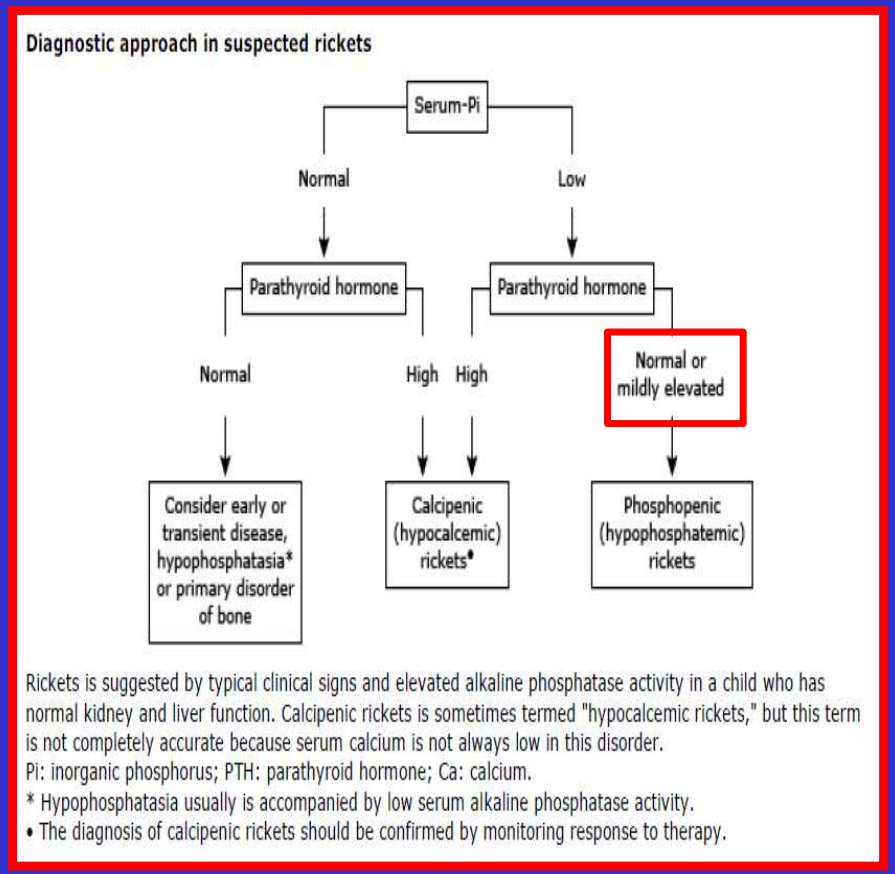
Pediatric Nephrology (2022) 37:2013–2036
https://doi.org/10.1007/s00467-021-05328-w

STORY NO: 2

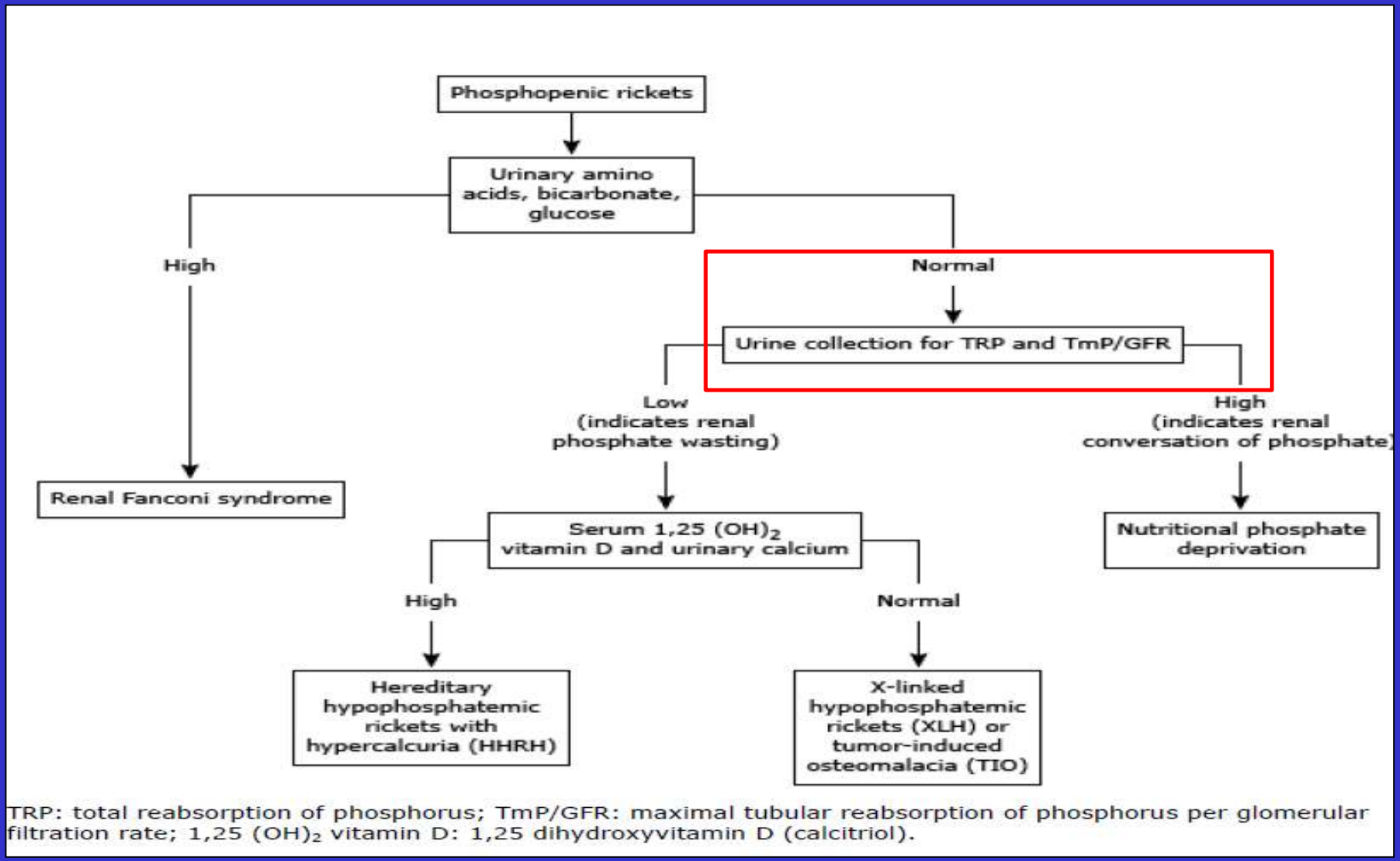
- 6-year old girl with bowed legs
- Multiple T/t with Vitamin D
- Wt (- 0.3 SDS), Ht (- 2.4 SDS)
- Examination showed widened ankles and wrist along with genu varum

STORY NO: 2

Biochem	Plasma
Calcium	8.1 mg/dl (↓)
ALP	989 IU(↑)
Phosphate	1.9 mg/dl (↓)
Creatinine	0.4 mg/dl
25 (OH) Vit D & iPTH	45 ng/ml (Normal) & 55 pg/ml (Normal)
Urine R/E	NAD



APPROACH TO HYPOPHOSPHATEMIC RICKETS



TRP: total reabsorption of phosphorus; TmP/GFR: maximal tubular reabsorption of phosphorus per glomerular filtration rate; 1,25 $(OH)_2$ vitamin D: 1,25 dihydroxyvitamin D (calcitriol).

Adapted from www.uptodate.com

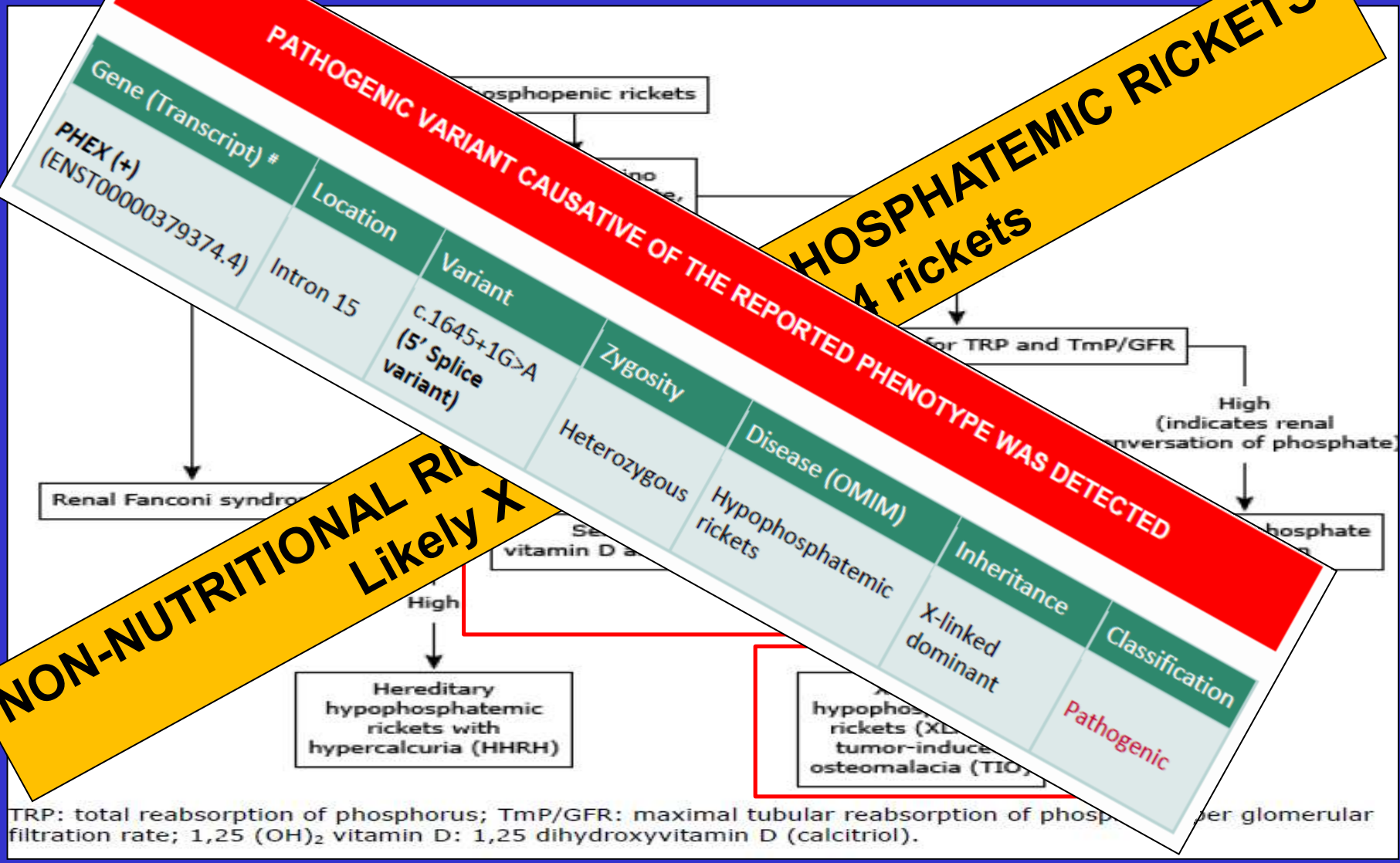
STORY NO: 2

Biochemistries	Plasma	Urine
Calcium	8.1 mg/dl (↓)	2.3 mg/kg/day
ALP	989 IU(↑)	
Phosphate	1.9 mg/dl (↓)	47.1 mg/dl
Creatinine	0.4 mg/dl	29.4 mg/dl
25 (OH) Vit D & iPTH	45 ng/ml (Normal) & 55 pg/ml (Normal)	----------
1, 25 (OH) Vit D	58 pg/ml	

Rest of electrolytes: NAD, Urine R/E: NAD

TRP: 66%; TmP/GFR = 1.4

APPROACH TO HYPOPHOSPHATEMIC RICKETS



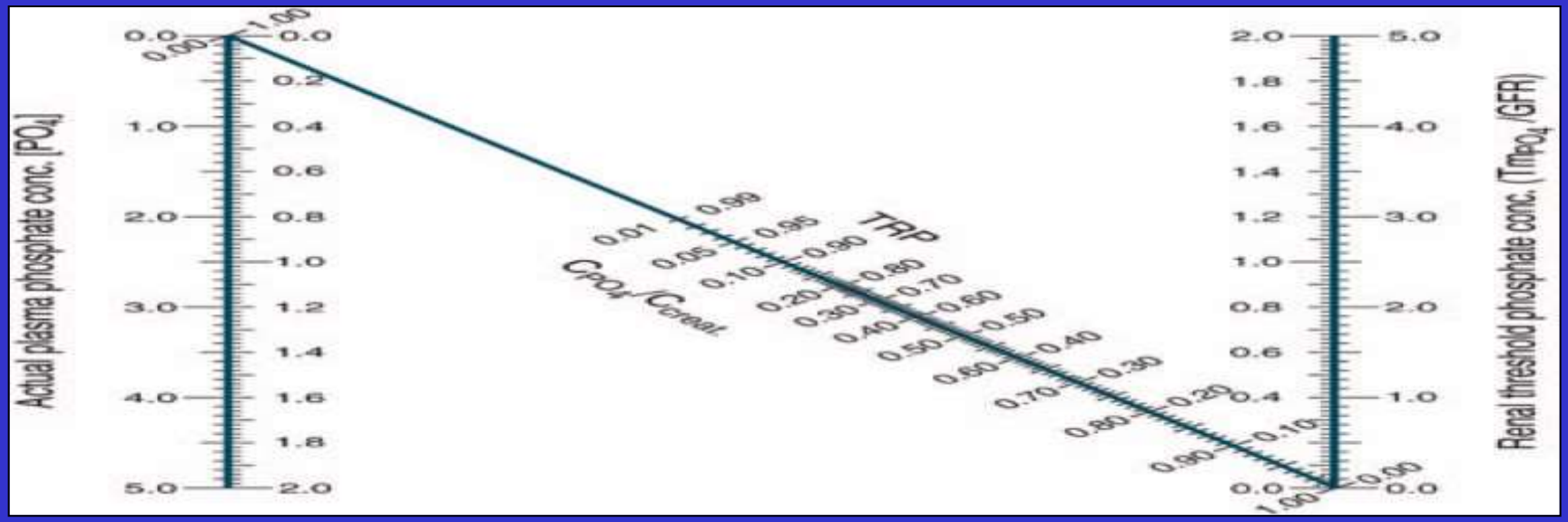
PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
PHEX (+) (ENST00000379374.4)	Intron 15	c.1645+1G>A (5' Splice variant)	Heterozygous	Hypophosphatemic rickets	X-linked dominant	Pathogenic

HOSPHATEMIC RICKETS
4 rickets

NON-NUTRITIONAL RI
Likely X

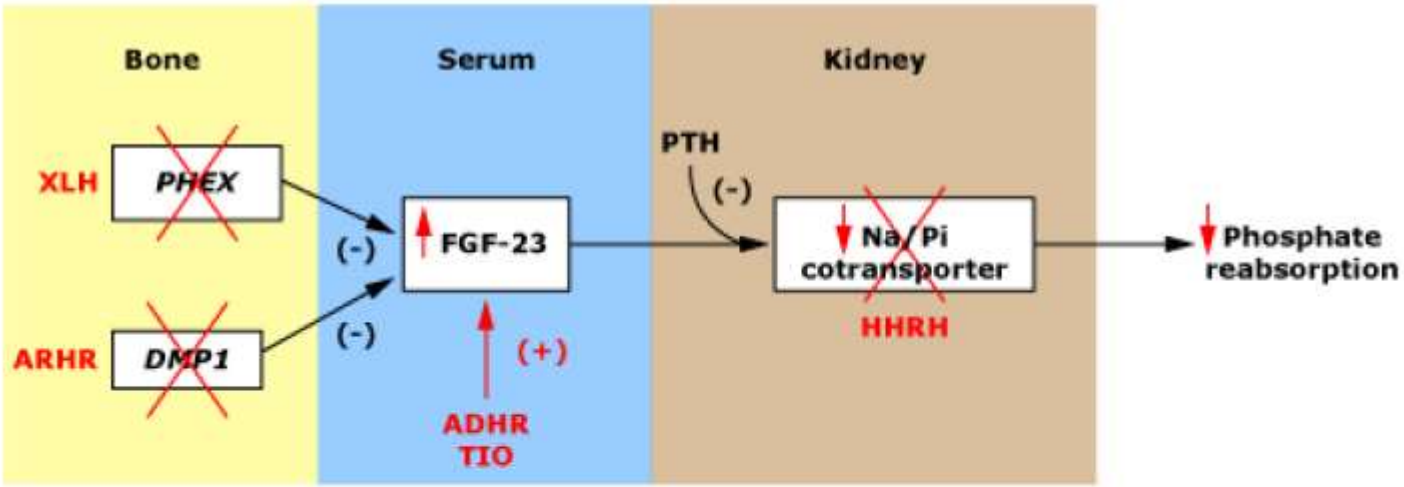
Adapted from www.uptodate.com



$$\text{TmP/GFR (mg/dL)} = \text{Plasma phosphate} - \frac{\text{urine phosphate} \times \text{plasma creatinine}}{\text{urine creatinine}}$$

(normal 2.8- 4.4 mg/dL)

HYPOHOSPHATEMIC RICKETS



Levels of FGF-23 are increased by inactivating mutations in PHEX (as in XLH) or DMP1 (as in ARHR), by activating mutations in FGF-23 (as in ADHR), or by tumor production of FGF-23 (as in TIO). Each of these disorders leads to excessive activity of FGF-23, which suppresses the Na/Pi cotransporter and causes renal phosphate wasting. In HHRH the renal phosphate wasting is caused by a mutation in the Na/Pi cotransporter itself.
XLH: X-linked hypophosphatemic rickets.

Pediatric Nephrology (2022) 37:2289–2302
https://doi.org/10.1007/s00467-022-05505-5

EDUCATIONAL REVIEW

Rickets guidance: part II—management

Dieter Haffner[1,2] · Maren Leifheit-Nestler[1,2] · Andrea Grund[1,2] · Dirk Schnabel[3]

- Children with X-linked hypophosphatemia should be treated with burosumab, if available, or with frequent doses of oral phosphate salts in combination with active vitamin D as used for other forms of fibroblast-growth factor 23 (FGF23)-associated hypophosphatemic rickets.
- Patients with tumor-induced osteomalacia should primarily undergo tumor resection, if possible.
- Forms of hypophosphatemic rickets independent of FGF23 due to selective genetic defects of renal tubular phosphate reabsorption, are treated with oral phosphate only, since they are associated with excessive 1,25-dihydroxyvitamin D production.
- Adjustment of medication should be done with consideration of treatment-associated side effects, including diarrhea, gastrointestinal discomfort, hypercalciuria, secondary hyperparathyroidism, and development of nephrocalcinosis or nephrolithiasis.

Table 4 Daily doses for phosphate and active vitamin D (conventional treatment) in children with X-linked hypophosphatemia (XLH) and tumor-induced hypophosphatemia (TIO)

Drug	XLH	TIO
Phosphate[a] (mg/kg)/(mmol/kg) given in 4–6 doses	20–60/0.7–2.0 Maximum 80 mg/kg	15–60/0.5–2
Calcitriol[b] (ng/kg) given in 1–2 doses	20–30 Alternatively, 0.5 µg[c] (age > 12 months)	15–60
Alphacalcidiol[b] (ng/kg) given once daily	30–50 Alternatively, 1 µg[c] (age > 12 months)	15–60

[a]Based on elemental phosphorus; infants and young children usually require more frequent phosphate administrations than older children and adolescents

[b]Phosphate should always be given in combination with either calcitriol or alphacalcidiol

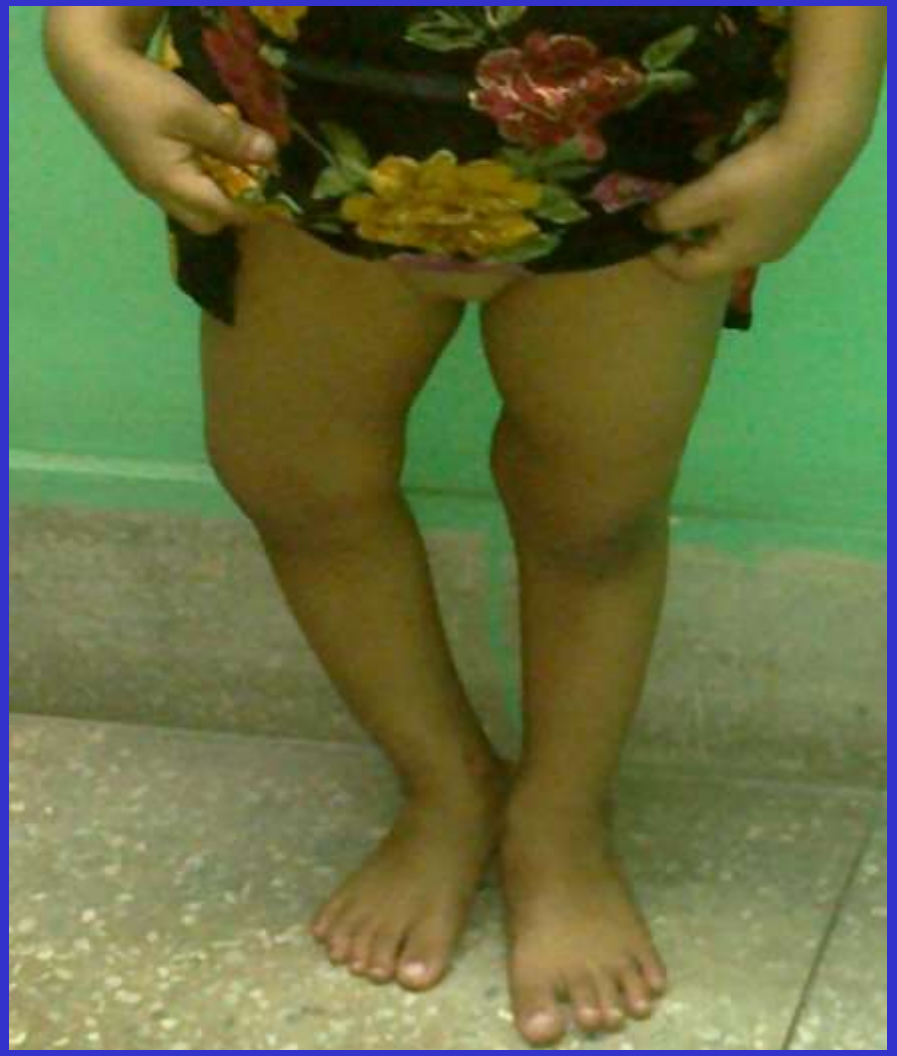
Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

Table 3 | **Summary of the recommendations for the follow-up of children and adults (both treated and untreated) with XLH**

Examination	0–5 years	5 years to start of puberty (9–12 years)	Puberty[a]	Adults
Frequency of visits	Monthly to thrice monthly	3–6 months	3 months	6–12 months
Height, weight, IMD and ICD	✓	✓	✓	✓
Head circumference and skull shape	✓	NA	NA	NA
Presence of rickets, pain, stiffness and fatigue	✓	✓	✓	✓[b]
Neurological examination (consequences of craniosynostosis and spinal stenosis)	✓	✓	✓	✓
Musculoskeletal function, 6MWT[c]	Not feasible	Once a year	Once a year	Once a year
Orthopaedic examination	Once a year in the presence of significant leg bowing			Once a year[d]
Dental examination	Twice yearly after tooth eruption	Twice yearly	Twice yearly	Twice yearly
Hearing test	Not feasible	From 8 years: hearing evaluation if symptoms of hearing difficulties		
Serum levels of ALP (children), BAP (adults), calcium, phosphate, PTH and creatinine; eGFR	✓	✓	✓	✓
25(OH) vitamin D levels	Once a year	Once a year	Once a year	Once a year
Urine test: calcium:creatinine ratio[e]	Every 3 to 6 months on conventional treatment and burosumab treatment			
Fasting serum phosphate levels and TmP/GFR	• On burosumab treatment: every 2 weeks during the first month, every 4 weeks during the following 2 months and thereafter as appropriate • Titration period: between injections, ideally 7–11 days after last injection to detect hyperphosphataemia • After achievement of a steady state (which can be assumed after 3 months of a stable dose): preferentially directly before injections (children) or during the last week before the next injection (adults) to detect underdosing • Also measured 4 weeks after dose adjustment			
1,25(OH)$_2$ vitamin D levels	Every 3 to 6 months in patients on burosumab treatment (analysed together with U_{Ca})			
Blood pressure	Twice yearly	Twice yearly	Twice yearly	Twice yearly
Renal ultrasonography	Every 1–2 years on conventional or burosumab treatment			
Left wrist and/or lower limbs radiographs	• If leg bowing does not improve upon treatment (children) • If surgery is indicated • Focused on any area of localized persistent bone pain • In case of short stature (bone age assessment)		In adolescents with persistent lower limb deformities when they are transitioning to adult care	NA
Dental orthopantogram	Not feasible	Based on clinical needs	Based on clinical needs	Based on clinical needs
Fundoscopy and brain MRI	If aberrant shape of skull, headaches or neurological symptoms	If recurrent headaches, declining school/cognitive performances or neurological symptoms		
Cardiac ultrasonography[f]	In presence of persistent elevated blood pressure (>95th percentile)			
QOL[g]	Not feasible	Every 2 years if available	Every 2 years if available	Every 2 years if available

STORY NO: 3a

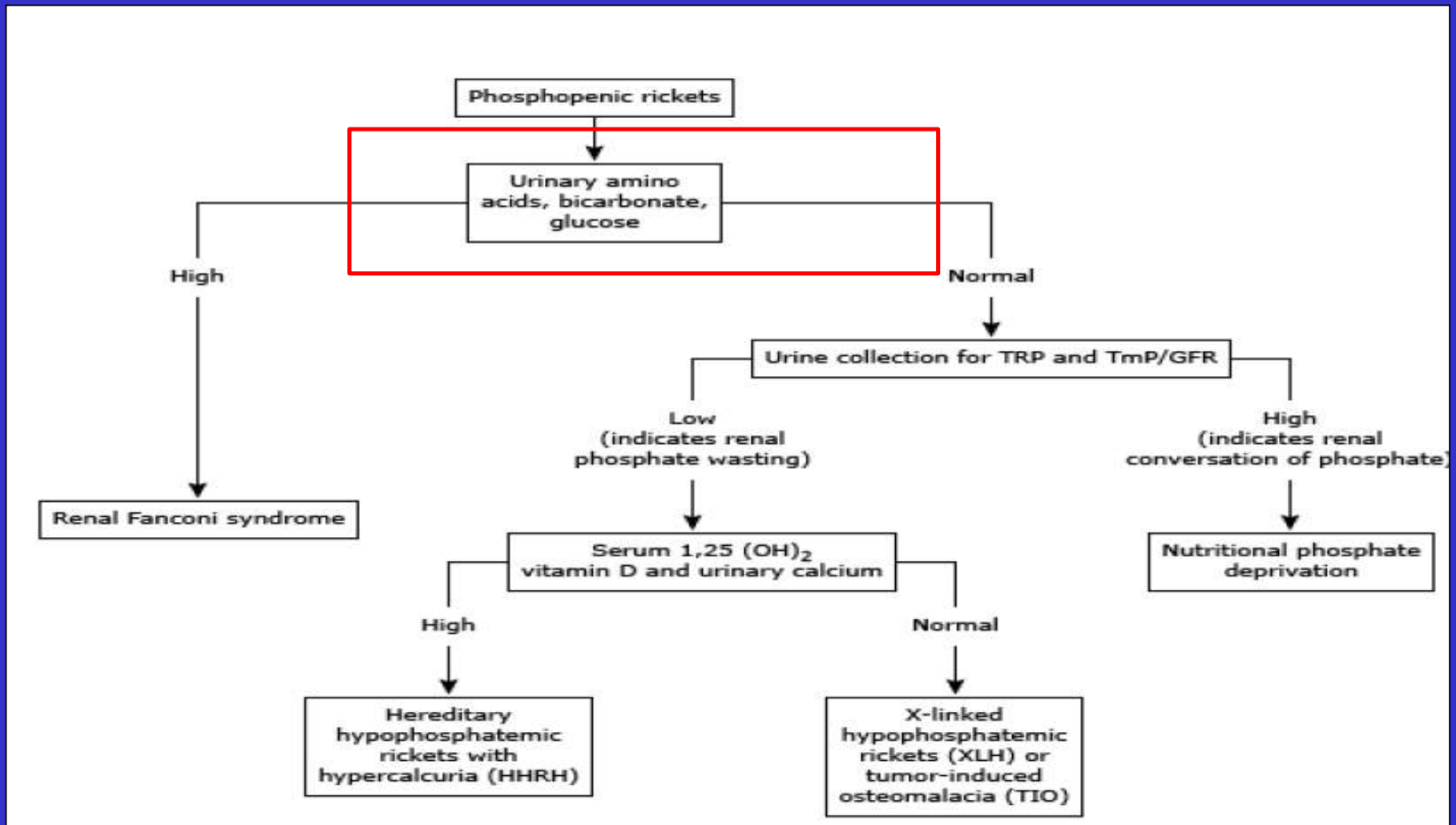
- 3 yrs old girl
- Failure to thrive
- Polyuric
- Polydipsic



STORY NO: 3a

	Initial investigation reports
BUN	11 mg/dl
Creat	0.4 mg / dl(eGFR = 93.4)
Ca	9.3 mg /dl
PO4	1.6 mg /dl
ALP	1261 U/L
Na	136 mmol/L
K	2.5 mmol / L
Cl	112 mmol/L
X-ray wrist	Consistent with rickets
25 (0H) Vit D & iPTH	44 ng/mL & 48 pg/ml
USG-KUB	Bilateral mild to moderate hydronephrosis

APPROACH TO HYPOPHOSPHATEMIC RICKETS



TRP: total reabsorption of phosphorus; TmP/GFR: maximal tubular reabsorption of phosphorus per glomerular filtration rate; 1,25 $(OH)_2$ vitamin D: 1,25 dihydroxyvitamin D (calcitriol).

Adapted from www.uptodate.com

STORY NO: 3a

	Initial investigation reports
BUN	11 mg/dl
Creat	0.4 mg / dl(eGFR = 93.4)
Ca	9.3 mg /dl
PO4	1.6 mg /dl
ALP	1261 U/L
Na	136 mmol/L
K	2.5 mmol / L
Cl	112 mmol/L
VBG	Ph- 7.19; HCO3-13, PCO2-37.9 Serum AG = 13.5
Urinalysis	U pH- 6.5, Alb-trace, Sugar +, Sp. Gravity- 1005
X-ray wrist	Consistent with rickets
25 (0H) Vit D & iPTH	44 ng/mL & 48 pg/ml
USG-KUB	Bilateral mild to moderate hydronephrosis

Renal Tubular Acidosis

Evaluation of Renal Tubular Acidosis

Arvind Bagga and Aditi Sinha

Indian J Pediatr 2020; 87: 733-44

TABLE 2. Investigations to Differentiate Types of Renal Tubular Acidosis (RTA)

	Proximal RTA	Distal RTA		Type 4 RTA
		Classic	Hyperkalemic	
Plasma K^+	Normal/low	Normal/low	High	High
Urine pH	< 5.5	> 5.5	> 5.5	< 5.5
Urine anion gap	Positive	Positive	Positive	Positive
Urine NH_4^+	Low	Low	Low	Low
Fractional HCO_3^- excretion	>10-15%	<5%	<5%	5-10%
U-B PCO_2 mm Hg	>20	< 20	</>20	>20
Urine Ca^{2+}	Normal	High	High	Normal/low
Other tubular defects	Often present	Absent	Absent	Absent
Nephrocalcinosis	Absent	Present	Present	Absent
Bone disease	Common	Often present	Uncommon	Absent

U-B PCO_2 urine to blood PCO_2 gradient.

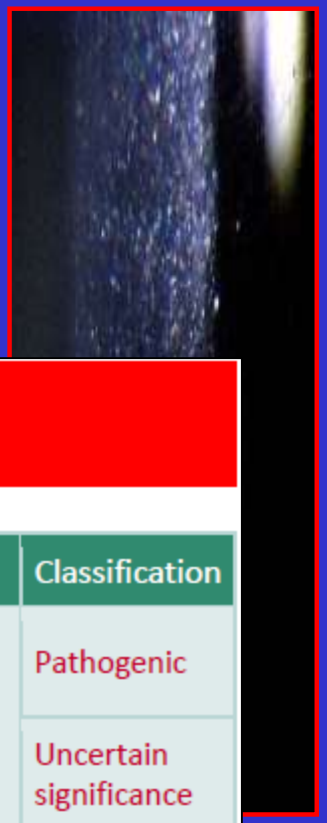
STORY NO: 3a

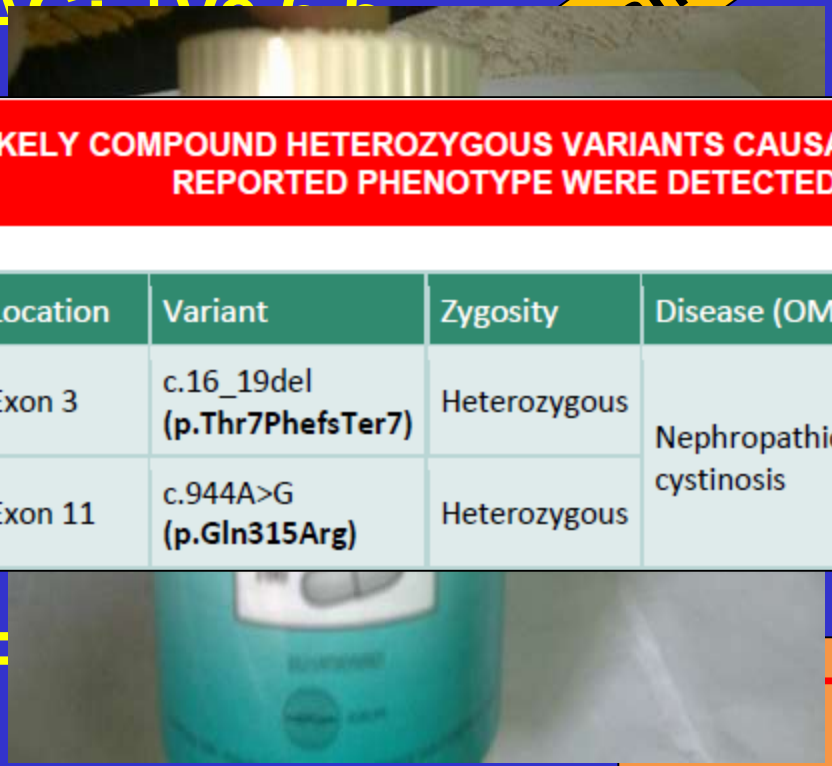
	Initial investigation reports
BUN	11 mg/dl
Creat	0.4 mg / dl(eGFR = 93.4)
Ca	9.3 mg /dl
PO4	1.6 mg /dl
ALP	1261 U/L
Na	136 mmol/L
K	2.5 mmol / L
Cl	112 mmol/L
VBG	Ph- 7.19; HCO3-13, PCO2-37.9 Serum AG = 13.5
Urinalysis	U pH- 6.5, Alb-trace, Sugar +, Sp. Gravity- 1005
X-ray wrist	Consistent with rickets
25 (0H) Vit D & iPTH	44 ng/mL & 48 pg/ml
USG-KUB	Bilateral mild to moderate hydronephrosis

CASE SCENARIO: 3a
FTT with NAG acidosis

- **Serum AG: 13.5**
- **Urine A**

nconi) 2nd CYSTINOSIS





LIKELY COMPOUND HETEROZYGOUS VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE WERE DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***CTNS* (+)** (ENST00000381870.3)	Exon 3	c.16_19del **(p.Thr7PhefsTer7)**	Heterozygous	Nephropathic cystinosis	Autosomal recessive	Pathogenic
	Exon 11	c.944A>G **(p.Gln315Arg)**	Heterozygous			Uncertain significance

NON-NU

mpGF

Ur PO4 x Sr Creatinine
Ur Creatinine

STORY NO: 3b

- Inve

Na 135,K 2.7,
Ca 7.3, P 1.1, ALP
94 ng/L, Vit D 31.58 ng

Serum AG: 14.7, Urin 10

Urine R/E: Prot , Glucose 1+

Fruse hallenge: Urine pH <5.5

O4: 18%, TmpGFR: 0.4

NON-NUTRITIONAL RICKE

coni) 2nd TO TYROSINEMIA 1

LIKELY COMPOUND HETEROZYGOUS VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE WERE IDENTIFIED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
FAH (+) (ENST00000407106.1)	Exon 12	c.928C>T (p.Gln310Ter)	Heterozygous	Tyrosinemia, type I	Autosomal recessive	Pathogenic
	Exon 3	c.192G>T (p.Gln64His)	Heterozygous			Likely Pathogenic

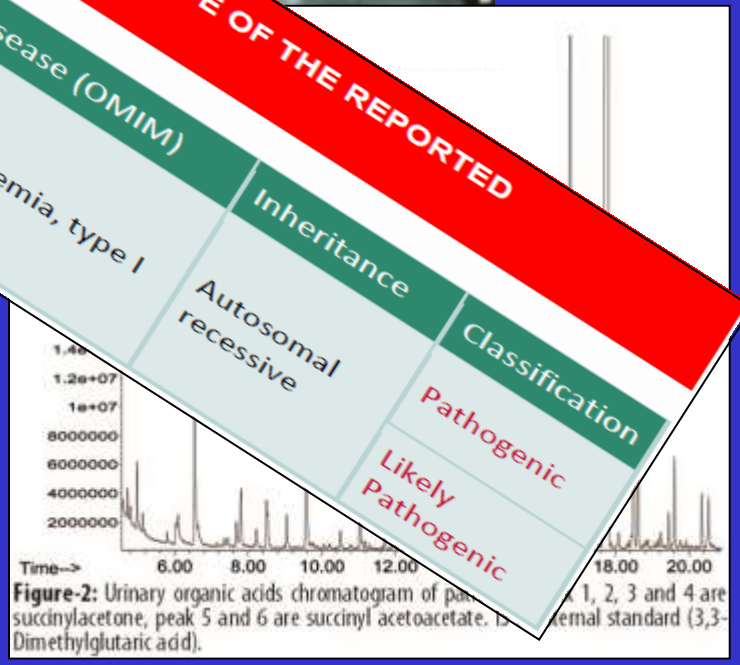


Figure-2: Urinary organic acids chromatogram of pa 1, 2, 3 and 4 are succinylacetone, peak 5 and 6 are succinyl acetoacetate. I ernal standard (3,3-Dimethylglutaric acid).

STORY NO: 3c

- 2.3 yrs old boy
- FTT
- Constipation
- Delayed walking-

Diagnosed as rickets and given Vit D twice

Initial biochemistry:

- Na = 135, K = 3.2, Ca = 8.1, PO4 = 3.2, 25 (OH) Vit D = 110, Cl= 109, iPTH 68.
- VBG: pH=7.2, HCO3=12

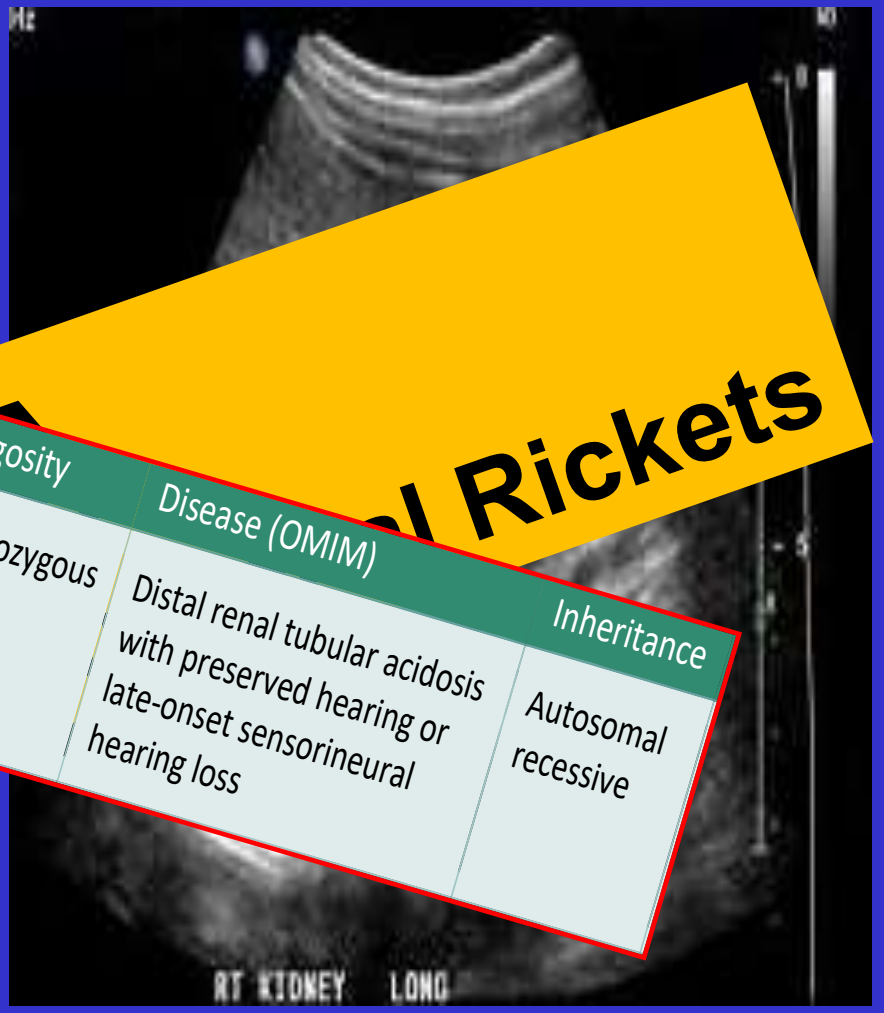
STORY NO: 3c

- Ur… …K 19, Cl 35
- …

…l Rickets

resulting in No…

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance
ATP6V0A4 **(-)** (ENST00000310018)	Exon 18	c.1955C>G **(p.Pro652Arg)**	Homozygous	Distal renal tubular acidosis with preserved hearing or late-onset sensorineural hearing loss	Autosomal recessive



Nephrol Dial Transplant (2014) 29: iv87–iv94
doi: 10.1093/ndt/gfu090

Full Review

Nephropathic cystinosis: an international consensus document

Recommendations for the management of tyrosinaemia type 1

Corinne de Laet[1], Carlo Dionisi-Vici[2], James V Leonard[3*], Patrick McKiernan[4], Grant Mitchell[5], Lidia Monti[6], Hélène Ogier de Baulny[7], Guillem Pintos-Morell[8] and Ute Spiekerkötter[9]

Abstract

The management of tyrosinaemia type 1 (HT1, fumarylacetoacetase deficiency) has been revolutionised by the introduction of nitisinone but dietary treatment remains essential and the management is not easy. In this review detailed recommendations for the management are made based on expert opinion, published case reports and investigational studies as the evidence base is limited and there are no prospective controlled studies.
The added value of this paper is that it summarises in detail current clinical knowledge about HT1 and makes recommendations for the management.

Keywords: Hepatorenal tyrosinaemia, Fumarylacetoacetase, Succinylacetone, Nitisinone, Cirrhosis, Acute live failure, Hepatocellular carcinoma, Low tyrosine diet

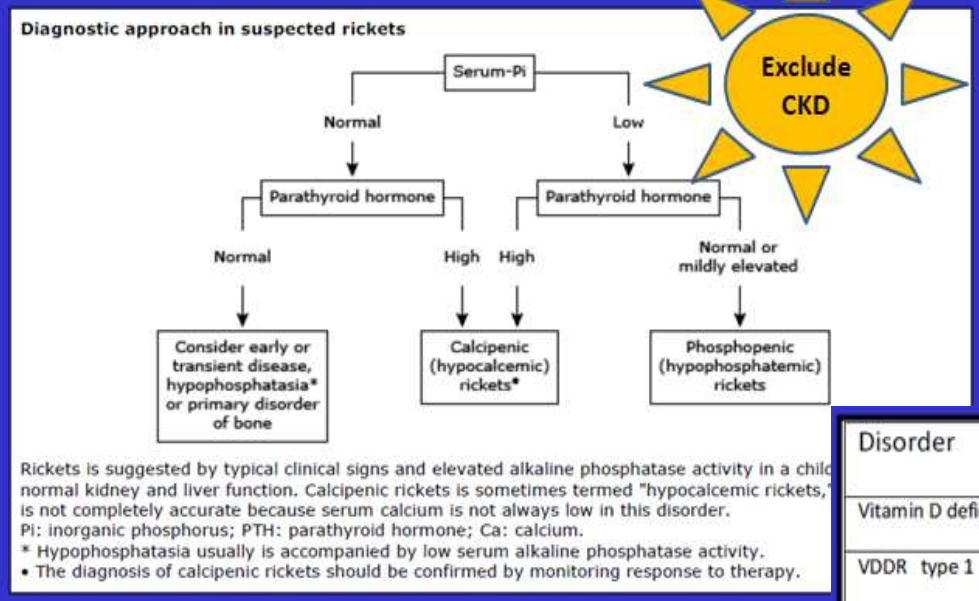
Nephrol Dial Transplant (2021) 36: 1585–1596
doi: 10.1093/ndt/gfab171
Advance Access publication 29 April 2021

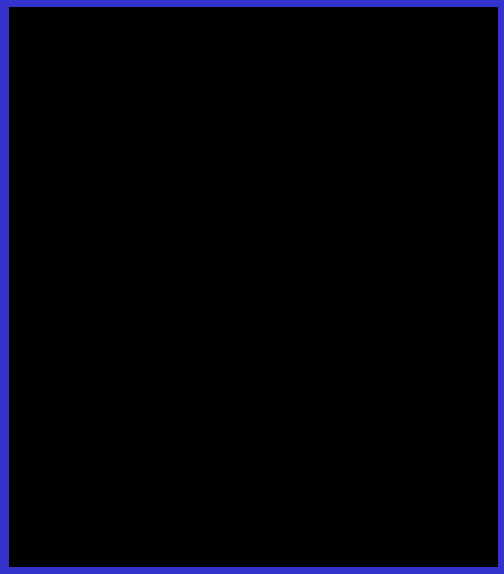
Distal renal tubular acidosis: ERKNet/ESPN clinical practice points

STORY NO: 4

- ✓ 11 yrs old girl initially presented with deformity of lower limb
- ✓ Wt (-2.2 SDS) & Ht (-3 SDS)
- ✓ T/t with 2 pulse of Vit D as well as variable doses of oral Vit D
- ✓ H/O being transfused thrice
- ✓ Hb 8.6 mg/dl (↓), Ca 9.9 mg/dl, PO4 7.1 mg/dl (↑), ALP 1009 IU (↑) , PTH 1421

STORY NO: 4





- ✓ **Urea 160 mg/dl**
- ✓ **Creatinine: 5.7 …**
- ✓ **…(↑),**
- ✓ **25 (OH) Vit D: 26 ng/ml**

Disorder	Ca	Pi	PTH	25 (OH) D	1,25 $(OH)_2$ D	ALK PHOS	URINE Ca	URINE
Vitamin D deficiency	N↓	↓	↑	↓	↓N	↑		
VDDR type 1	N↓	↓	↑	N				
VDDR type 2	N↓	↓	↑					↑
Chr renal failure						↑	N↓	↓
					↑	↑	↑	↓
		↓	N↑	N	RD	↑	↓	↑
	N	↓	N	N	RD	↑	↓	↑
HHRH	N	↓	N↓	N	RD	↑	↑	↑
ARHR	N	↓	N	N	RD	↑	↓	↑
Tumour induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi Syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dietary Ca deficiency	N↓	↓	↑	N	↑	↑	↓	↑

NON-NUTRITIONAL RICKETS: RENAL

AJKD

Am J Kidney Dis. 2011;58(6):1022-1036

Core Curriculum in Nephrology

CKD–Mineral and Bone Disorder: Core Curriculum 2011

Ranjani N. Moorthi, MD,[1] and Sharon M. Moe, MD[1,2]

Box 1. Definition of CKD-MBD

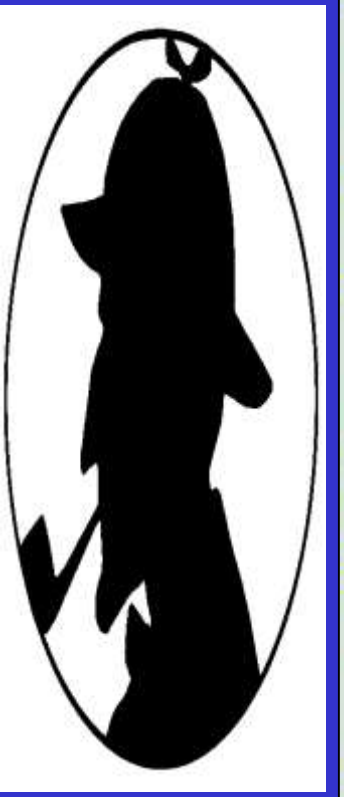
A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft-tissue calcification

Table 1. Recommendations for Ranges of Mineral Metabolism Parameters in CKD

	CKD Stage 3	CKD Stage 4/5	CKD Stage 5D
Phosphorus	Maintain in "normal" range (2C)	Maintain in "normal" range (2C)	Decrease toward the "normal" range (2C)
Calcium	Maintain in "normal" range (2C)	Maintain in "normal" range (2C)	Maintain in "normal" range (2C)
Intact PTH	Ideal level unknown	Ideal level unknown	Maintain within >2 and <9× the upper limit of normal (if there is a trend changing within that range, adjust prescription) (2C)

WHEN TO SUSPECT NON-NUTRITIONAL RICKETS



Panel 4: **Factors suggesting that rickets may not be due to simple vitamin D deficiency** THE LANCET • Vol 362 • October 25, 2003

Age

Below 6 months—Radiological bone changes are unusual at this age except in very-low-birthweight babies; in such cases calcium and phosphorus deficiency should also be considered. Vitamin D deficiency generally presents as hypocalcaemia, is accompanied by maternal osteomalacia, and only occasionally has the classic radiographic signs of rickets.

3–10 years—The risk of toddler rickets has passed and the increased demands of the prepubertal growth spurt and adolescence are not yet apparent.

Radiographs

Show a periosteal reaction, motheaten metaphysis, or both, rather than only the classic cupping, splaying, and fraying.

Plasma biochemistry

Urea >7 mmol/L (5 mmol/L in newborn infant). Creatinine >100 µmol/L. Alkaline phosphatase not raised. Phosphorus >2·0 mmol/L (2·5 mol/L in newborn infant) or less than 1·2 mmol/L (1·5 mmol/L in newborn infant). Plasma calcidiol not low, so long as early treatment can be excluded. Very high or very low plasma calcitriol. Vitamin D metabolites rarely measured in a routine case.

Geography

Child in tropical or subtropical Africa and Turkey, where calcium deficiency may have a role.

Response to treatment

Oral calciferol is not followed by radiographic evidence of some healing after 2–4 months. Early biochemical signs of success are an initial rise to well above normal concentrations of alkaline phosphatase and calcitriol then a gradual fall, and a rise to normal concentrations of calcidiol; however, this monitoring is not necessary in most cases.

WHEN TO SUSPECT NON-NUTRITIONAL RICKETS

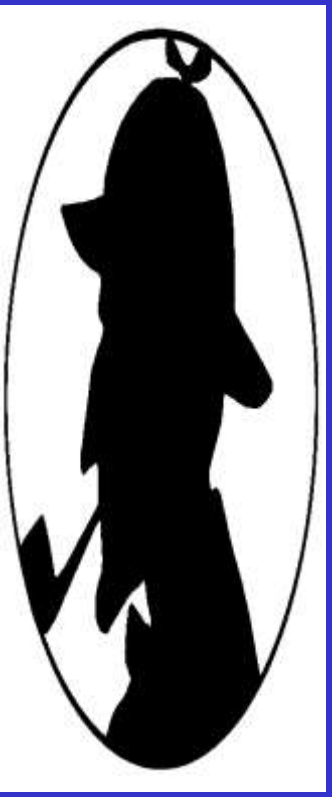


Table 3 Typical clinical features of certain causes of rickets

Clinical features	Suggested underlying disease
At all ages: Symptomatic hypocalcemia: seizures, tetany, and hypotonia *Young infants:* irritability, poor feeding, apnea, stridor, craniotabes, large fontanelle	Nutritional rickets and VDDR
Older infants: failure to thrive, delayed development, hypotonia, frontal bossing, thickened wrists and ankles (widened metaphysis) and enlarged costochondral junctions of the ribs (rachitic rosary), heart failure (tachycardia, tachypnea, hepatomegaly and edema)	Frontal bossing, swollen joints and rachitic rosary, also seen in other forms of rickets
Children: abnormal dentition/ enamel hypoplasia, frontal bossing, thickened wrists and ankles (widened metaphysis), leg bowing, fractures	Leg bowing, fractures and frontal bossing, also seen in other forms of rickets
Adolescents: bone pain, muscle weakness, waddling gait, leg bowing and fractures	Also noted in other forms of rickets
Partial or complete alopecia	VDDR type 2A and 2B
At all ages: disproportionate short stature *Infants:* craniosynostosis	Hereditary forms of FGF23-mediated hypophosphatemia, e.g., XLH, ADHR, ARHR1 and 2
Children and adolescents: dental abscesses, hearing loss, thickened wrists and ankles (widened metaphysis), leg bowing, waddling gait, frontal bossing	Enlarged joints, leg bowing, and waddling gait, and frontal bossing also seen in other forms of rickets
Adolescents: periodontitis, pseudofractures	
Syringomyelia, Arnold-Chiari malformation,enthesopathy, osteoarthritis (adults)	XLH
Clinical symptoms after early childhood	ADHR, TIO, nutritional rickets
Anemia	ADHR
Café-au-lait macules	McCune Albright syndrome / fibrous dysplasia
Facial dysmorphism, failure of tooth eruption, short stature	Osteoglophonic dysplasia
Craniofacial anomalies including hypoplastic nose, midface hypoplasia, exophthalmus, intracranial calcification, sensorineural hearing loss, developmental delay, epilepsy, large fontanelle, and amelogenesis imperfecta	Raine syndrome
Hypercalciuria, nephrocalcinosis or nephrolithiasis	HHRH, nephropathic cystinosis, Dent disease, distal renal tubular acidosis (dRTA)
Polyuria, polydipsia, fever episodes due to dehydration	Fanconi syndrome, e.g., nephropathic cystinosis

Pediatric Nephrology (2022) 37:2013–2036

Biochemical clues to D/D

Disorder	Ca	Pi	PTH	25 (OH) D	1,25 $(OH)_2$ D	ALK PHOS	URINE Ca	URINE Pi
Vitamin D deficiency	N↓	↓	↑	↓	↓N	↑	↓	↑
VDDR type 1	N↓	↓	↑	N	↓	↑	↓	↑
VDDR type 2	N↓	↓	↑	N	↑	↑	↓	↑
Chr renal failure	N↓	↑	↑	N	↓	↑	N↓	↓
Dietary Pi def	N	↓	N↓	N	↑	↑	↑	↓
XLH	N	↓	N↑	N	RD	↑	↓	↑
ADHR	N	↓	N	N	RD	↑	↓	↑
HHRH	N	↓	N ↓	N	RD	↑	↑	↑
ARHR	N	↓	N	N	RD	↑	↓	↑
Tumour induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi Syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dietary Ca deficiency	N↓	↓	↑	N	↑	↑	↓	↑

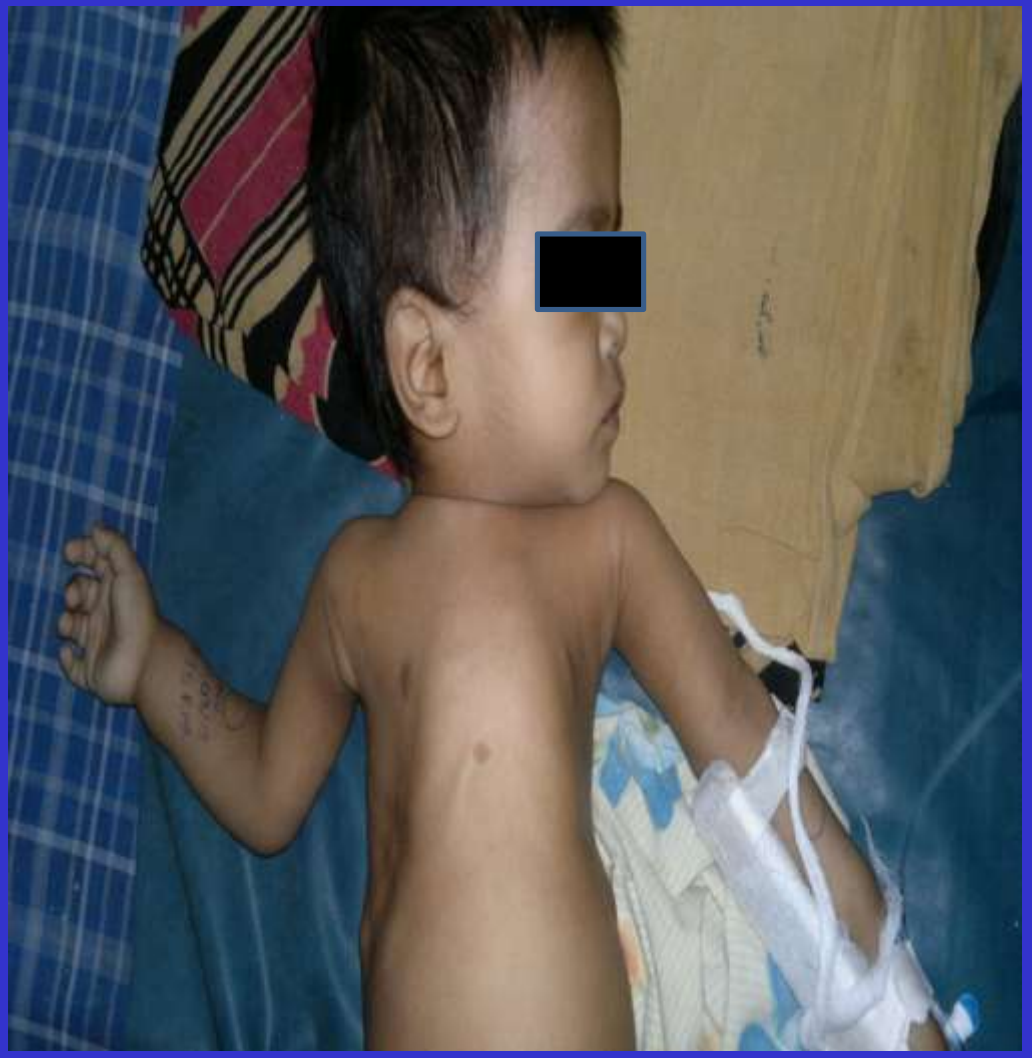
Adapted from Nelson Text book of Paediatrics, 19th Edition

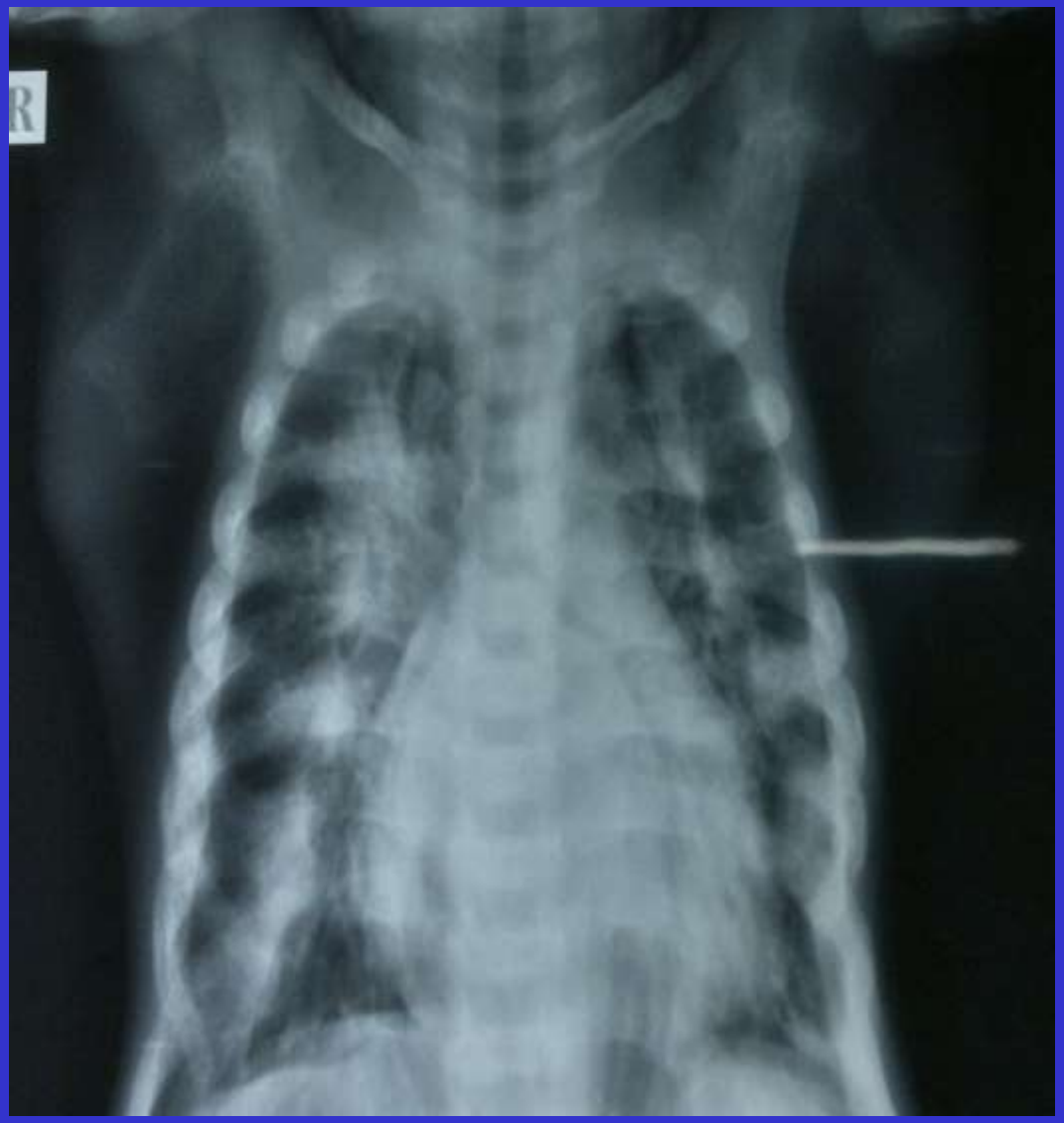
PSEUDO RICKETS

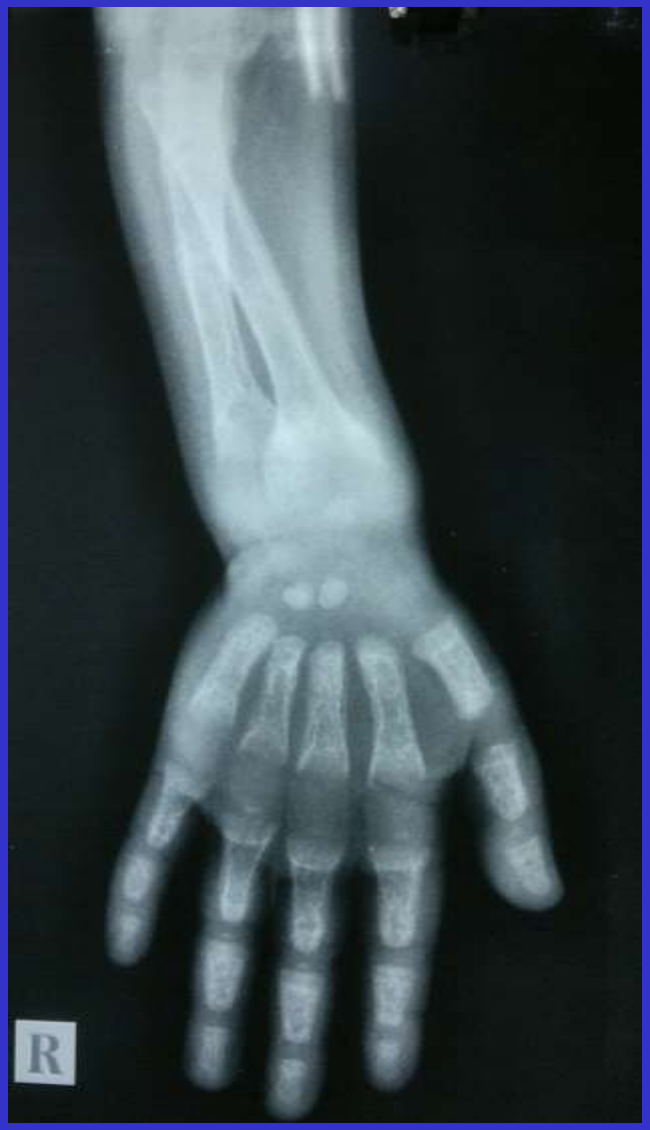
- **Hypophophatasia**
- **Primary chondrodystrophy**
  - **Jansen type**
  - **Schmidt type**
  - **Metaphyseal dysostosis**
- **Transient hyperphosphatemia**

THE FINAL STORY
Story No 5

- 2 yrs old boy
- Respiratory distress
- Severe FTT
- Painful left elbow

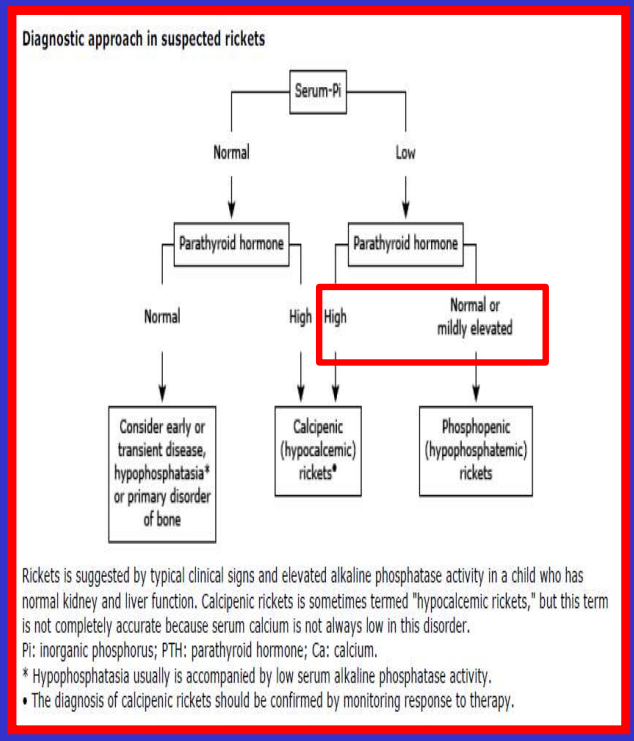



R


R

Biochemistries	Plasma	Urine
Calcium (mg/dl)	7.4	----------
Phosphate (mg/dl)	1.4	46.9
Creatinine (mg/dl)	0.2	28
Sodium (mmol/L)	135	25
Potassium (mmol/L)	3.3	8
Chloride (mmol/L)	109	13
Bicarbonate	15	----------
ALP	544 IU	----------
iPTH / 25 (OH) Vit D	120 pg/ml & 6 ng/ml	
Aminoaciduria	----------	Yes

Serum AG = 14, Urine AG = 10, TmpGFR = 1.1 mg/dl, TRP =76.1



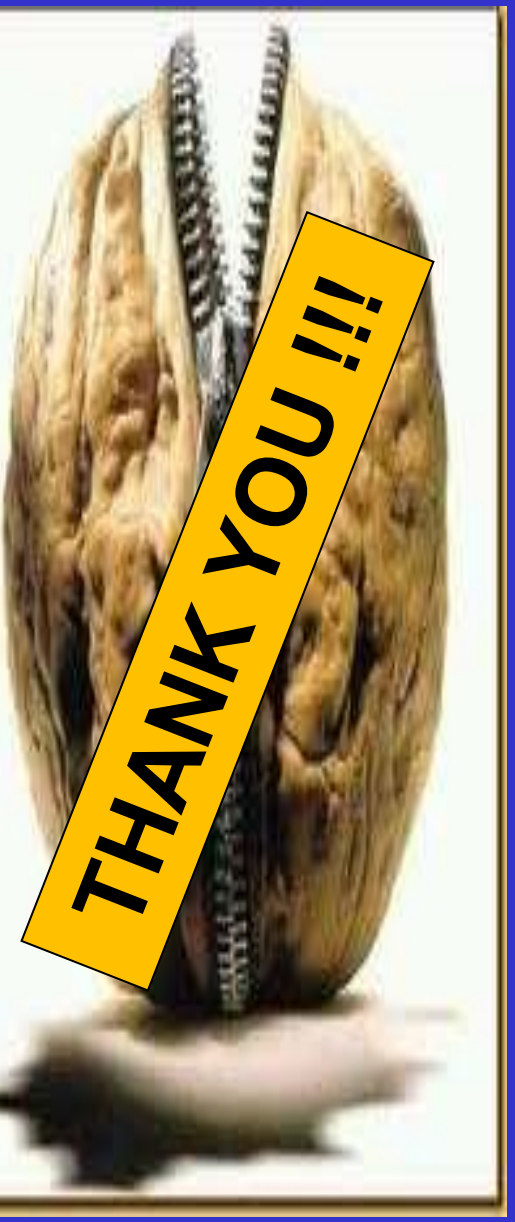
T/t with 25 (OH) Vit D, Calcium and nutritional rehabilitation

NUTRITIONAL: VIT D DEFICIENCY RICKETS

Biochemistries	Plasma	[illegible]
Calcium (mg/dl)		----------
Phosphate (mg/dl)	[illegible]	26.9
Creatinine (mg/dl)	0.3	38
Sodium (mmol/L)	137	29
Potassium (mmol/L)	3.4	5
Chloride (mm[illegible]	101	----------
Bicarb[illegible]	19	----------
A[illegible]	785 IU	----------
A[illegible]noaciduria	NA	----------
PTH & 25 (OH) Vit D	70 pg/ml & 20 ng/ml	----------

TmpGFR = 3.6 mg/dl, TRP =92.1

IN A NUT SHELL



- Although nutritional rickets is common, one needs to be aware of features of non-nutritional rickets
- Polyuria/polydipsia, abnormal urinalysis, electrolyte imbalance, acidosis, severe FTT, alopecia and H/O multiple T/t can be useful clues
- HypoPO4 is usually the ROOT cause
- PTH level is useful in differentiating hypoPO4 rickets from hypocalcemic rickets.
- PO4 is raised in only CKD
- ALP is usually raised except in hypophosphatesia
- 1, 25 (OH) Vit D is undetectable in VDDR I and raised in VDDR II
- Alopecia is usually present in VDDRII

Targeted Therapies and Monoclonals in Kidney Diseases

Prasad Devarajan MD FAAP FASN
Director of Nephrology and Hypertension
Cincinnati Children's Hospital Medical Center
SAT ISN SCR Update, 2024

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Outline – Recent Advances

- Targeted Therapies for Primary Hyperoxaluria: RNAi
- Targeted Therapies for X-linked Hypophosphatemia: Burosomab as FGF-23 inhibitor
- Monoclonals in Nephrotic Syndrome: Rituximab
- Monoclonals in atypical HUS: Eculizumab, Ravulizumab
- Monoclonals in lupus nephritis: Belimumab
- Monoclonals to treat transplant rejection

Outline

- Targeted Therapies for Primary Hyperoxaluria: RNAi
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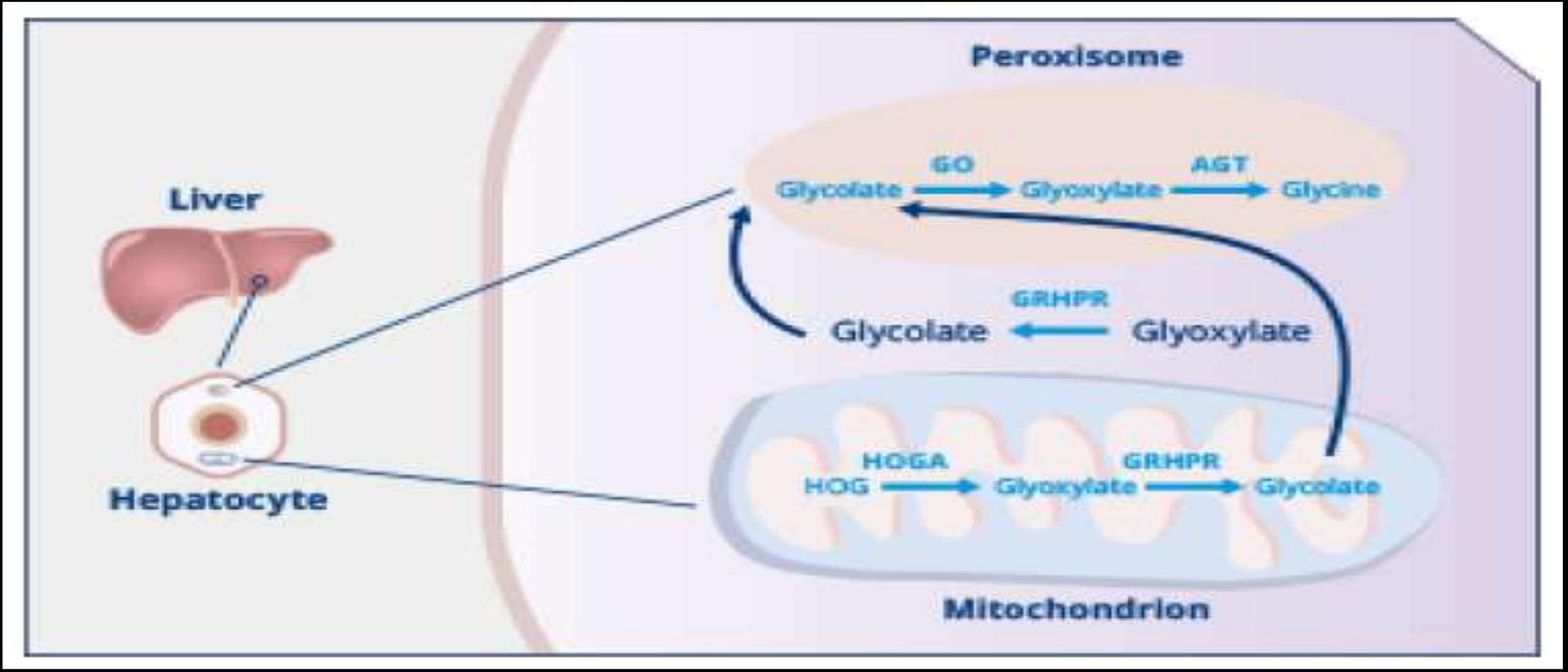
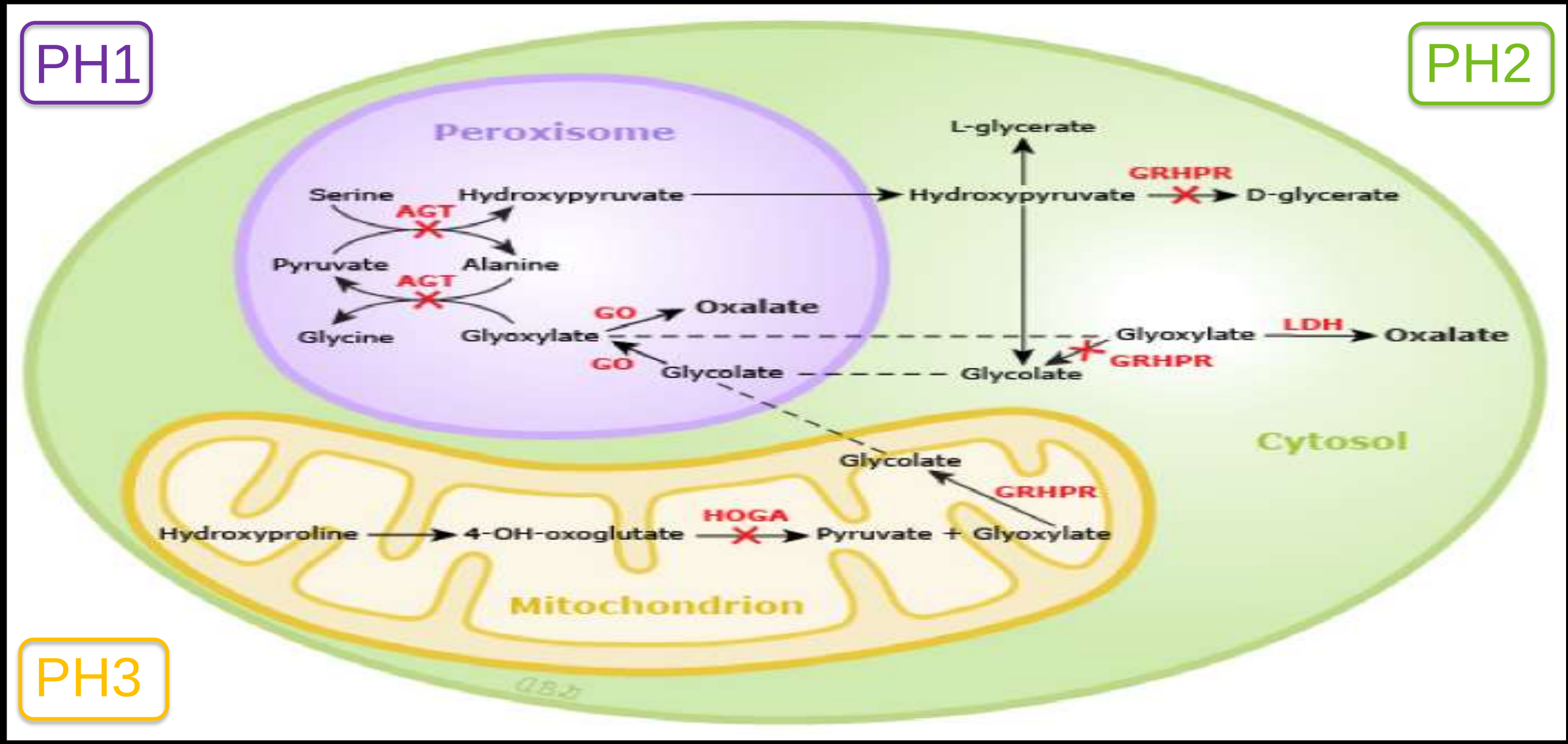
- Monoclonals to treat transplant rejection

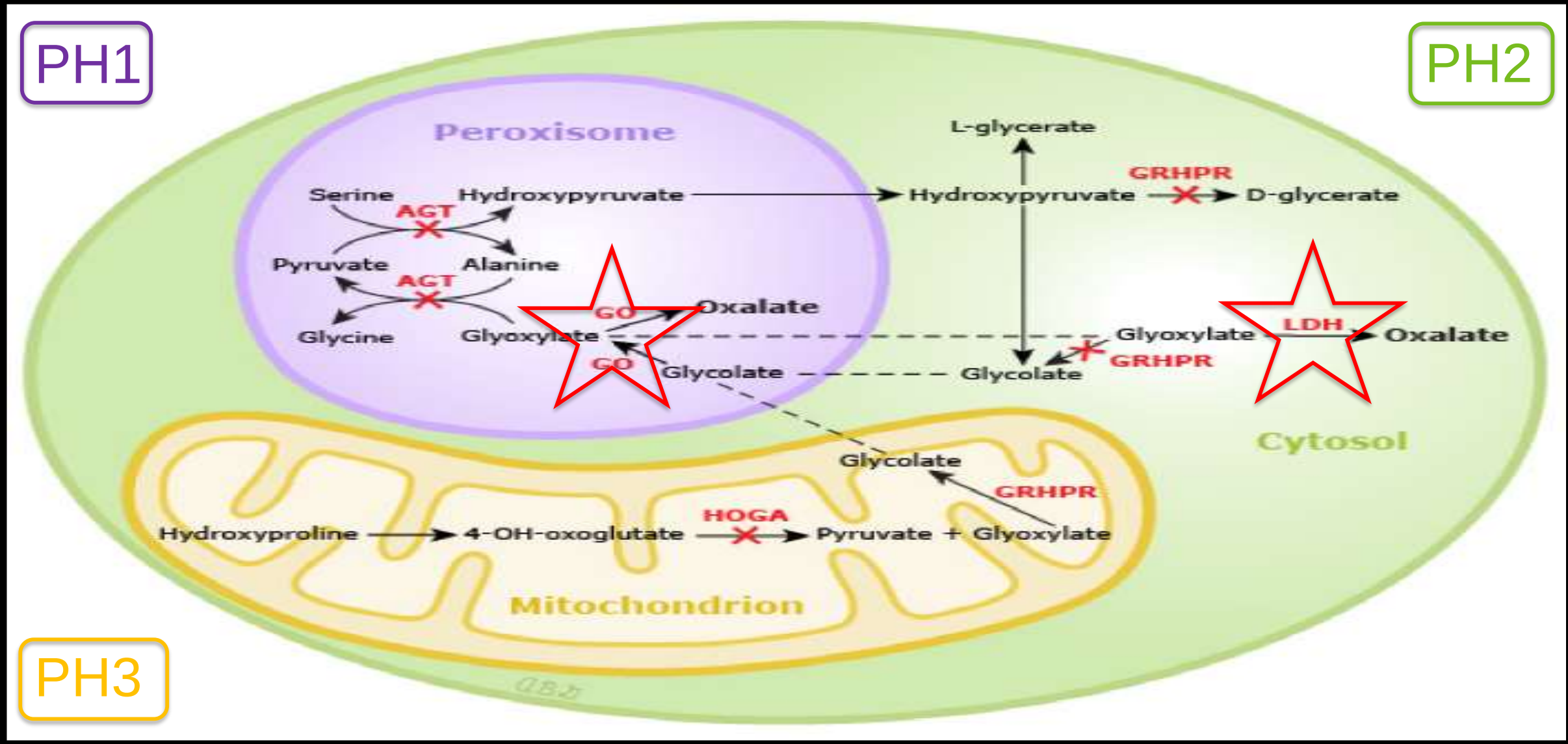
Hyperoxaluria starts as a Liver Disease: Normal Liver Glyoxylate Pathway



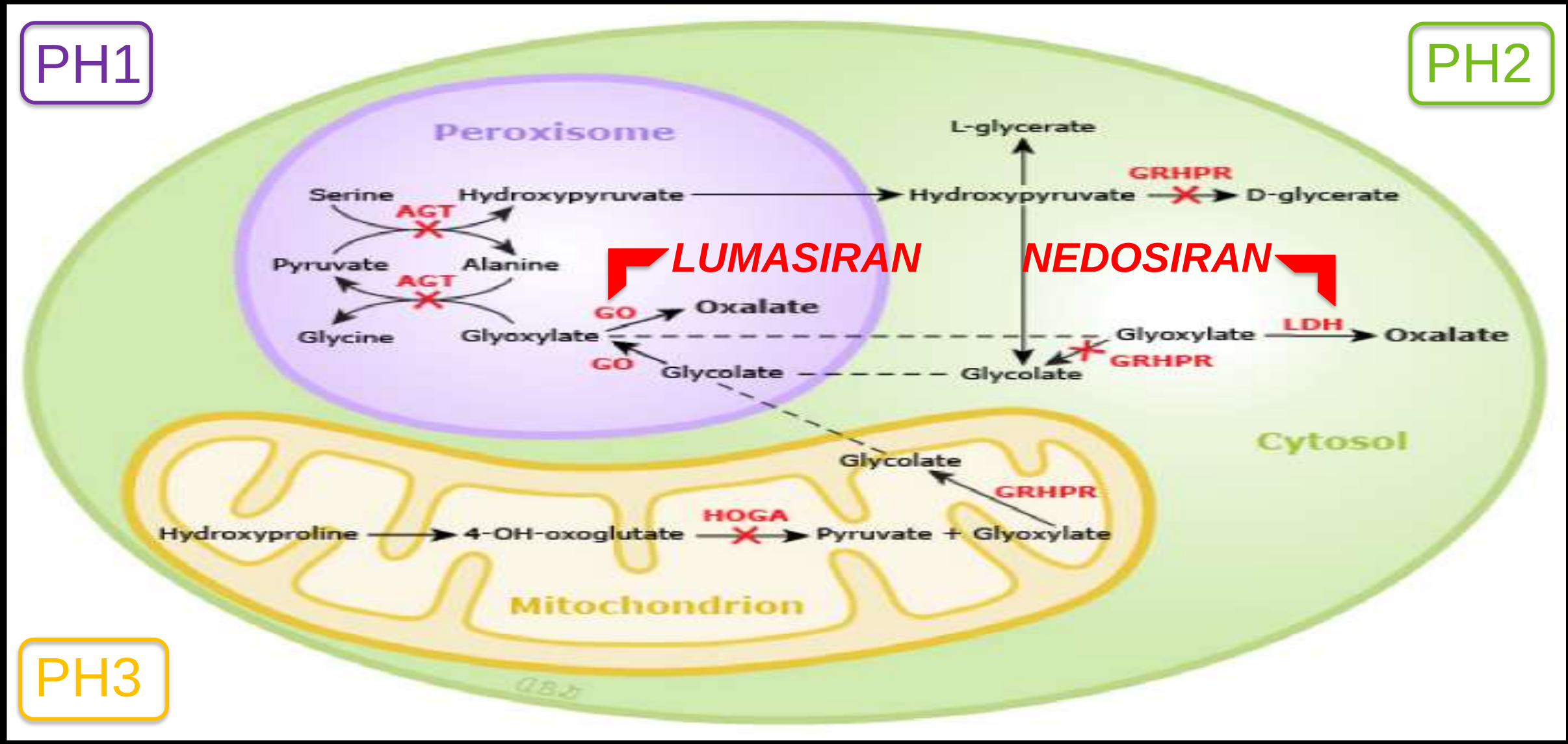
Hyperoxaluria starts as a Liver Disease



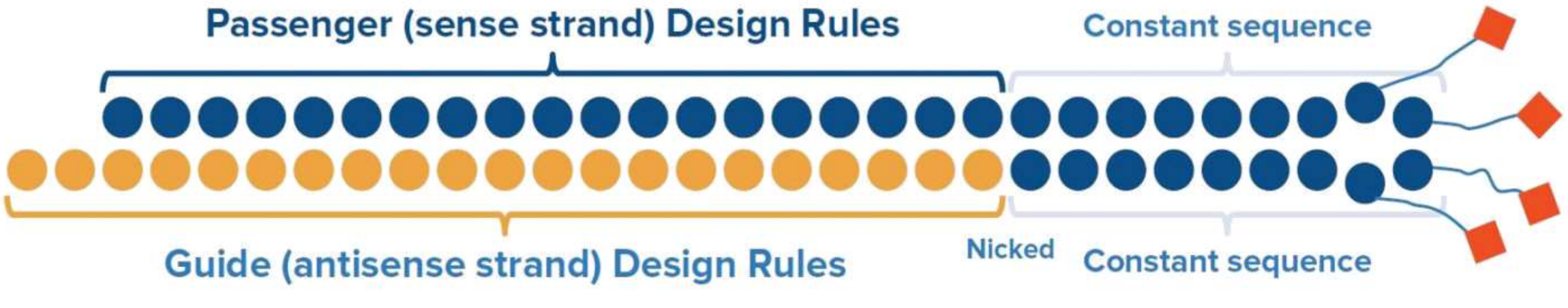
RNAi For Hyperoxaluria Treatment



RNAi For Hyperoxaluria Treatment



Liver-specific RNA Interference



- Stable molecule selectively taken up by hepatocytes
- Lumasiran given as SQ injection once a month for 3 months, then once every 3 months
- Nedosiran given as SQ injection once a month
- Both are very safe: only local injection site reactions

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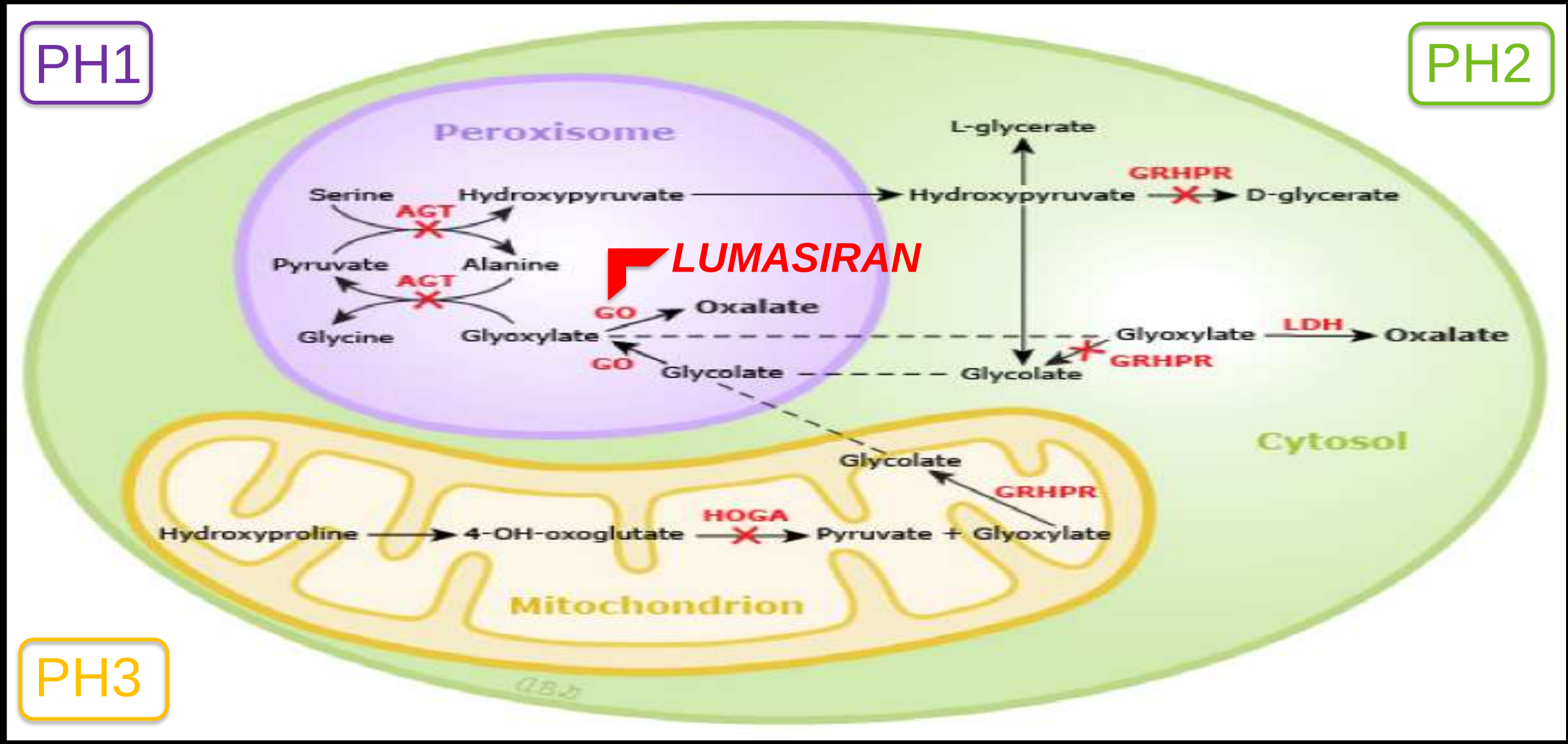
Lumasiran inhibits GO and decreases Oxalate production



Lumasiran: Does it work?

Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1: Results from a Phase III Clinical Trial

Check for updates

ILLUMINATE-A

Jeffrey M. Saland[1], John C. Lieske[2], Jaap W. Groothoff[3], Yaacov Frishberg[4], Hadas Shasha-Lavsky[5], Daniella Magen[6], Shabbir H. Moochhala[7], Eva Simkova[8], Martin Coenen[9], Wesley Hayes[10], Julien Hogan[11], Anne-Laure Sellier-Leclerc[12], Richard Willey[13], John M. Gansner[13] and Sally-Anne Hulton[14]

Kidney Int Rep (2024) **9**, 2037–2046; https://doi.org/10.1016/j.ekir.2024.04.048

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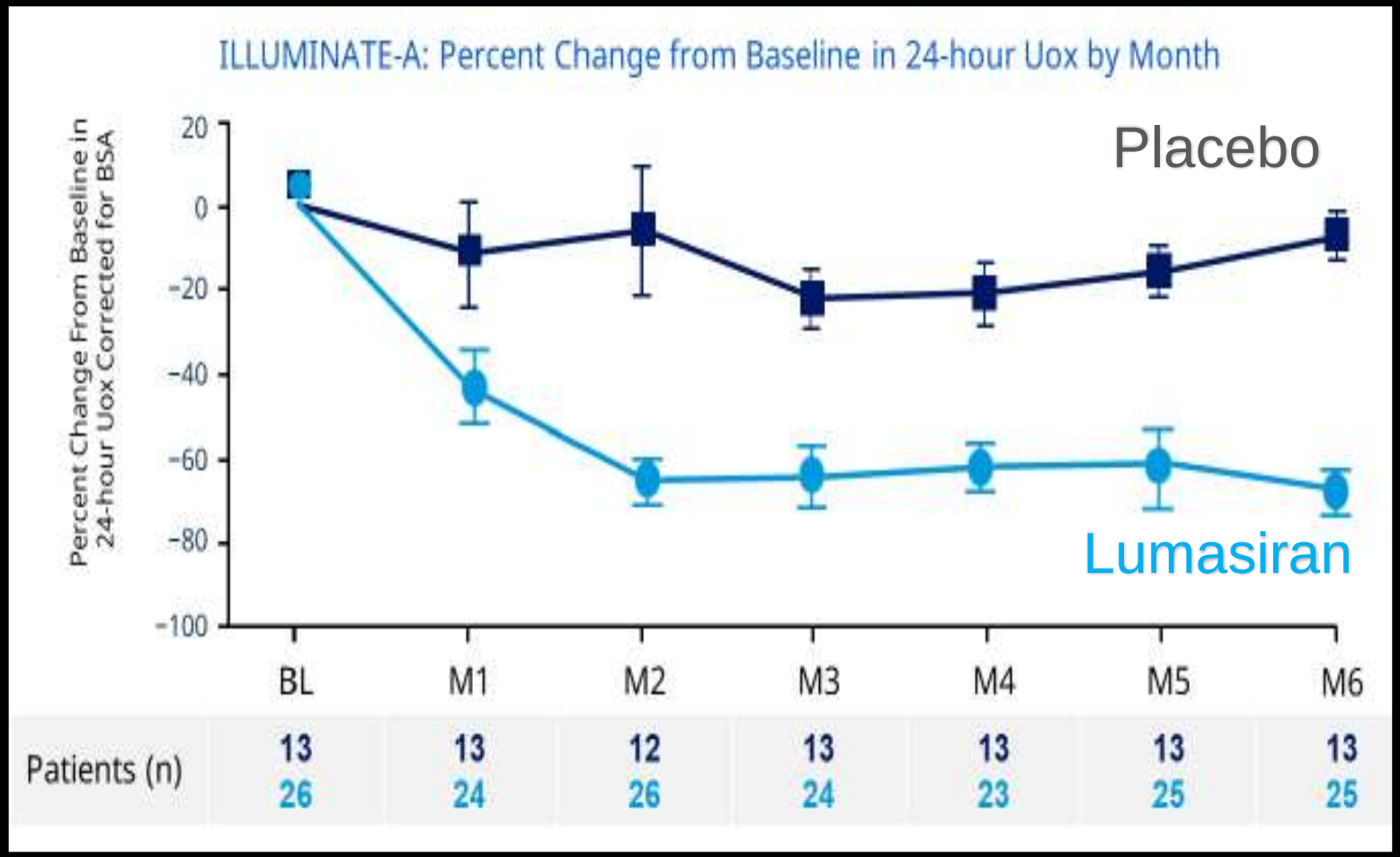
Lumasiran: Urine Oxalate at 6 months



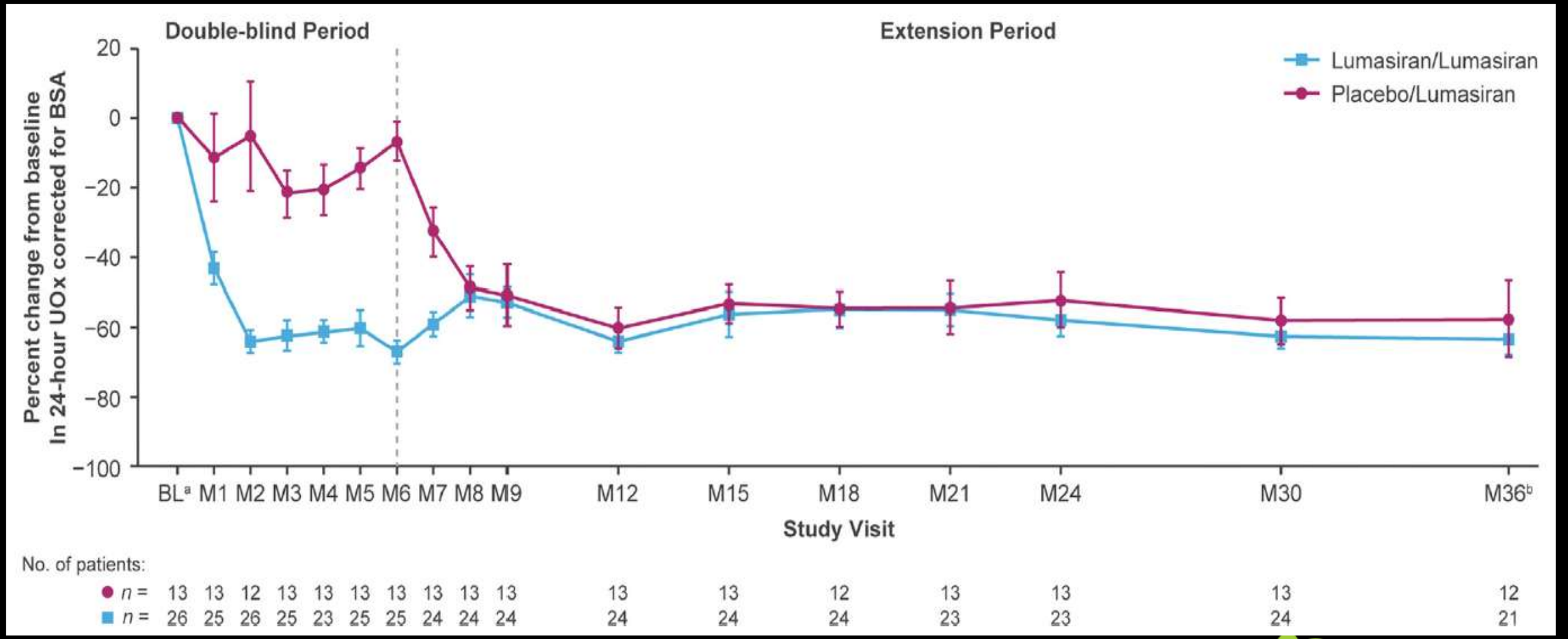
Primary Endpoint:
LS Mean % change in 24-hour urine oxalate from baseline over M3-M6

Placebo: - 12%
Lumasiran: - 65%

LS Mean difference Lumasiran versus Placebo: 53% (*P*<0.001)

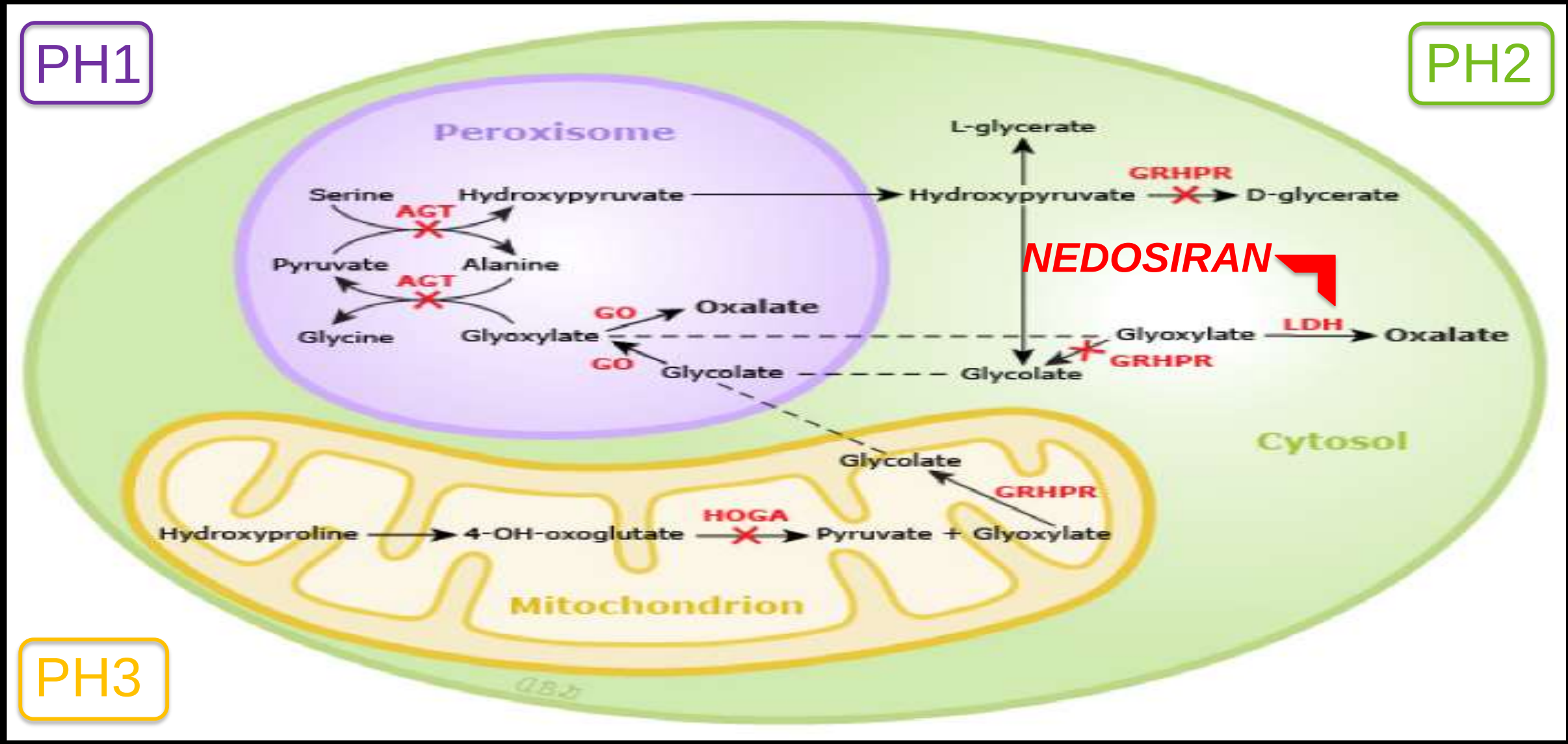
Kidney Int Rep (2024) **9**, 2037–2046; https://doi.org/10.1016/j.ekir.2024.04.048

Lumasiran: Urine Oxalate at 3 years



Kidney Int Rep (2024) **9**, 2037–2046; https://doi.org/10.1016/j.ekir.2024.04.048

Nedosiran inhibits LDH and decreases Oxalate production



Nedosiran: Does it work?

PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2

Check for updates

OPEN

Michelle A. Baum[1], Craig Langman[2], Pierre Cochat[3], John C. Lieske[4], Shabbir H. Moochhala[5], Shuzo Hamamoto[6], Hiroyuki Satoh[7], Chebl Mourani[8], Gema Ariceta[9], Armando Torres[10,11], Martin Wolley[12], Vladimir Belostotsky[13], Thomas A. Forbes[14,15], Jaap Groothoff[16], Wesley Hayes[17], Burkhard Tönshoff[18], Tatsuya Takayama[19,22], Ralf Rosskamp[20,23], Kerry Russell[20], Jing Zhou[20], Aniruddha Amrite[20,23] and Bernd Hoppe[20,21,23]; for the PHYOX2 study investigators

Kidney International (2023) **103**, 207–217

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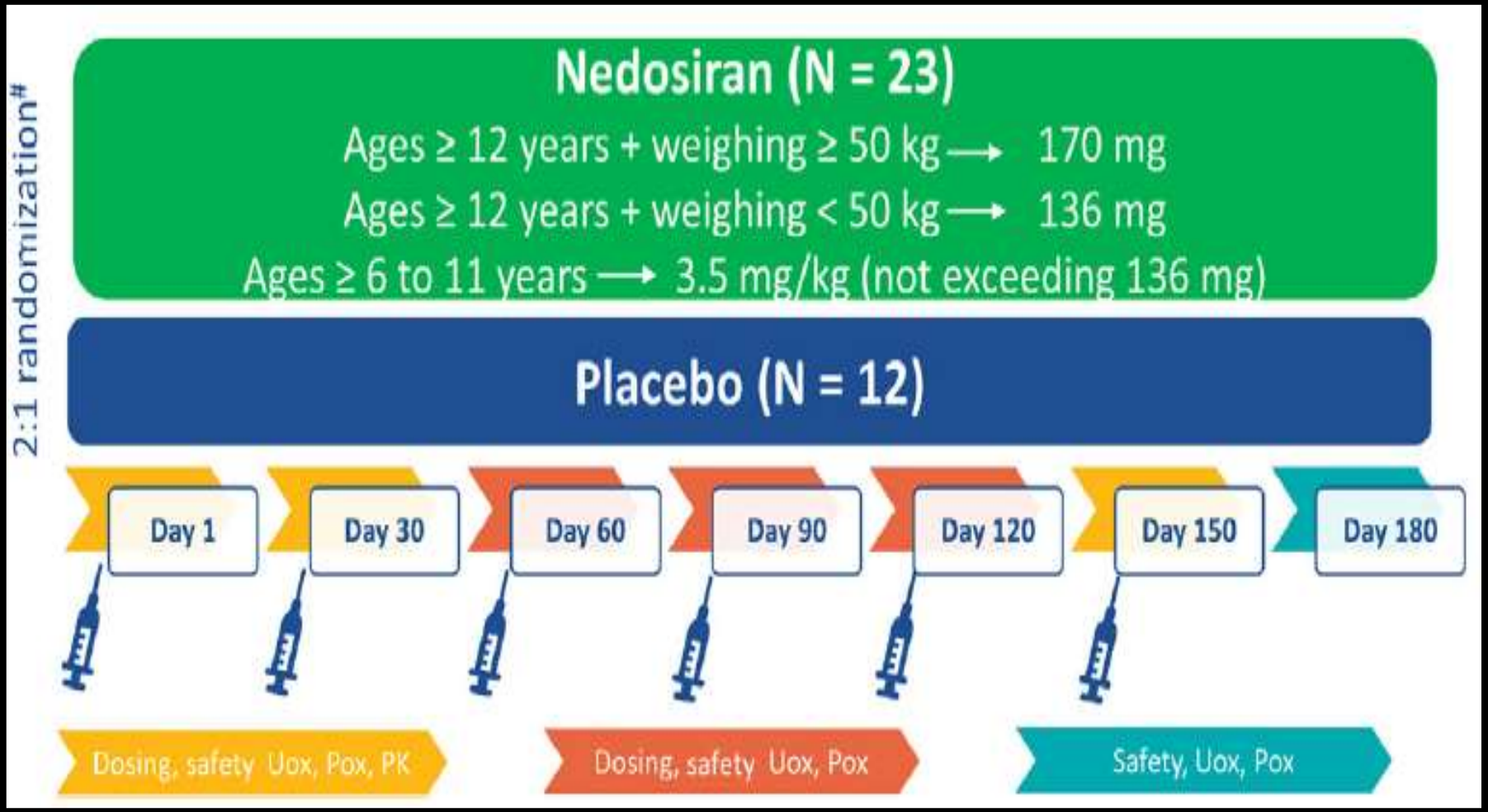
PHYOX2: Study Design: 6 months

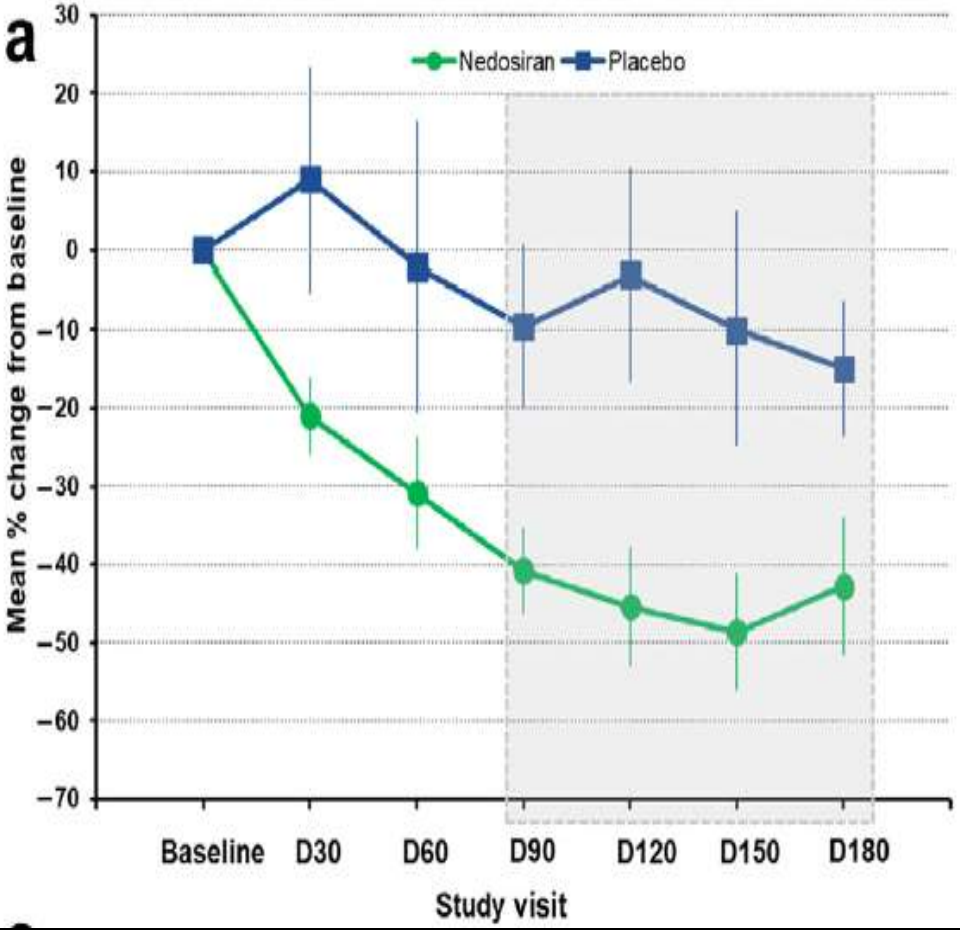


Primary endpoint:
Percent change from baseline in 24-hour UOx excretion from Day 90 to Day 180 (LS mean assessed by area under the curve 24-hour UOx [$AUC_{24\text{-hour UOx}}$])

Kidney International (2023) **103**, 207–217

PHYOX2: Urine Oxalate at 6 months

a



b

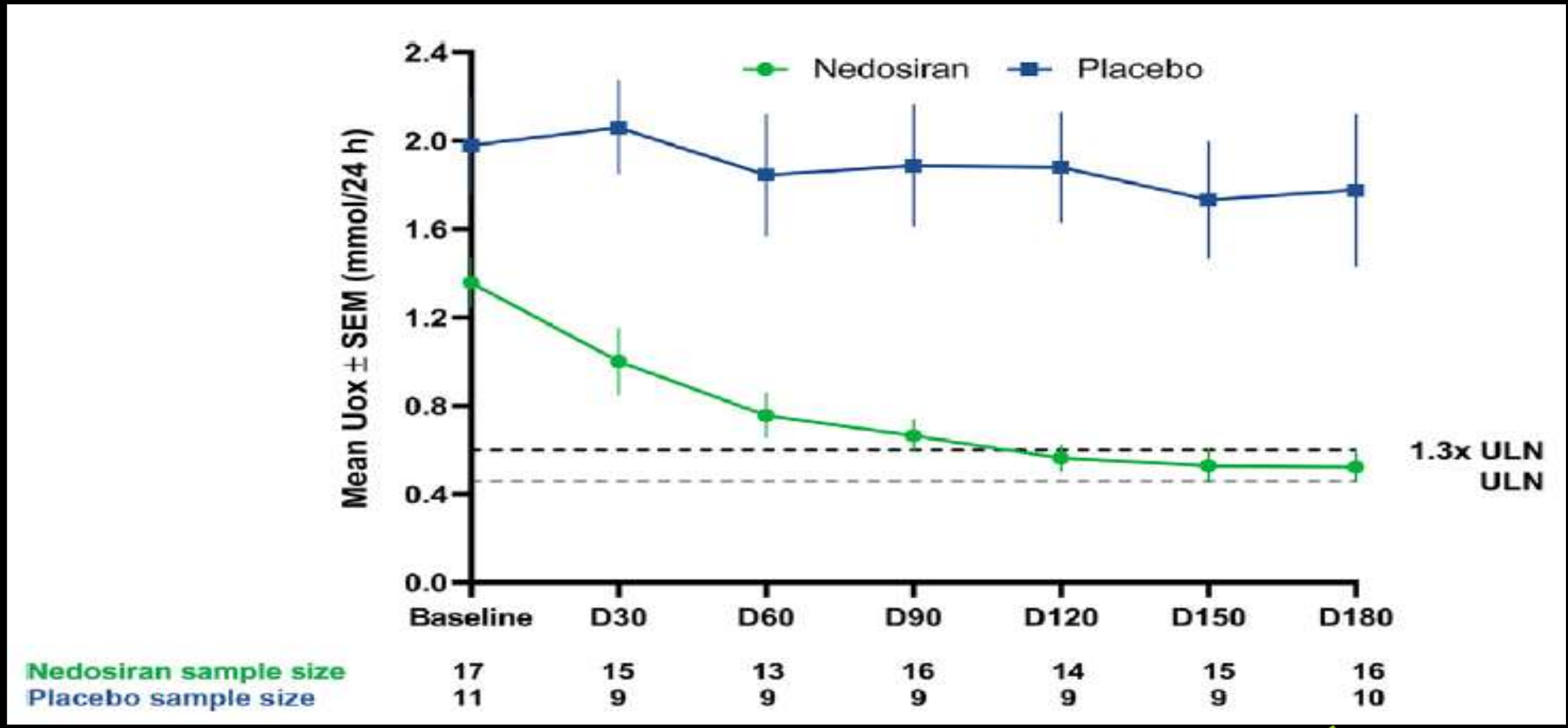
Standardized AUC 24-h Uox from day 90 to day 180	Nedosiran (N = 22)	Placebo (N = 12)
LS mean (SE)	3507.4 (788.49)	−1664.4 (1189.96)
95% CI for LS mean	1961.7, 5053.1	−3397.2, 668.4
LS mean differences from placebo (SE)	5171.7 (1144.07)	
95% CI for difference from placebo	2929.3, 7414.2	
P value for difference from placebo	<0.001	

Among patients with PH1, LS mean between group difference was

56% (95% CI: 33%, 80%)

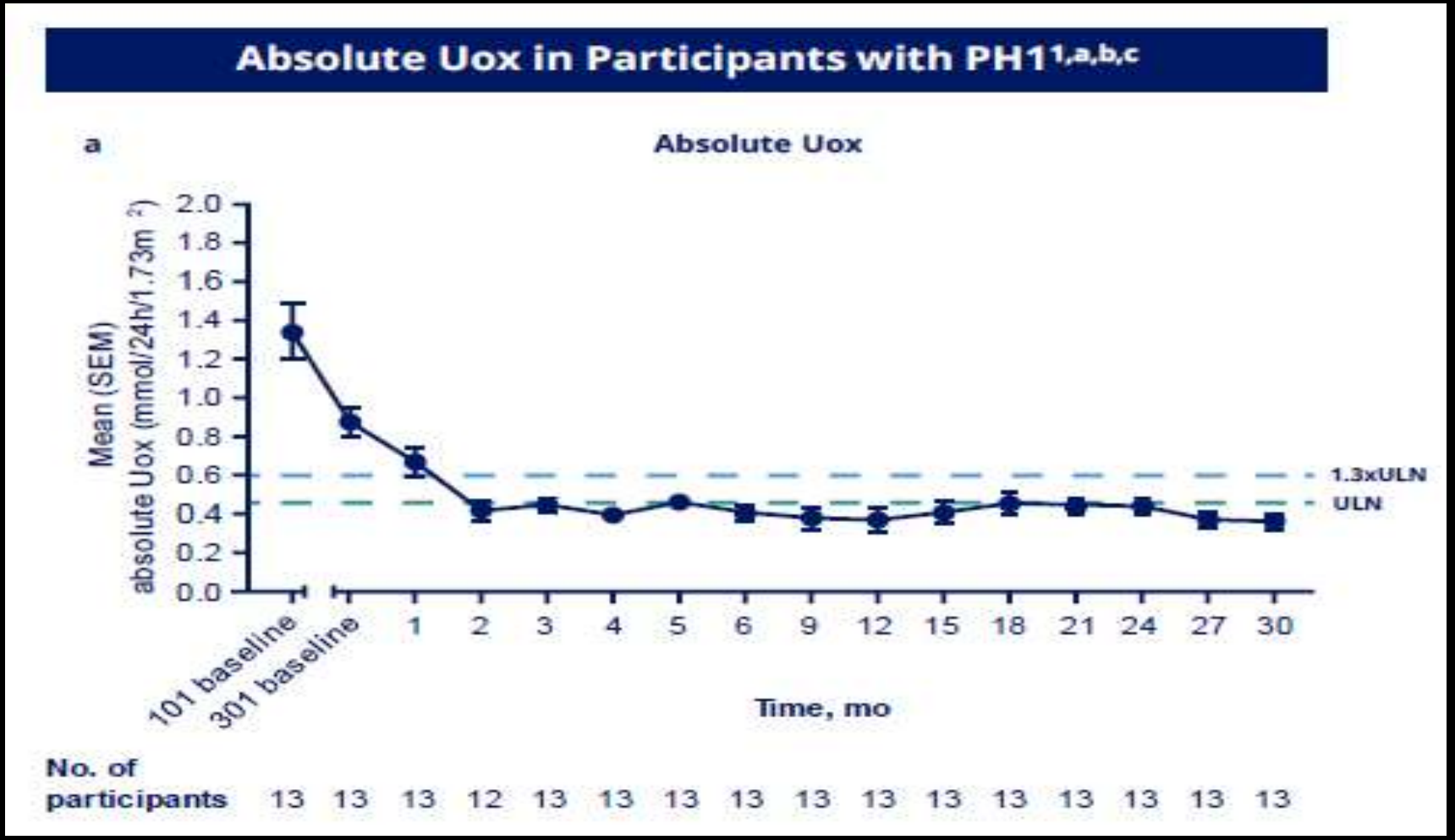
Kidney International (2023) **103**, 207–217

PHYOX2: Urine Oxalate at 6 months



Kidney International (2023) **103**, 207–217

Nedosiran: Three Year Uox Data



- **>60% Uox reduction from baseline**
- **85% reached normal Uox levels – eligible for stopping hyperhydration and other therapies**

Kidney Int Rep (2024) 9, 1387–1396; https://doi.org/10.1016/j.ekir.2024.02.1439

Nedosiran vs Lumasiran: Comparison of Data

	Lumasiran	Nedosiran
FDA-cleared?	Yes for > 6 years of age	Yes for > 9 years of age
Mean 24-hr Uox reduction at 3 years	63%	63%
% patients with Uox < 1.5 X ULN at 3 years	76%	Not reported
% patients with Uox NORMAL at 3 years	Not reported	85% - candidates to get off hyperhydration and other medical therapies
Stone surface area reduction by ultrasound	Not reported	Decreased 24% vs placebo
Annualized stone events	Decreased but no placebo data	0.37 vs 1.28 for placebo
Adverse Events	**Rare, mild, injection site**	**Rare, mild, injection site**
Manufacturer	Alnylam	Novo Nordisk
Free Genetic Testing (in US)	Yes	Yes
Genetic Platform	Prevention Genetics	Blueprint Genetics

Outline

- Targeted Therapies for Genetic Diseases: PH1 RNAi
- Targeted Therapies for X-linked hypophosphatemia: Burosomab as FGF-23 inhibitor
- Monoclonals in Nephrotic Syndrome: Rituximab
- Monoclonals in atypical HUS: Eculizumab, Ravulizumab
- Monoclonals in lupus nephritis: Belimumab
- Monoclonals to treat transplant rejection

Treatment of Steroid Sensitive Nephrotic Syndrome

Steroid Sensitive Nephrotic Syndrome: Revised Guidelines

ADITI SINHA,[1] ARVIND BAGGA,[1] SUSHMITA BANERJEE,[2] KIRTISUDHA MISHRA,[3] AMARJEET MEHTA,[4] INDIRA AGARWAL,[5] SUSAN UTHUP,[6] ABHIJEET SAHA,[7] OM PRAKASH MISHRA[8] AND EXPERT GROUP OF INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY*

Sinha et al, Indian Pediatr 2021;58:461-481

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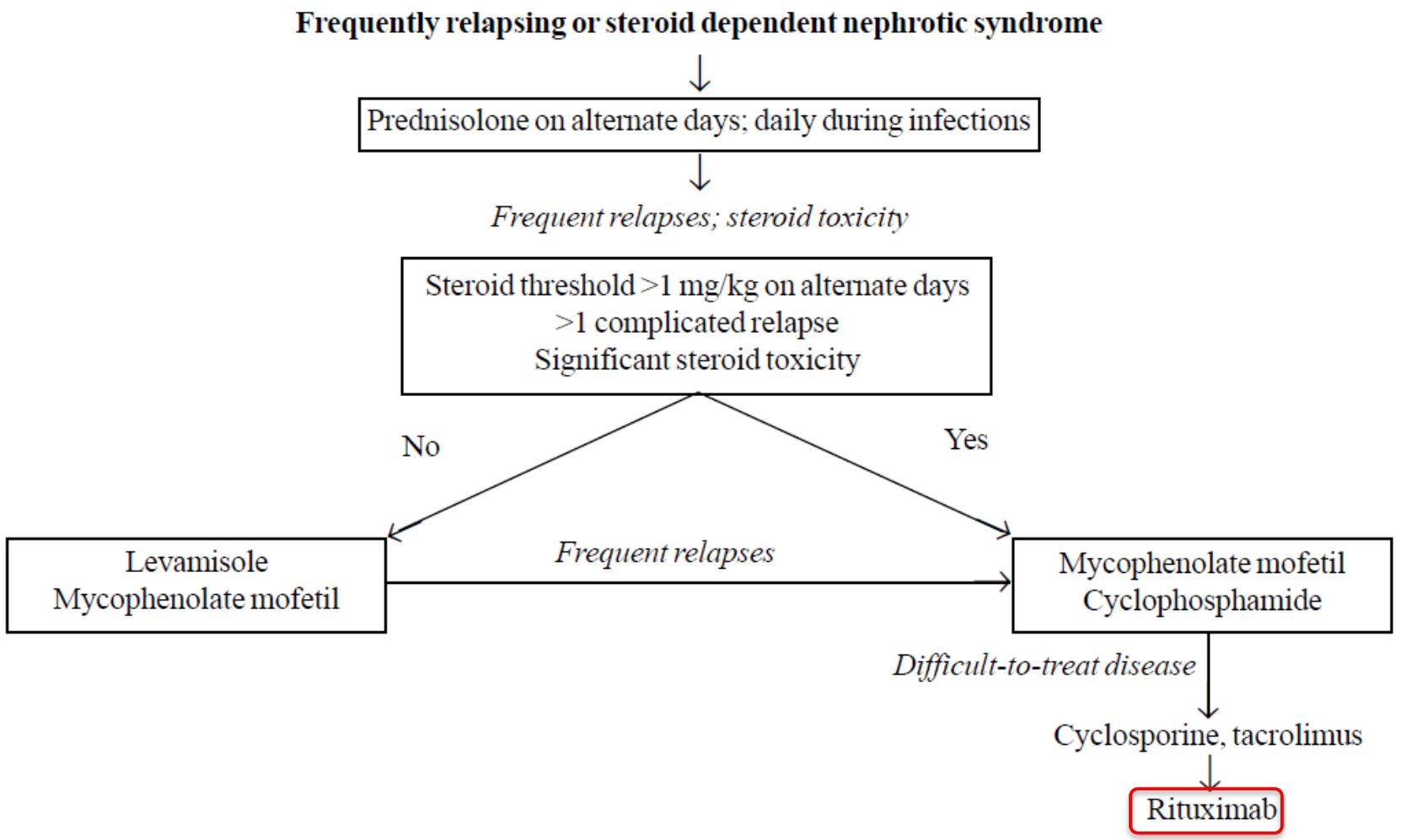
Treatment of Steroid Sensitive Nephrotic Syndrome

RECOMMENDATIONS — STEROID SENSITIVE NEPHROTIC SYNDROME



Sinha et al, Indian Pediatr 2021;58:461-481

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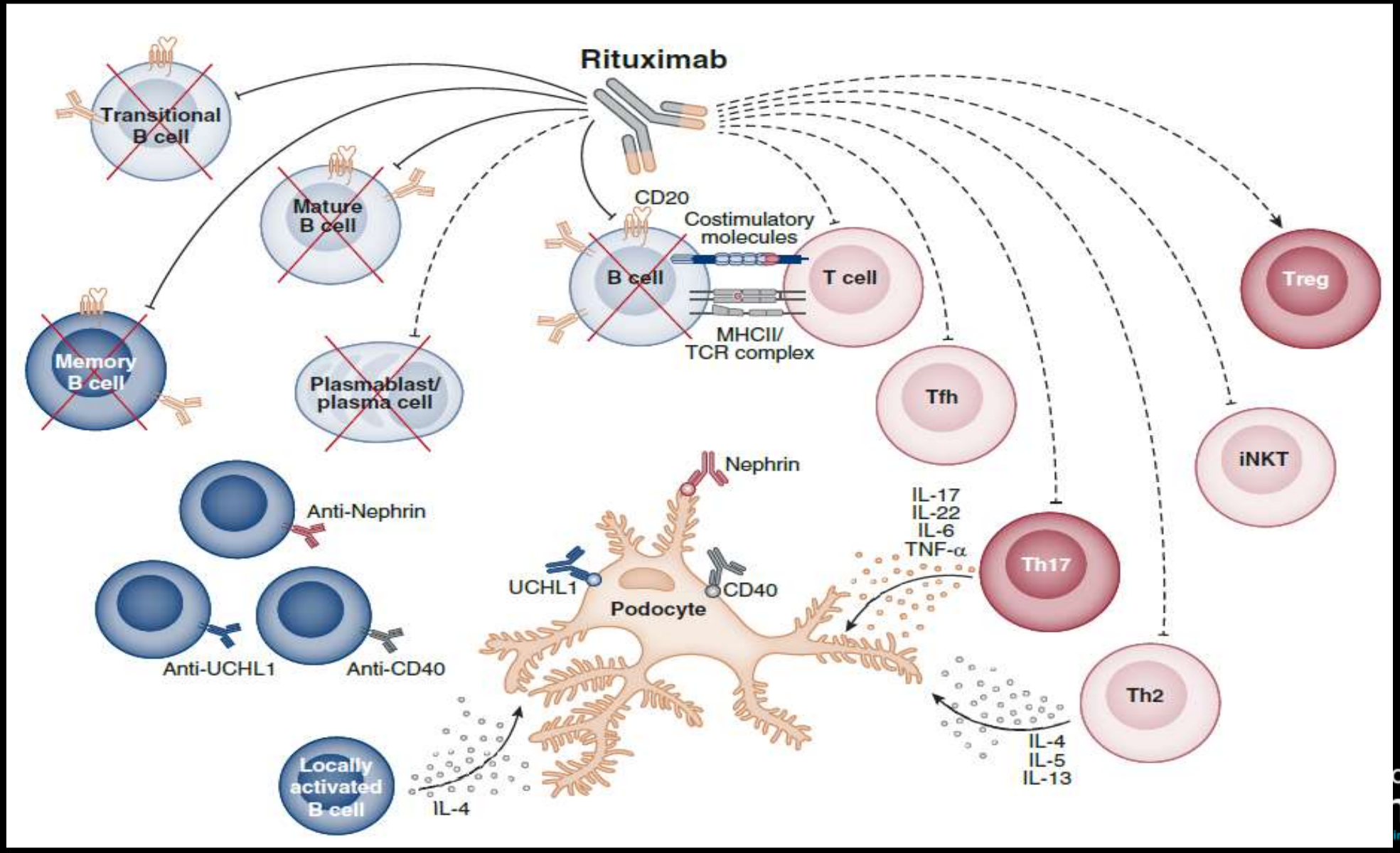
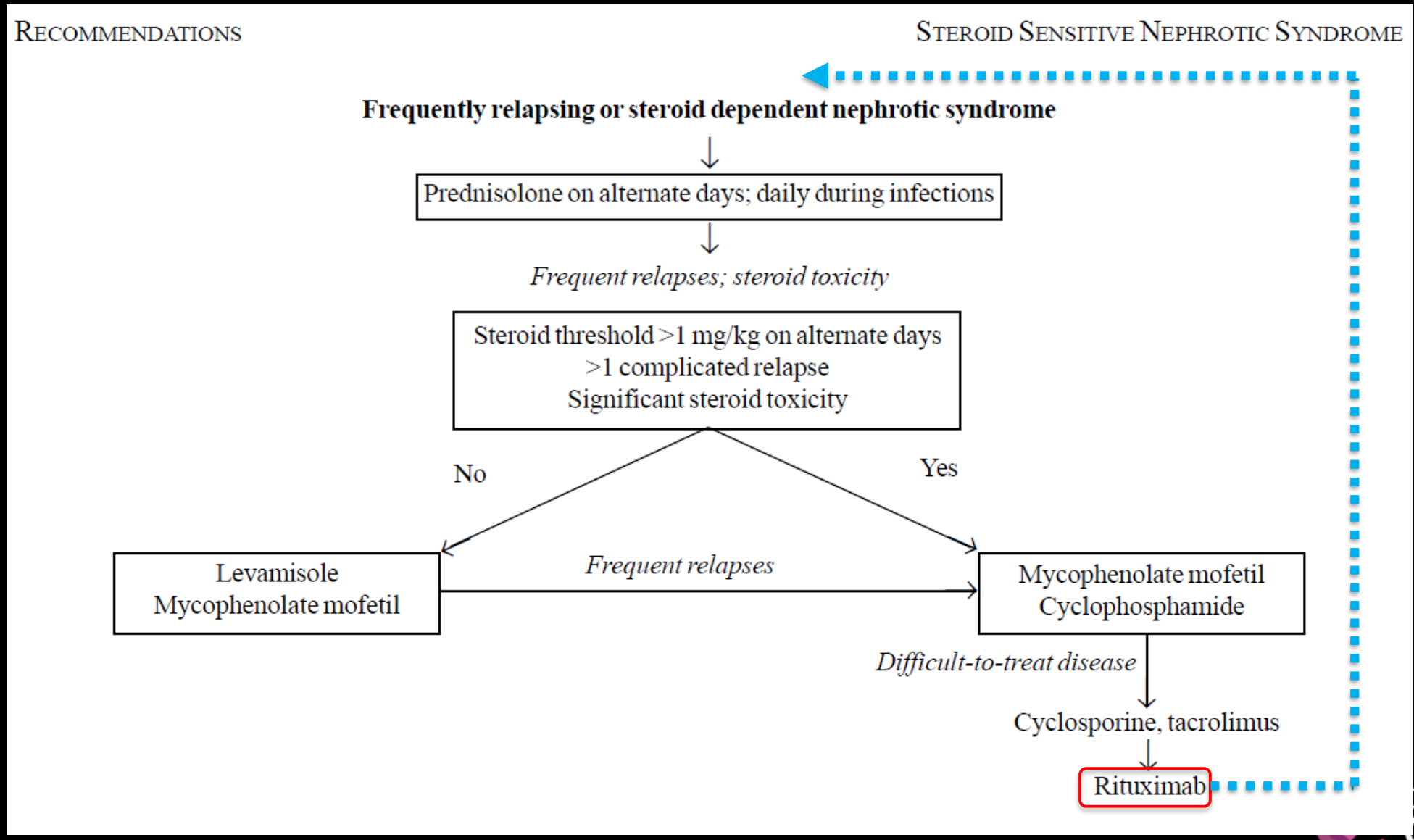
Rituximab in Pediatric Nephrotic Syndrome



Ritux in Early Steroid Sensitive Nephrotic Syndrome



Sinha et al, Indian Pediatr 2021;58:461-481

Ritux in Early Steroid Sensitive Nephrotic Syndrome?

KI REPORTS
KIReports.org

Rituximab as Initial Therapy in Adult Patients With Minimal Change Disease

Nan Guan[1,2], Min Zhang[1,2], Min Zhang[1], Ruiying Chen[1], Qionghong Xie[1] and Chuan-Ming Hao[1]

[1]Division of Nephrology, Huashan Hospital, Fudan University, Shanghai, China

Kidney Int Rep (2023) 8, 1102–1104

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Ritux in Early Steroid Sensitive Nephrotic Syndrome?

- Nine adult patients with new-onset minimal change disease
- They all had comorbidities or indications to avoid steroids and received rituximab as initial therapy instead
- Seven out of the nine received only one dose of rituximab
- Seven out of the nine had complete or particle remission
- Six out of the seven had NO RELAPSES after a minimum of 1 year follow up

Kidney Int Rep (2023) 8, 1102–1104

Ritux in Early Steroid Sensitive Nephrotic Syndrome?

Patient No.	Gender	Age (yrs)	Proteinuria (g/d)	Scr (μmol/l)	Salb (g/l)	Comorbidity	Indication for RTX
1	Male	57	3.81	107	25	none	Osteoporosis
2	Male	66	3.49	71	23	HTN	Gastric ulcer hemorrhage
3	Male	22	6.32	58	18	none	Refusal of GCs[a]
4	Male	73	8.88	75	26	HTN	Refusal of GCs[b]
5	Male	58	8.5	95	14	DM	DM
6	Male	67	4.65	79	29	DM	DM
7	Male	20	8.02	61	15	none	Refusal of GCs[a]
8	Male	26	5.22	69	20	none	Refusal of GCs[a]
9	Female	39	8.65	72	15	none	Refusal of GCs[a]

Kidney Int Rep (2023) **8**, 1102–1104

Ritux in Early Steroid Sensitive Nephrotic Syndrome?

Patient No.	RTX regimen	Response	Time to remission (d)	Follow-up duration (d)	Relapse
1	375 mg/m^2 once	CR	48	339	No
2	375 mg/m^2 once	CR	15	303	No
3	375 mg/m^2 once	CR	12	884	No
4	375 mg/m^2 once	CR	41	407	No
5	375 mg/m^2 once	CR	24	657	No
6	375 mg/m^2 twice	PR	93	789	No
7	375 mg/m^2 once	PR	16	374	yes
8	375 mg/m^2 once	NR	/	159	/
9	1 g twice	NR	/	351	/

Kidney Int Rep (2023) **8**, 1102–1104

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Ritux in Early Steroid Sensitive Nephrotic Syndrome?

KI REPORTS
KIReports.org

Successful Treatment of New-Onset Pediatric Nephrotic Syndrome With Rituximab as a First-Line Therapy

Xiaojing Zhang[1], Yanyan Jin[1], Qiuyu Li[1], Yi Xie[1], Fei Liu[1], Guoping Huang[1], Junyi Chen[1], Haidong Fu[1], Jingjing Wang[1], Huijun Shen[1] and Jianhua Mao[1]

[1]Department of Nephrology, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China

Kidney Int Rep (2022) **7**, 2750–2751

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Ritux in Early Steroid Sensitive Nephrotic Syndrome?

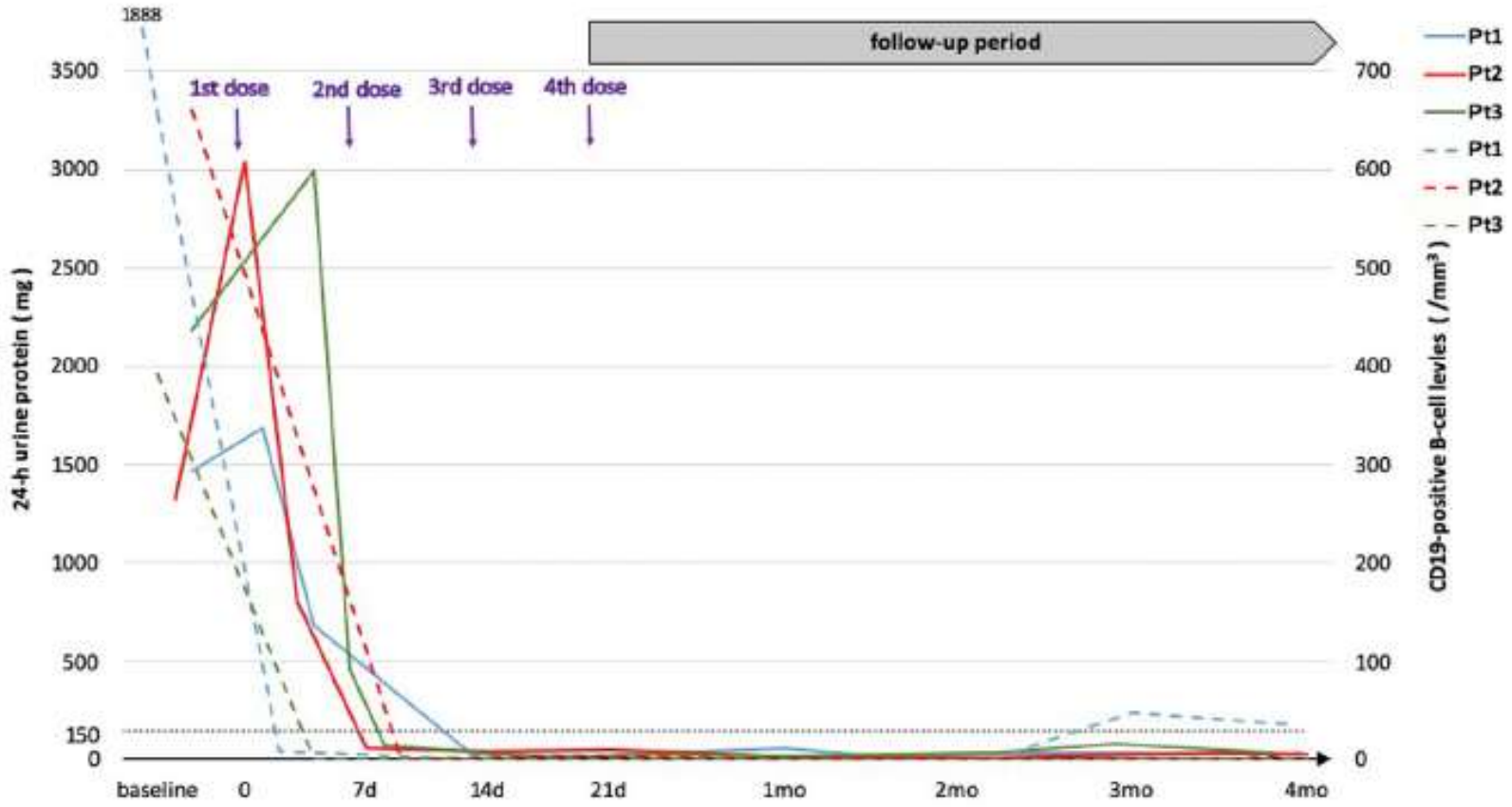

Figure 1. Evolution of proteinuria and trends of circulating CD19-positive B-cell levels. Solid line indicates evolution of proteinuria, and dashed line indicates trends of circulating CD19-positive B-cell levels. Pt, patient.

Kidney Int Rep (2022) 7, 2750–2751

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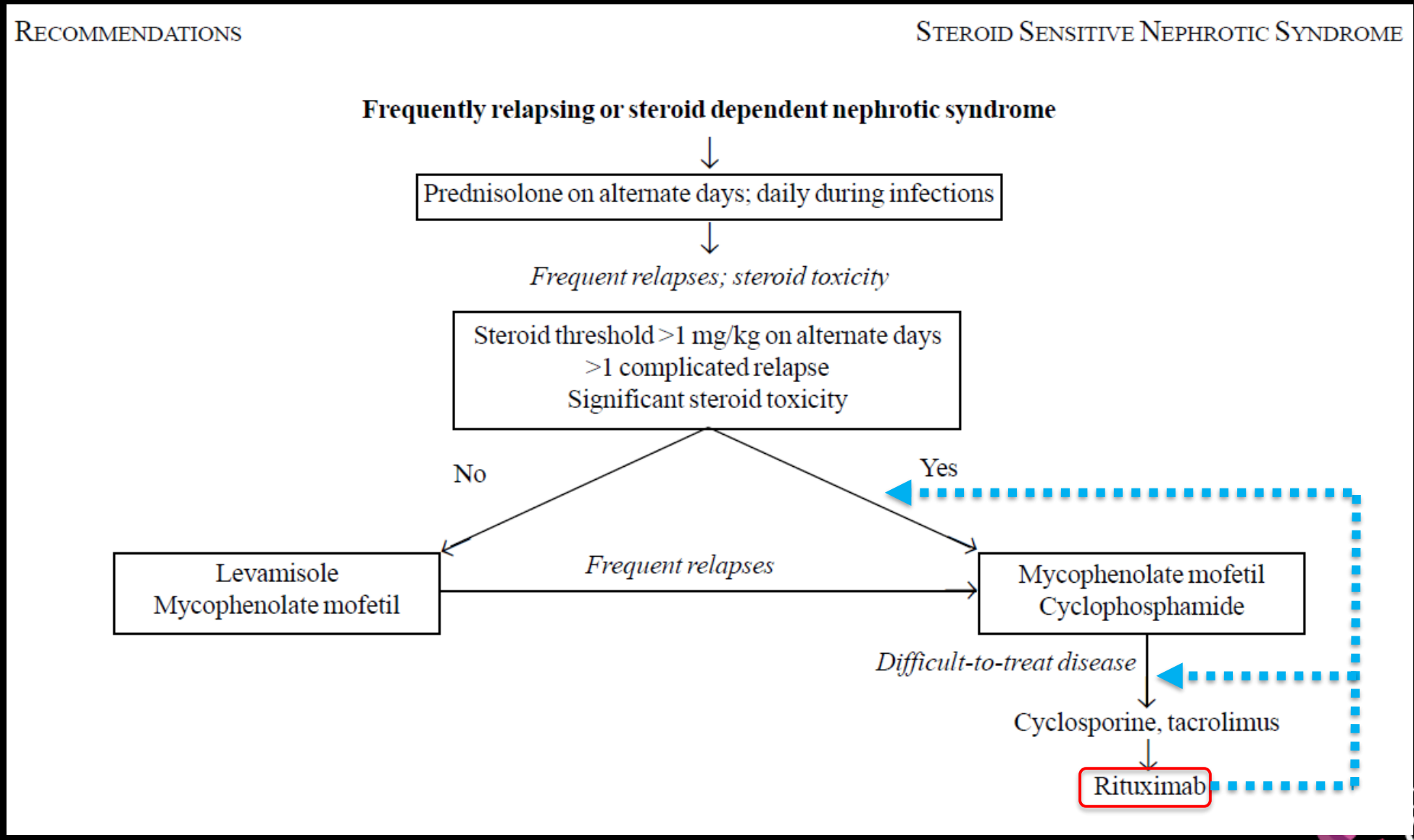
Ritux in Steroid Dependent Pediatric Nephrotic Syndrome?



Sinha et al, Indian Pediatr 2021;58:461-481

Ritux in Steroid Dependent Pediatric Nephrotic Syndrome?

Author, publication year, country	Types of study	*n*	
		Tacrolimus, *n* (%)	Rituximab, *n* (%)
Basu *et al.*, 2018, India [21]	Randomized clinical trial	60	60
Sinha *et* Mathew *et al.*, 2012, Ind 2022, India [20]	Randomized controlled trial	20 (48.78)	21 (51.22)
Wang *et al.*, 2022, China [18]	Prospective randomized study	17 (33.33)	17 (33.33)
Mathew *et al.*, 2022, India [20]	Randomized controlled trial	20 (48.78)	21 (51.22)

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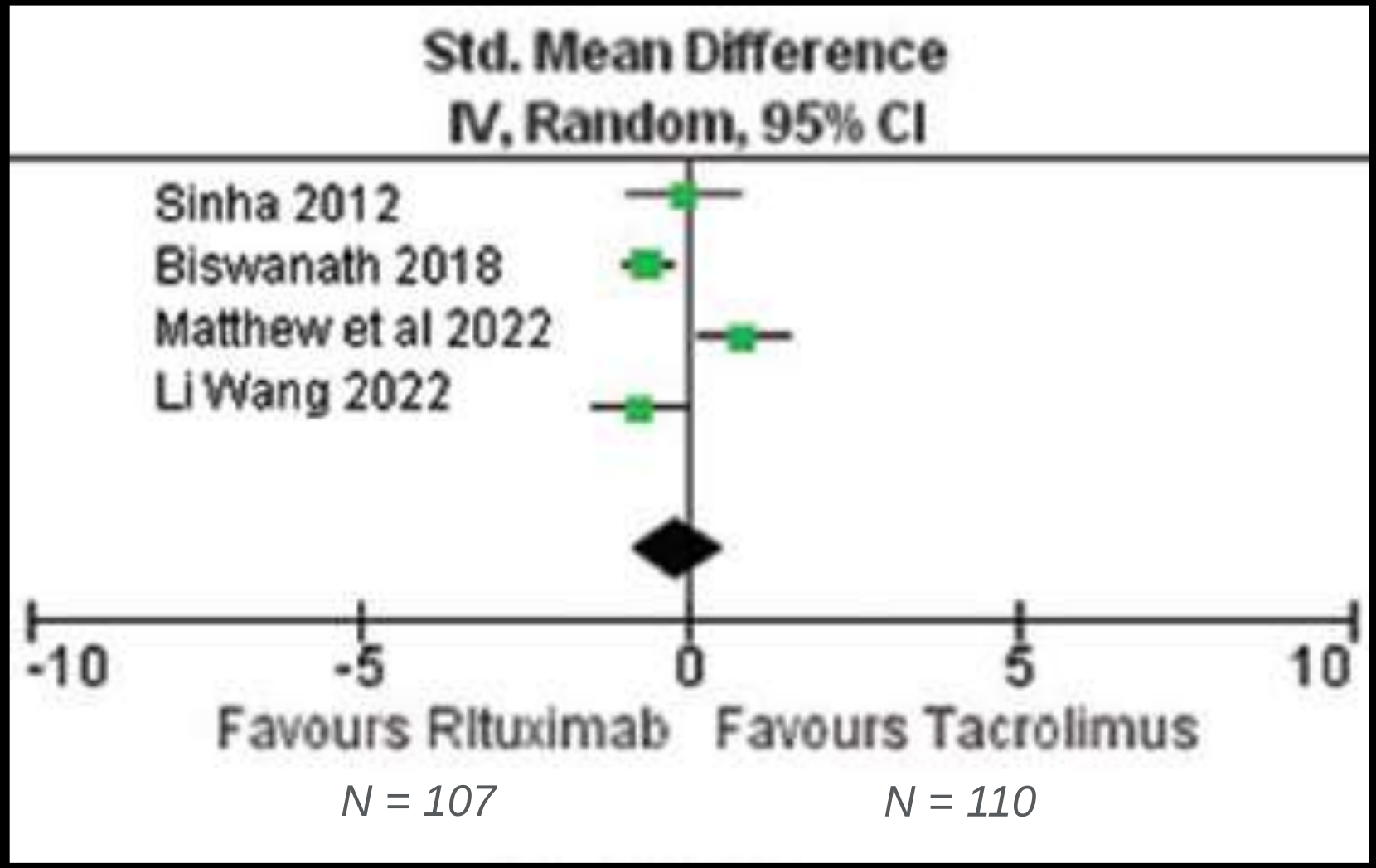
Ritux in Steroid Dependent Pediatric Nephrotic Syndrome?



Forest Plot for Frequency of Relapses

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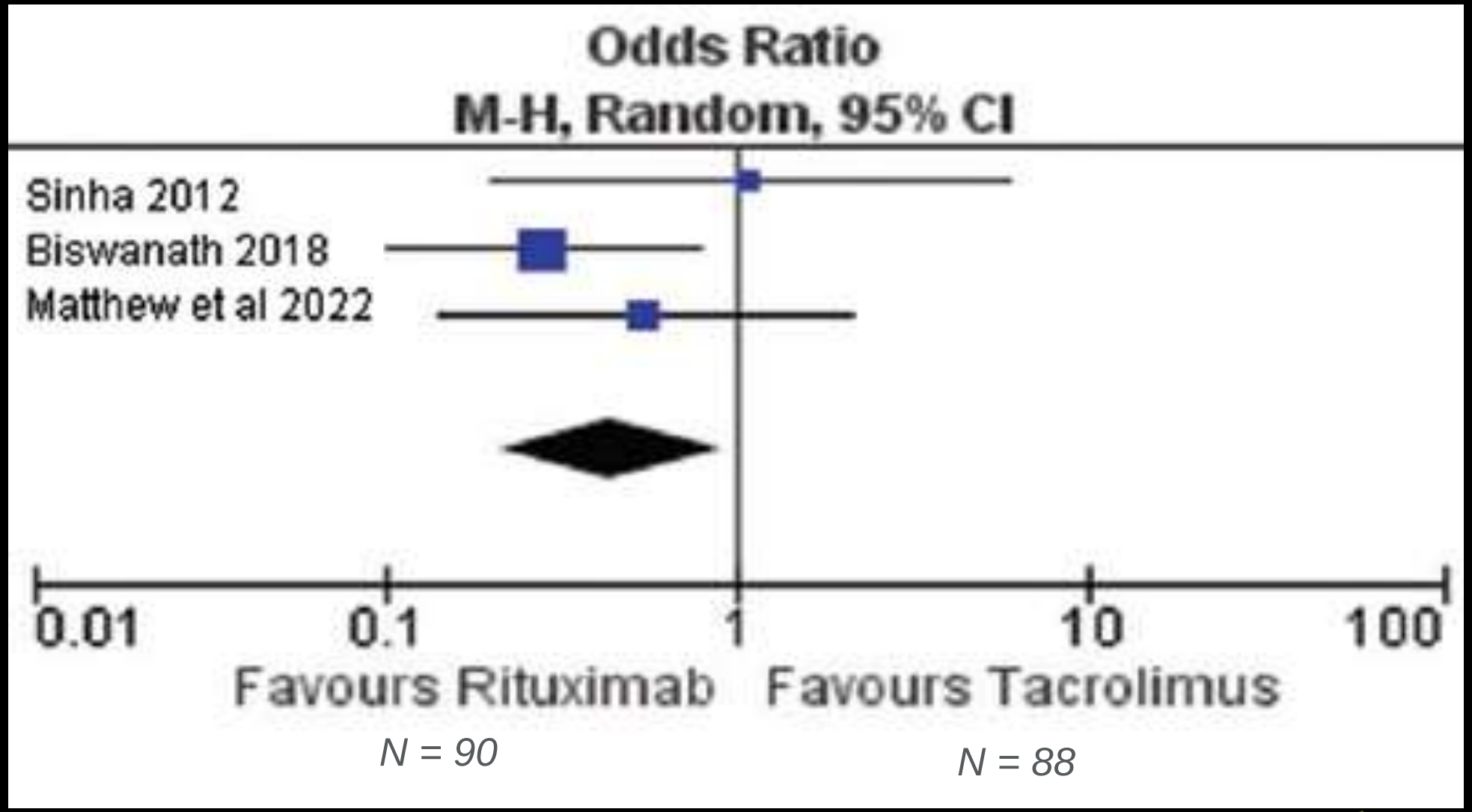
Ritux in Steroid Dependent Pediatric Nephrotic Syndrome?



Forest Plot for 1-2 Relapses

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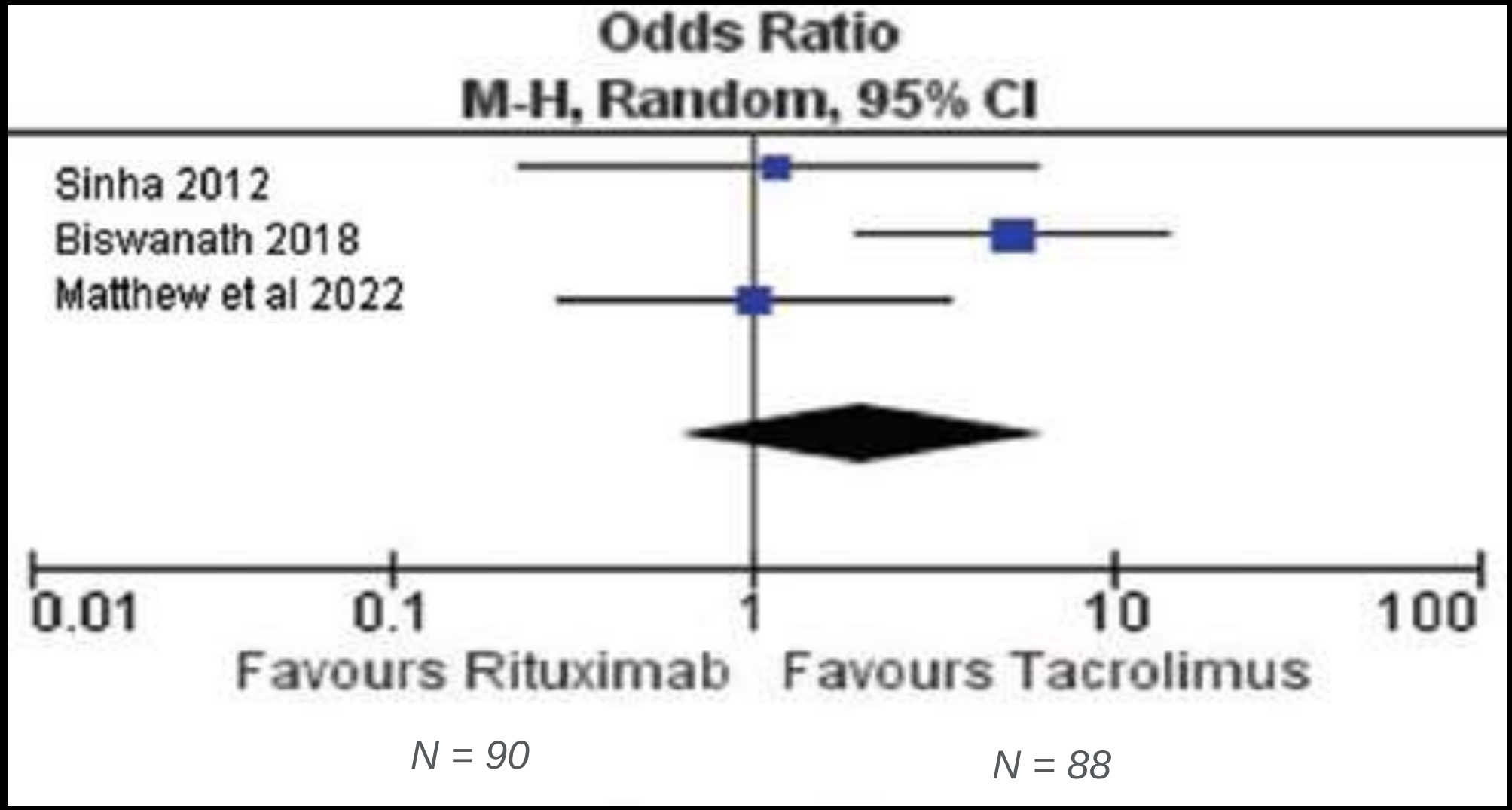

Forest Plot for Sustained Remission

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Ritux in Steroid Resistant Nephrotic Syndrome?

Consensus Guidelines on Management of Steroid-Resistant Nephrotic Syndrome

ANIL VASUDEVAN,[1] RANJEET THERGAONKAR,[2] MUKTA MANTAN,[3] JYOTI SHARMA,[4] PRIYANKA KHANDELWAL,[5] PANKAJ HARI,[5] ADITI SINHA,[5] ARVIND BAGGA,[5] EXPERT GROUP OF INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY*

Vasudevan et al, Indian Pediatr 2021; 58

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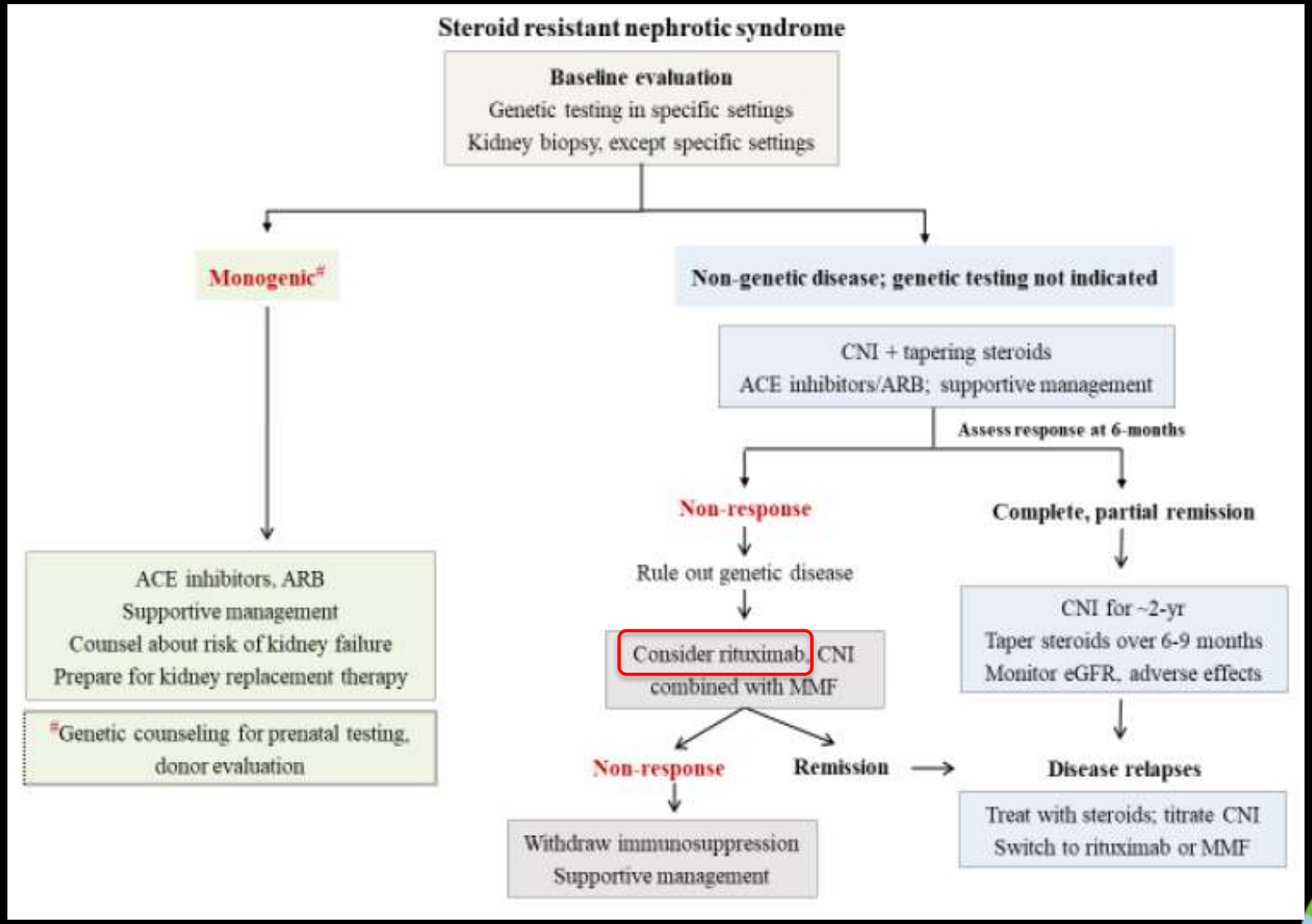
Ritux in Steroid Resistant Nephrotic Syndrome?



Vasudevan et al, Indian Pediatr 2021; 58

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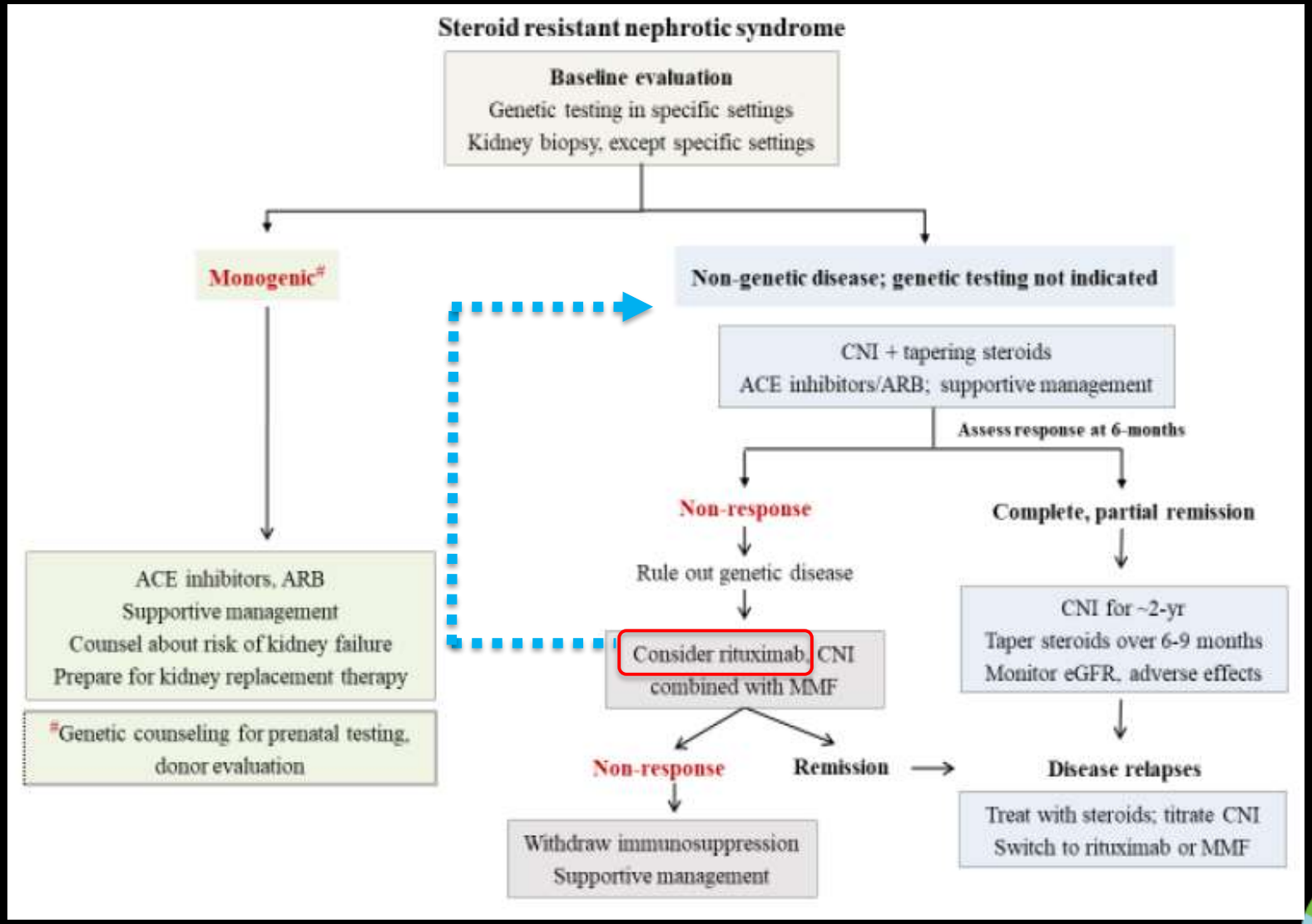
Ritux in Steroid Resistant Nephrotic Syndrome?



Vasudevan et al, Indian Pediatr 2021; 58

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Ritux in Steroid Resistant Nephrotic Syndrome?

An international, multi-center study evaluated rituximab therapy in childhood steroid-resistant nephrotic syndrome

OPEN

Eugene Yu-hin Chan[1,2], Aditi Sinha[3], Ellen L.M. Yu[4], Naureen Akhtar[5], Andrea Angeletti[6], Arvind Bagga[3], Sushmita Banerjee[7], Olivia Boyer[8], Chang-Yien Chan[9,10], Anna Francis[11], Gian Marco Ghiggeri[6], Riku Hamada[12], Pankaj Hari[3], Nakysa Hooman[13], Luke Sydney Hopf[14], Mohamad Ikram I[15], Iftikhar Ijaz[16], Dmytro D. Ivanov[17,18], Suprita Kalra[19], Hee Gyung Kang[20], Laura Lucchetti[21], Francesca Lugani[6], Alison Lap-tak Ma[2], William Morello[22], María Dolores Camargo Muñiz[23], Subal Kumar Pradhan[24], Larisa Prikhodina[25,26], Reem H. Raafat[27], Rajiv Sinha[28], Sharon Teo[9,10], Kouki Tomari[29], Marina Vivarelli[30], Hazel Webb[31], Hui Kim Yap[9,10], Desmond Yat-hin Yap[32] and Kjell Tullus[31]

Chan et al, Kidney Internat 2024

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Ritux in Steroid Resistant Nephrotic Syndrome?

An international, multi-center study evaluated rituximab therapy in childhood steroid-resistant nephrotic syndrome.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

Retrospective cohort study

28 paediatric nephrology centres in 19 countries

246 children with SRNS
Age 6.9±4.2; 55% boys

FSGS 57%; MCD 33%

Follow-up 32.4 months

Intervention

CNIs treatment before rituximab

≥ 6 months (CNI-resistant)

N=146

< 6 months

N=100

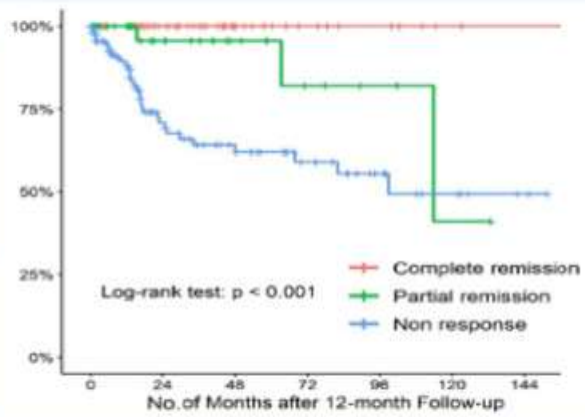
Rituximab
750mg/m2 (46.3%)
1500mg/m2 (40.7%)

Findings

Complete/ partial remission

	3m	6m	12m
≥ 6 months (CNI-resistant)	26%	36%	35%
< 6 months	42%	52%	55%

Worse kidney survival with non-response at 12-months



Adverse events (35%) | **Hypo-IgG (12.6%)** | **Infusion reaction (11.8%)** | **Infection (5.7%)** | **Neutropenia (1.6%)**

Chan et al. 2024

CONCLUSION *Rituximab enhances remission in a subset of children with SRNS, and is generally safe. Complete remission following rituximab is associated with favourable kidney outcome.*

Chan et al, Kidney Internat 2024

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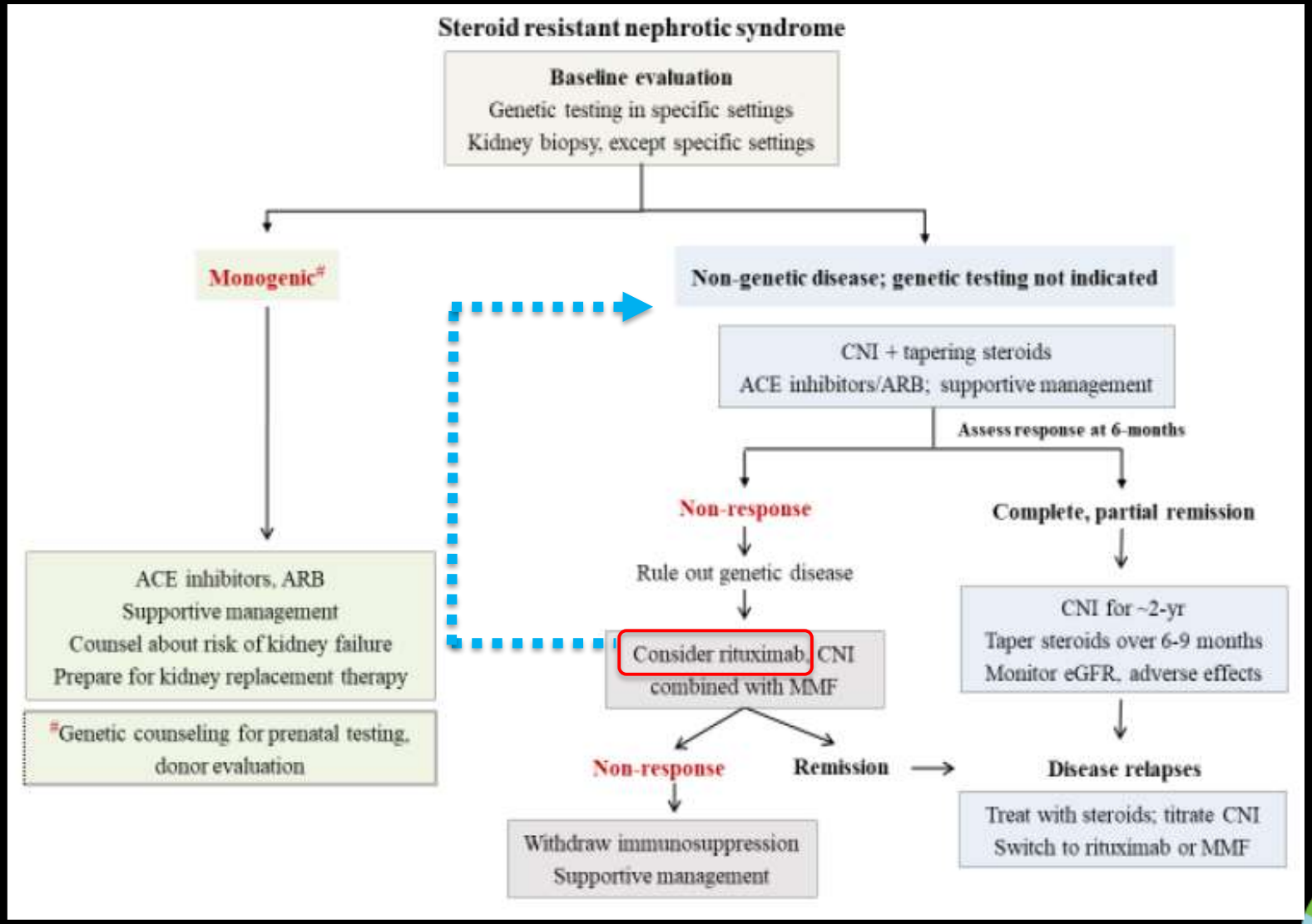
Ritux in Steroid Resistant Nephrotic Syndrome?



Vasudevan et al, Indian Pediatr 2021; 58

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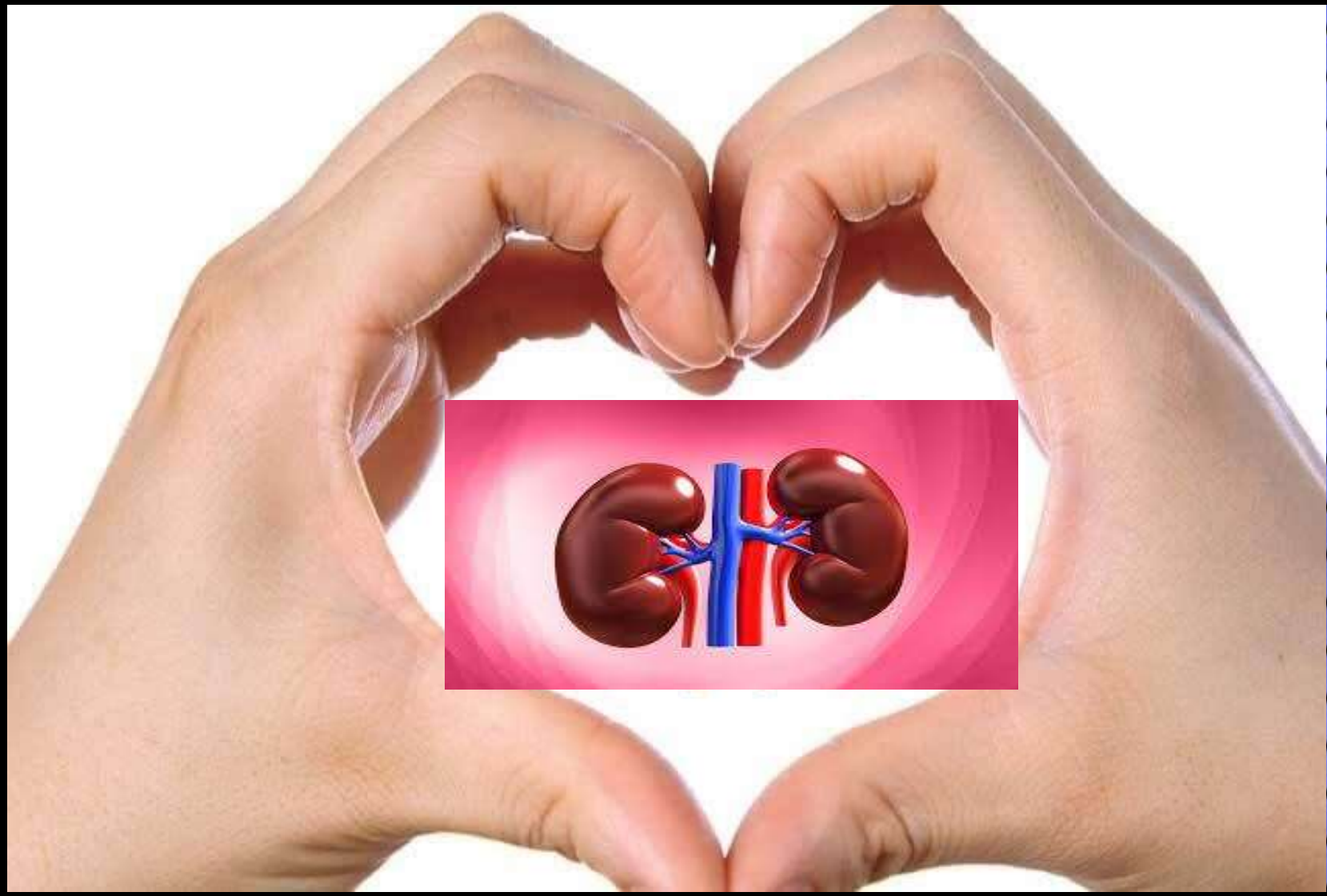
Outline

- Targeted Therapies for Genetic Diseases: PH1 RNAi
- Targeted Therapies for X-linked hypophosphatemia: Burosomab as FGF-23 inhibitor
- Monoclonals in Nephrotic Syndrome: Rituximab
- Monoclonals in atypical HUS: Eculizumab, Ravulizumab
- Monoclonals in lupus nephritis: Belimumab
- Monoclonals to treat transplant rejection

Love your Kidneys!



Thank you for your attention!

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