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Theme : Acute care Nephrology : Evidence to Bedside

IPNA endorsed AIIMS Jodhpur Pediatric Nephrology Workshop cum CME

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28th - 29th January 2023

LT-1 & Skill Lab
AIIMS Jodhpur

2nd ANNUAL PEDIATRIC KIDNEY MEET and IPNA endorsed - AIIMS Jodhpur Pediatric Nephrology Workshop cum CME

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Annual Pediatric Kidney Meet
2nd IPNA endorsed AIIMS Jodhpur
Pediatric Nephrology Workshop cum CME
Theme: Acute Care Nephrology- Evidence to bedside

Day 1 (Saturday, 28th January 2023) VENUE LT-1

Time	Topic	Speaker	Chairperson
08:30-9.00	***Registration***		
09:00-09:30	Approach to refractory rickets	Prof. Ranjeet Thergaonkar	Dr. Vinod Choudhary Dr. Varuna Vyas
09:30-10:00	Renal tubular acidosis	Dr. Girish Bhatt	
10:00–10:45	Urinary tract infection in children: The new ISPN guidelines 2023	Prof. Pankaj Hari	Prof. JP Soni Dr. Bharat Choudhary
10:45 – 11:00	***Coffee Break***		
11:00–11:45	Management of nephrotic syndrome in children- What's new	Prof. Arvind Bagga	Prof. Kuldeep Singh Dr. Manish Chaturvedi
11.14-12.45	**Panel discussion** Evaluation and management of kidney stone	Moderator: Dr. Aliza Mittal Panelist: Prof. AS. Sandhu Prof. Arvind Sinha Prof. Ranjeet Thergaonkar Dr. Girish Bhatt Dr. Rajesh Jhorawat	
12:45-13:15	***Inauguration***		
13:15-14:00	***Lunch Break***		
14:00-14:30	Approach to Chronic Kidney Disease	Prof. Amarjeet Mehta	Prof. Rakesh Jora Dr. Siyaram Didel
14:30-15:00	Approach to Dysnatremias	Prof. Ranjeet Thergaonkar	
	Coffee Break		
15:00- 15:30	Approach to Dyskalemias	Prof. Abhijeet Saha	Prof. Mohan Makwana Dr. Prawin Kumar
15:30-16:00	Approach to Nocturnal enuresis	Prof. Susan Uthup	
16:00-17:00	**Case-based discussion** Case 1 Cystinosis (Dr. Sumantra Raut) Case 2 Primary Hyperoxaluria (Dr. Georgie Mathew) Case 3 Hypophosphatemic Rickets (Dr. Sudarshan K)	Prof. Susan Uthup Prof. Ranjeet Thergaonkar Dr. Girish Bhatt Dr. Suprita Kalra Dr. Aliza Mittal Dr. Sumantra Raut Dr. Jitendra Meena Dr. Georgie Mathew Dr. Sudarshan K	

Day 2 (Sunday 29th January 2023)

Time	Topic	Speaker	
08:30-9.00	***Registration***		
09:00-09.30	Hypertensive Emergencies	Dr Abhijeet Saha	Prof. Manish Parakh Dr. Lokesh Saini Dr. Archana Bajpai
09.30-10.10	Hemolytic Uremic Syndrome	Dr. Aditi Sinha	
10.10-10.40	Rapidly progressive Glomerulonephritis	Prof. Anil Vasudevan	Dr Nitin Bajpai Dr. Saptrishi Mandal
10.40-11.00	Plasmapheresis	Dr. Aditi Sinha	
11.00-11.20	***Coffee Break***		
11.20–12.00	AKI	Dr. Jitendra Meena	Prof. Anurag Singh Dr. Neeraj Gupta Dr. Daisy Khera
12.00- 12.20	Neonatal AKI	Dr. Suprita Kalra	
12.30-13.20 pm	Break-out sessions- Case based scenario Case 1 Neonatal AKI (HIE) (Dr. Suprita K+ Dr. Karalanglin) Case 2 Hypernatremic dehydration (Dr. Amit S+ Dr. Neha Aggarwal) Case 3 Sepsis (Dr. Georgie +Dr. Sudarshan) Case 4 Contrast induced (Dr. Anshuman S+ Dr. Sumantra)	 Dr. Suprita Kalra Dr. Anshuman Saha Dr. Amit Satpathy Dr. Aliza Mittal Dr. Sumantra Raut Dr. Georgie Mathew Dr. Jitendra Meena Dr. Sudarshan K Dr. Neha Aggarwal	
13.20-14.00	***Lunch Break***		
14.00-14.25	Primer on dialysis (Hemodialysis and Peritoneal Dialysis)	Dr. Aliza Mittal	
Hands on Session-Venue-Skill Lab			
14.40-16.30	**Extra Corporeal Therapies and Peritoneal Dialysis** 1. PD Hands on insertion (Dr Suprita+ Dr. Amit Satpathy) 2. Case Scenarios for dialysis prescription with CAPD Demonstration (Dr Neha Aggarwal+ Dr. Anshuman Saha) 3. Hemodialysis prescription (Dr. Karalanglin +Dr Georgie) 4. Modification of dialysis prescriptions (Dr Sudarshan +Dr Sumantra) Case : Malaria AKI-PD (UF)(Dr. Neha) Case : Septic Shock- PD (Hyperglycemia) (Dr. Sumantra) Case : Hypernatremic dehydration (Hypernatremia) (Dr. Sudarshan)	 Dr. Suprita Kalra Dr. Amit Satpathy Dr. Anshuman Saha Dr. Neha Aggarwal Dr. Karalanglin Tiewsoh Dr. Georgie Mathew Dr. Aliza Mittal Dr. Sumantra Raut Dr. Jitendra Meena	
16:30-17:00	MCQ Test and feedback		
17:00-17:30	Closing remarks and vote of thanks		

Approach to refractory rickets

RW Thergaonkar, MD, PhD

Overview

Physiology

- Pi metabolism
- Ca metabolism
- Vit D, PTH, FGF 23 axis

What is rickets?

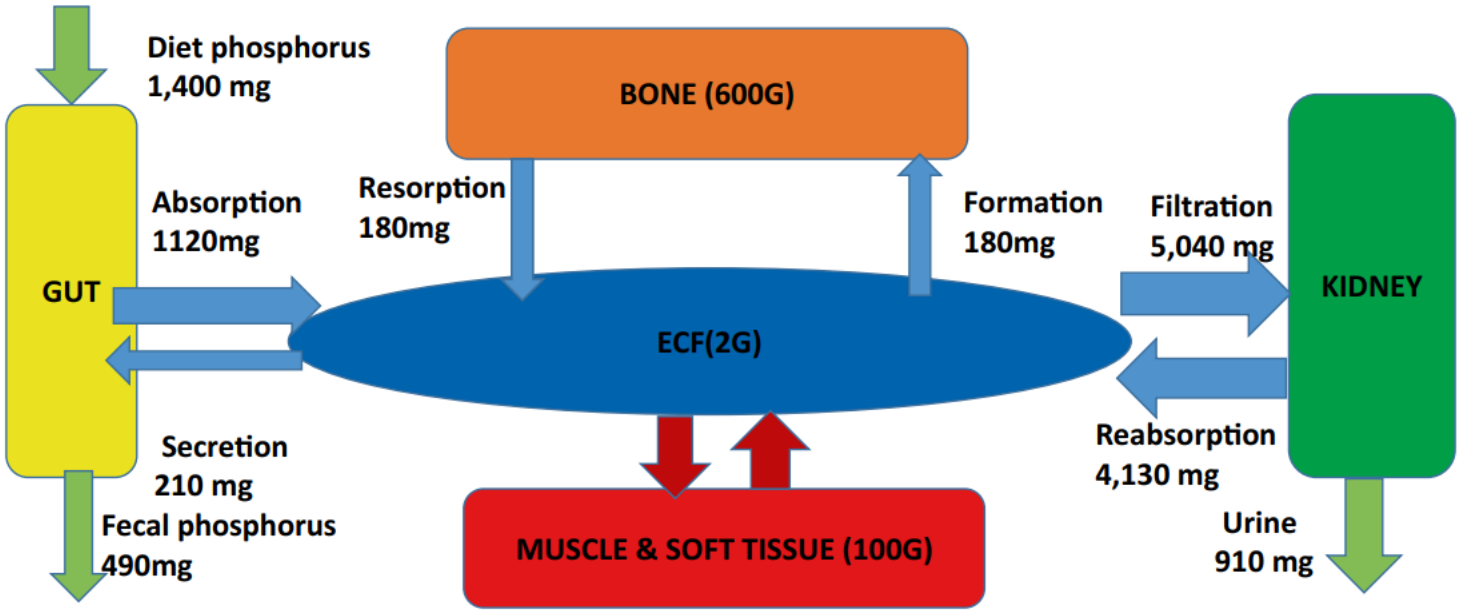
What is refractory rickets?

Specific entities

- Vit D Dependent rickets
- Hypophosphatemic rickets
- Other causes of “renal rickets”
- Clinical approach

Physiology

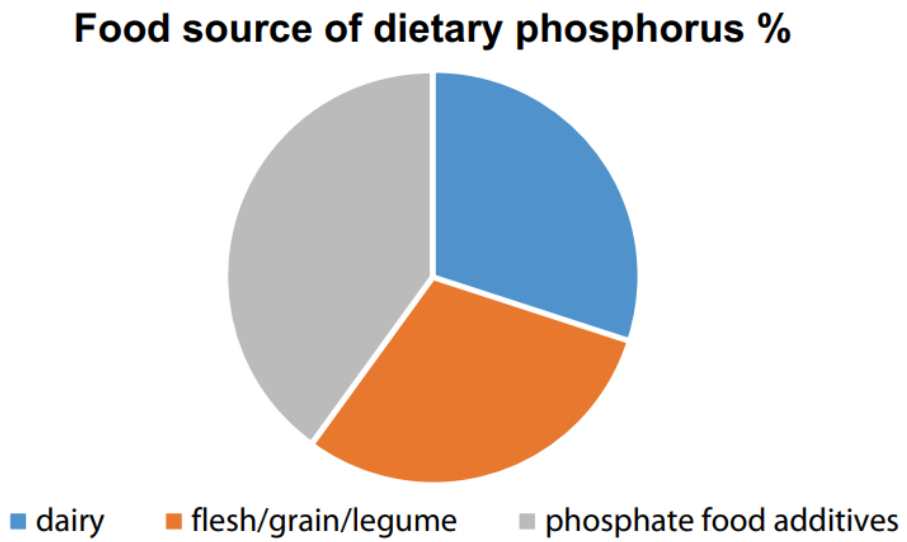
Phosphate metabolism



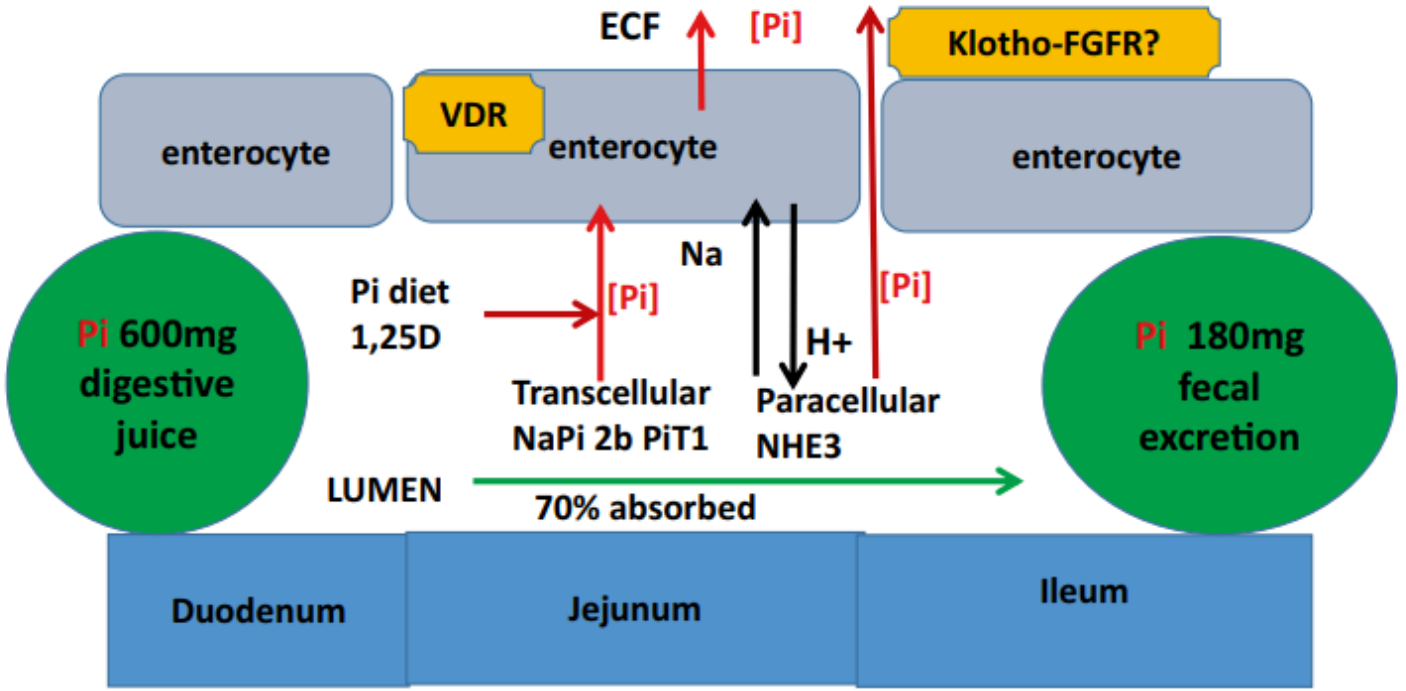
- Constitutes 0.6% mass of the organism
- 80% - bones as apatite
- Cellular functions: biochemical energy transfer, maintenance of genetic information, intracellular signaling & membrane structural integrity

Peacock M. Phosphate Metabolism in Health and Disease. Calcif Tissue Int. 2021 Jan;108(1):3-15

Phosphate metabolism



RDA: 700 mg, usually exceeded
Thumb rule: 15 mg/gram protein



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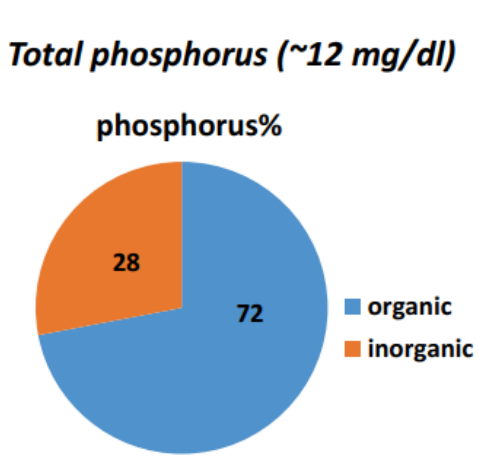
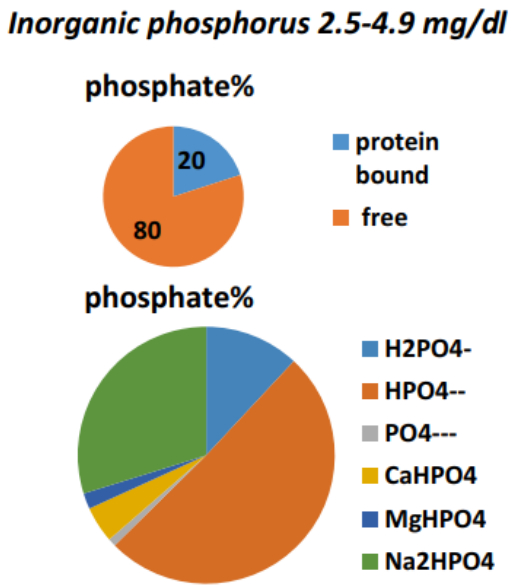
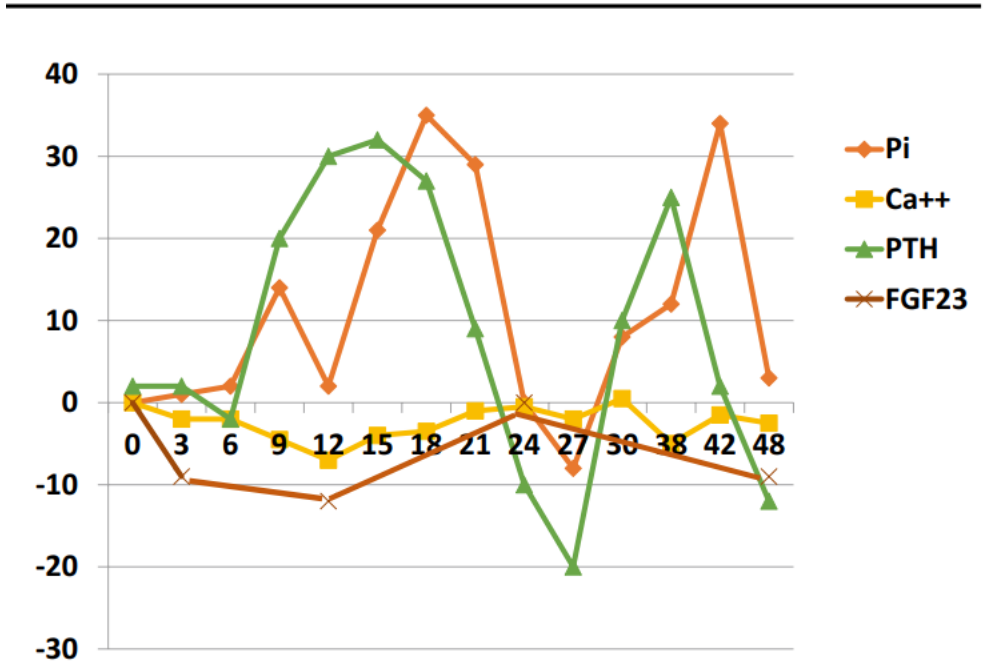
Phosphate metabolism







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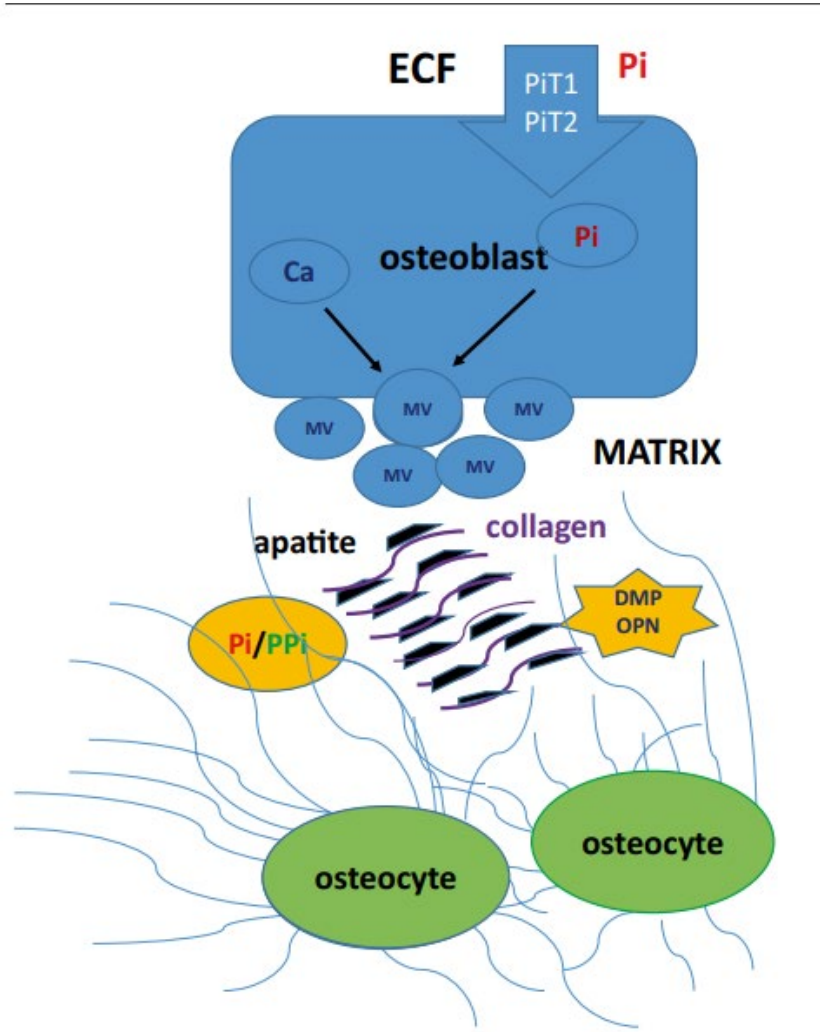
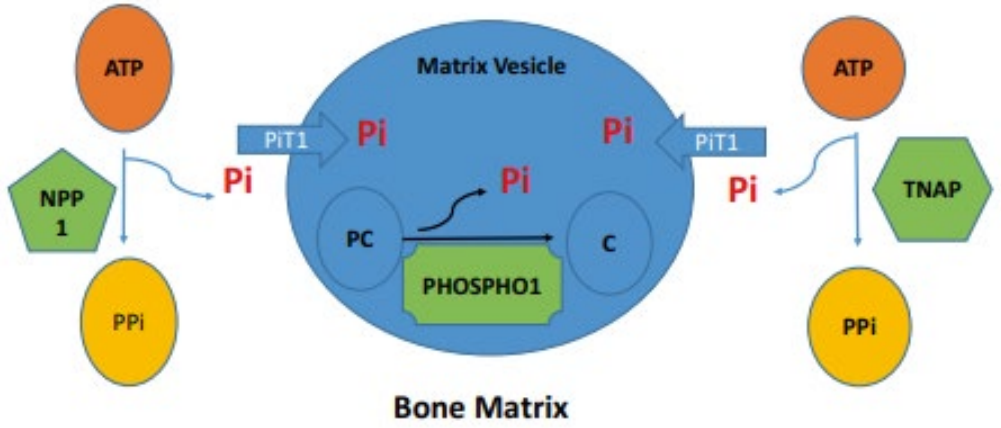
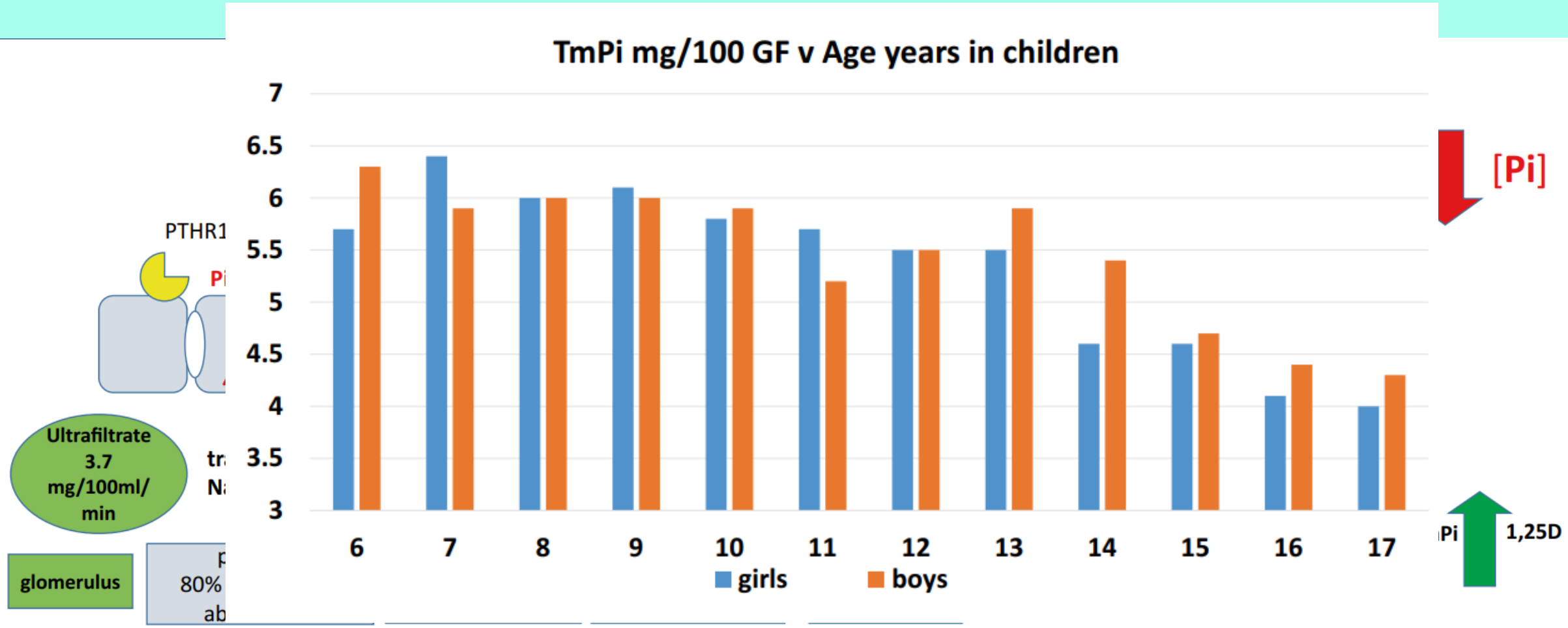
Phosphate metabolism





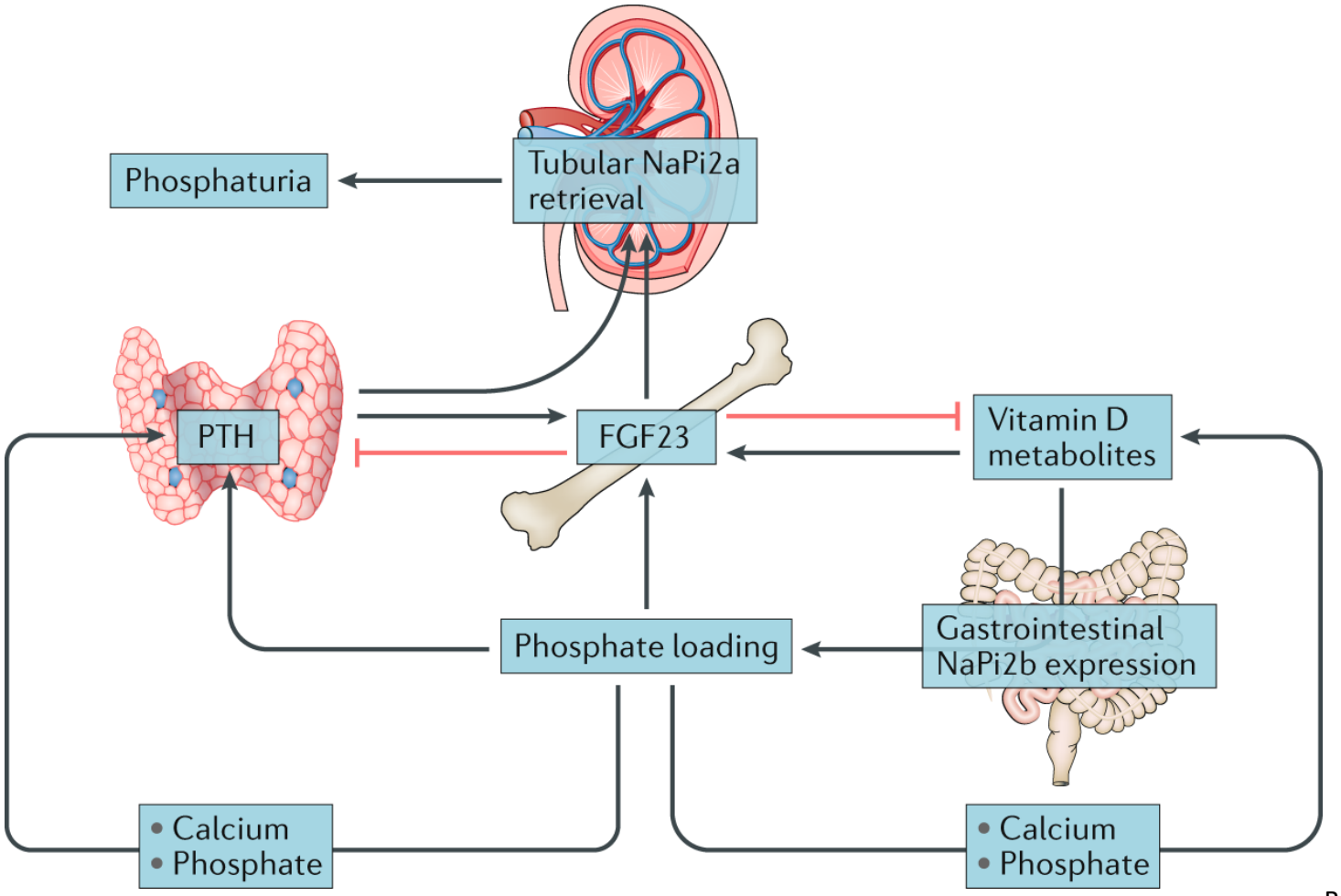
Peacock M. Phosphate Metabolism in Health and Disease. Calcif Tissue Int. 2021 Jan;108(1):3-15

Phosphate metabolism

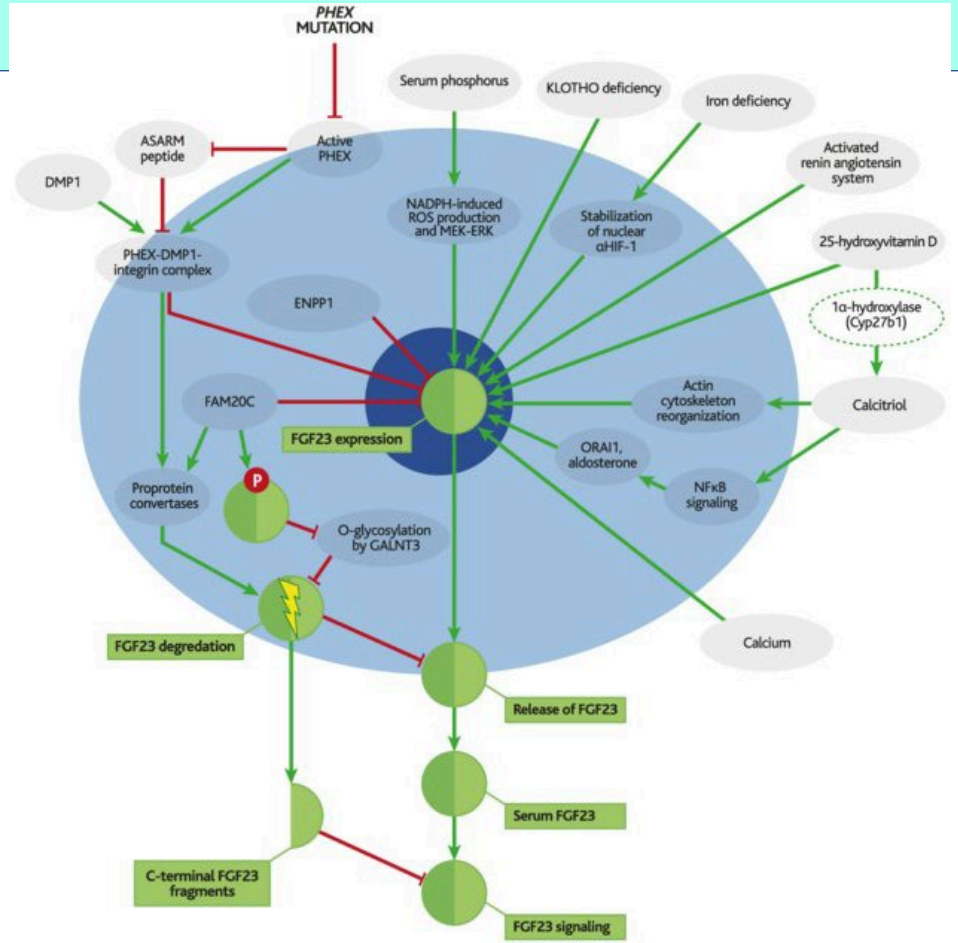


Peacock M. Phosphate Metabolism in Health and Disease. Calcif Tissue Int. 2021 Jan;108(1):3-15

Phosphate regulation: focus on FGF23

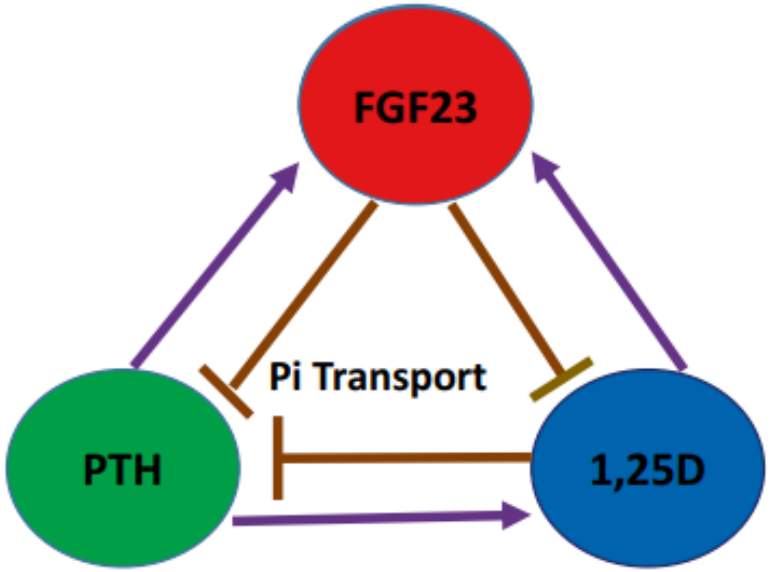


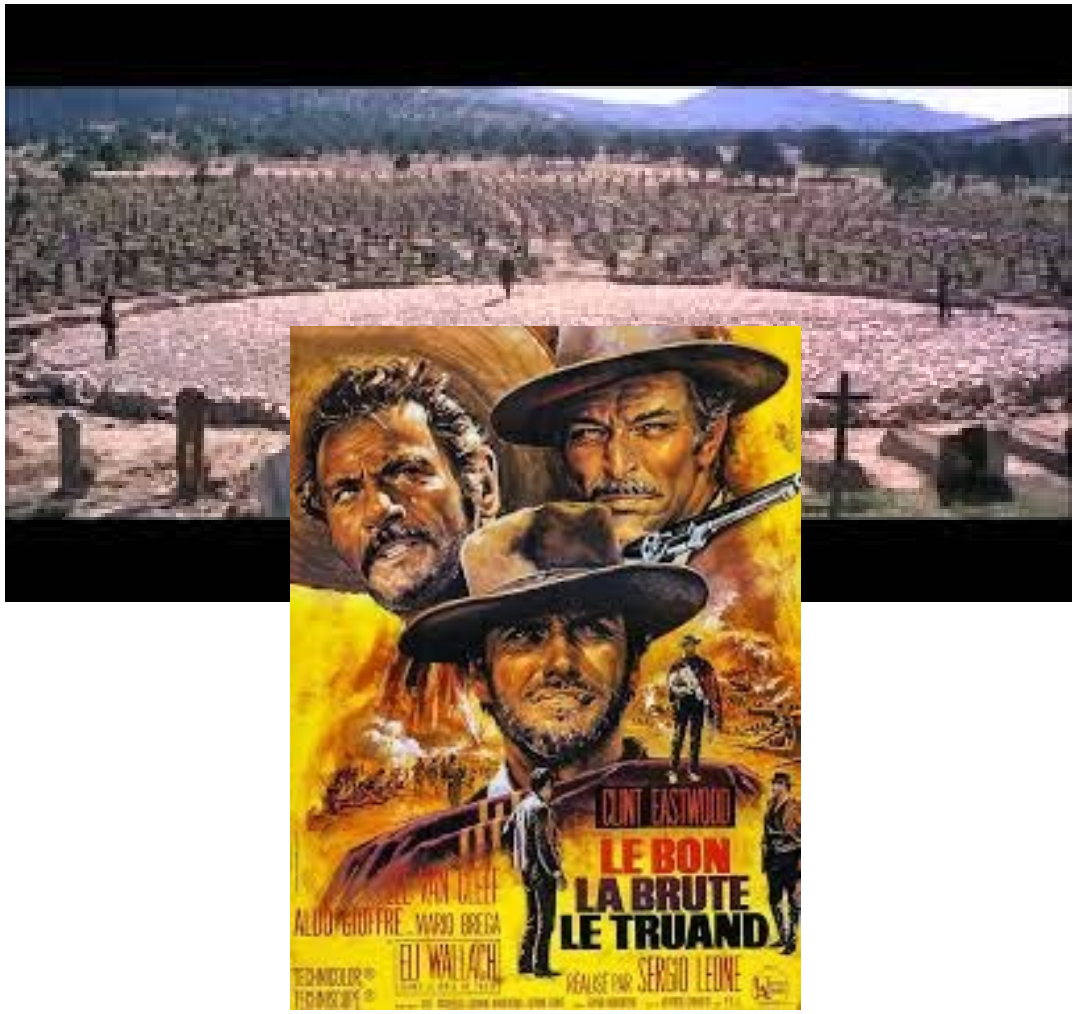
Vervloet, M. Renal and extrarenal effects of fibroblast growth factor 23. *Nat Rev Nephrol* **15**, 109–120 (2019)



Beck-Nielsen et al. Orphanet Journal of Rare Diseases (2019) 14:58

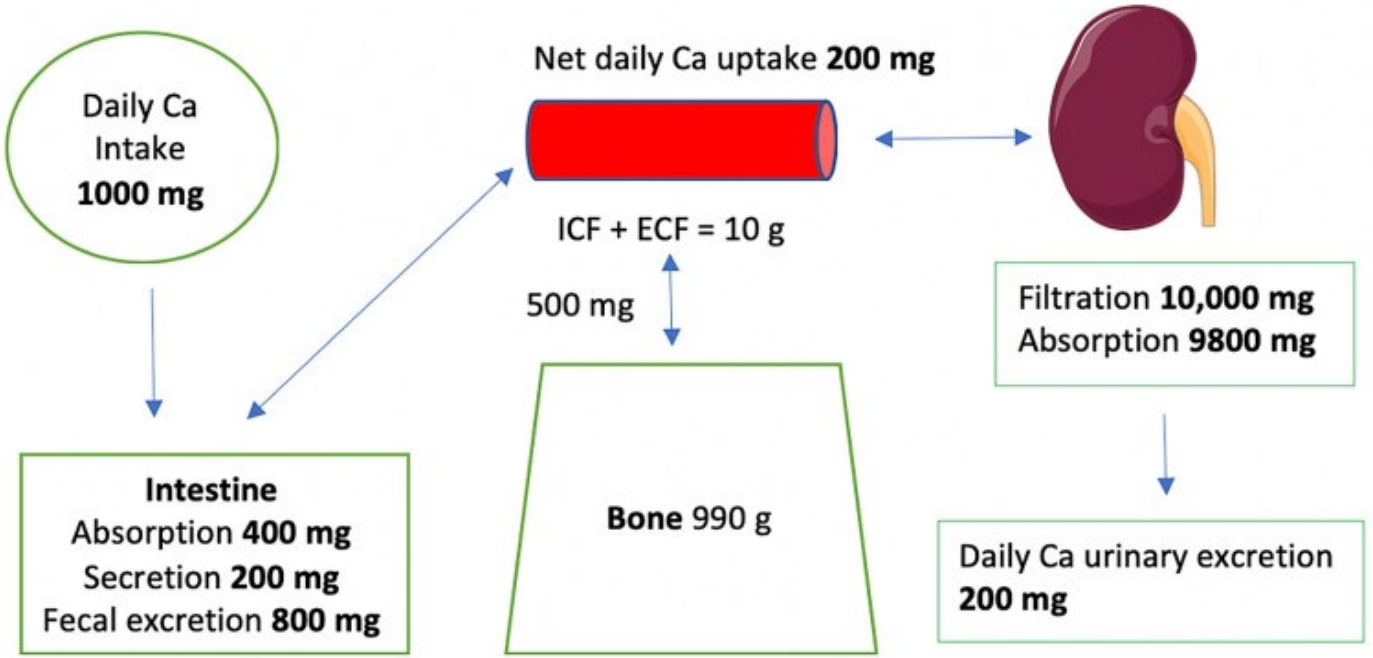
Phosphate metabolism



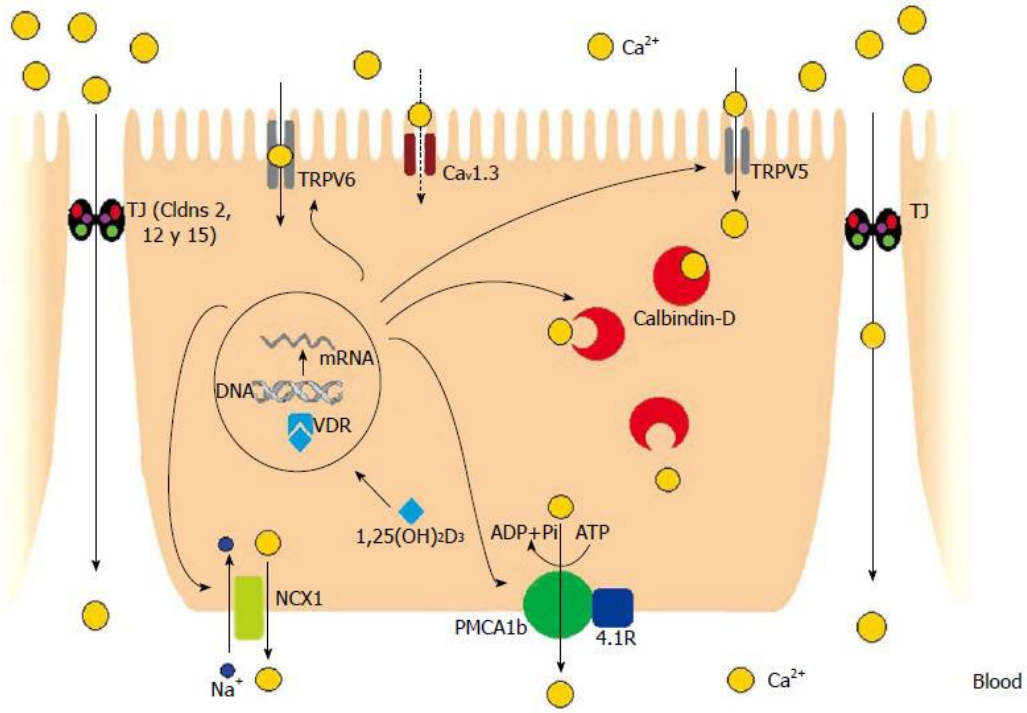


Peacock M. Phosphate Metabolism in Health and Disease. Calcif Tissue Int. 2021 Jan;108(1):3-15

Calcium metabolism

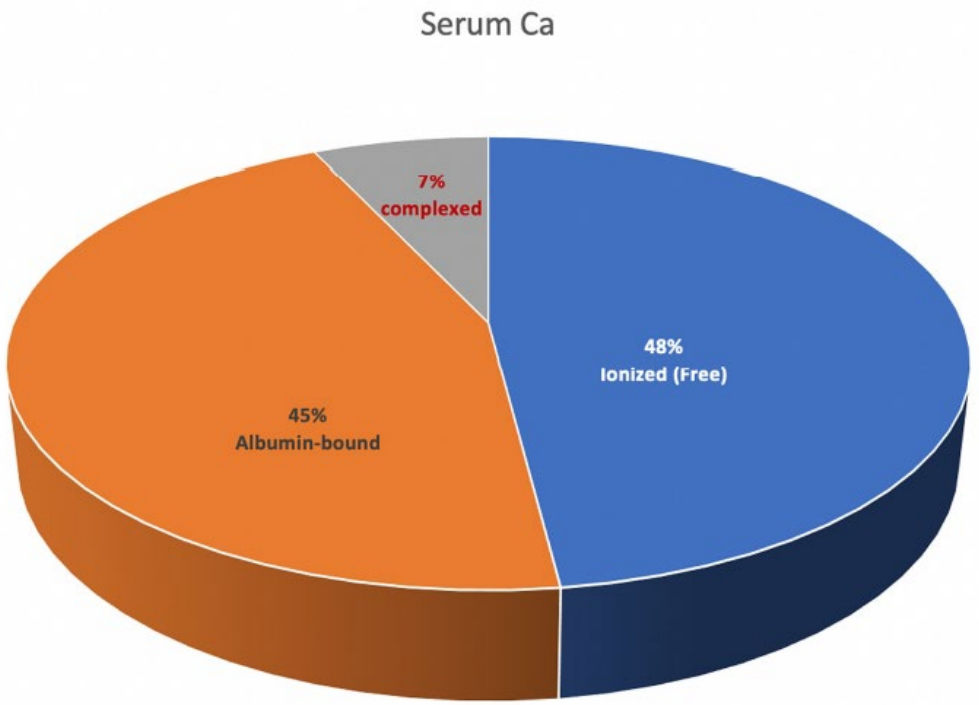


Tinawi M. Disorders of Calcium Metabolism: Hypocalcemia and Hypercalcemia. Cureus. 2021 Jan 1;13(1)



Diaz de Barboza et al Molecular aspects of intestinal calcium absorption. World J Gastroenterol. 2015 Jun 21;21(23):7142-54.

Calcium metabolism



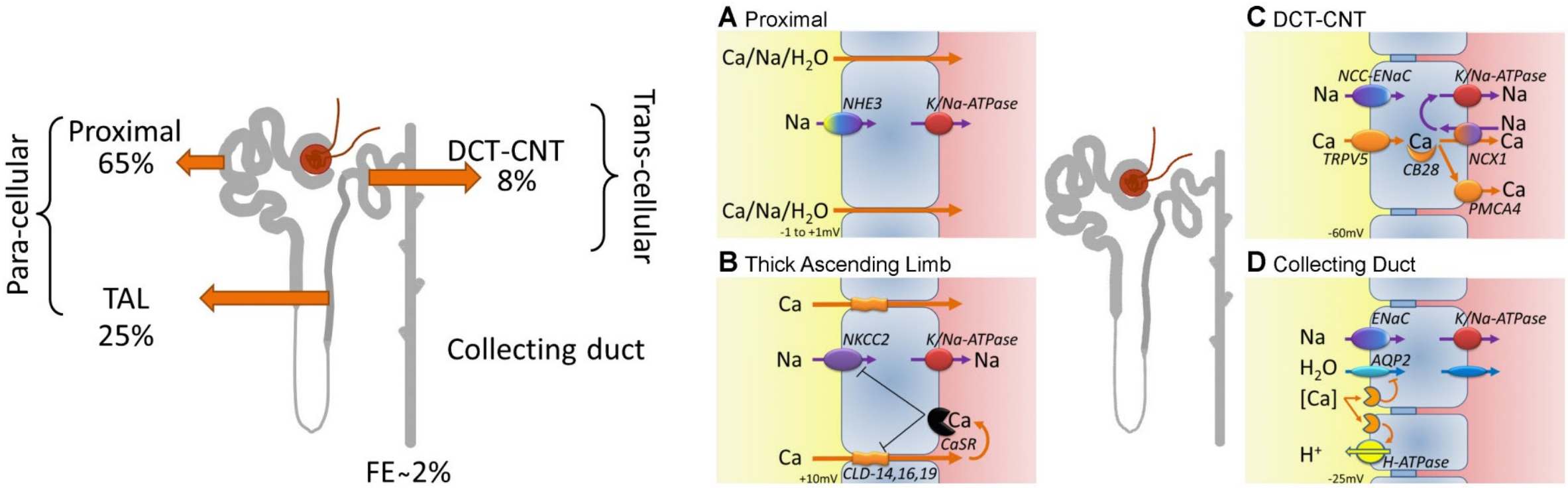
Tinawi M. Disorders of Calcium Metabolism: Hypocalcemia and Hypercalcemia. Cureus. 2021 Jan 1;13(1)

Thumb rule

Total calcium = 2 X ionized

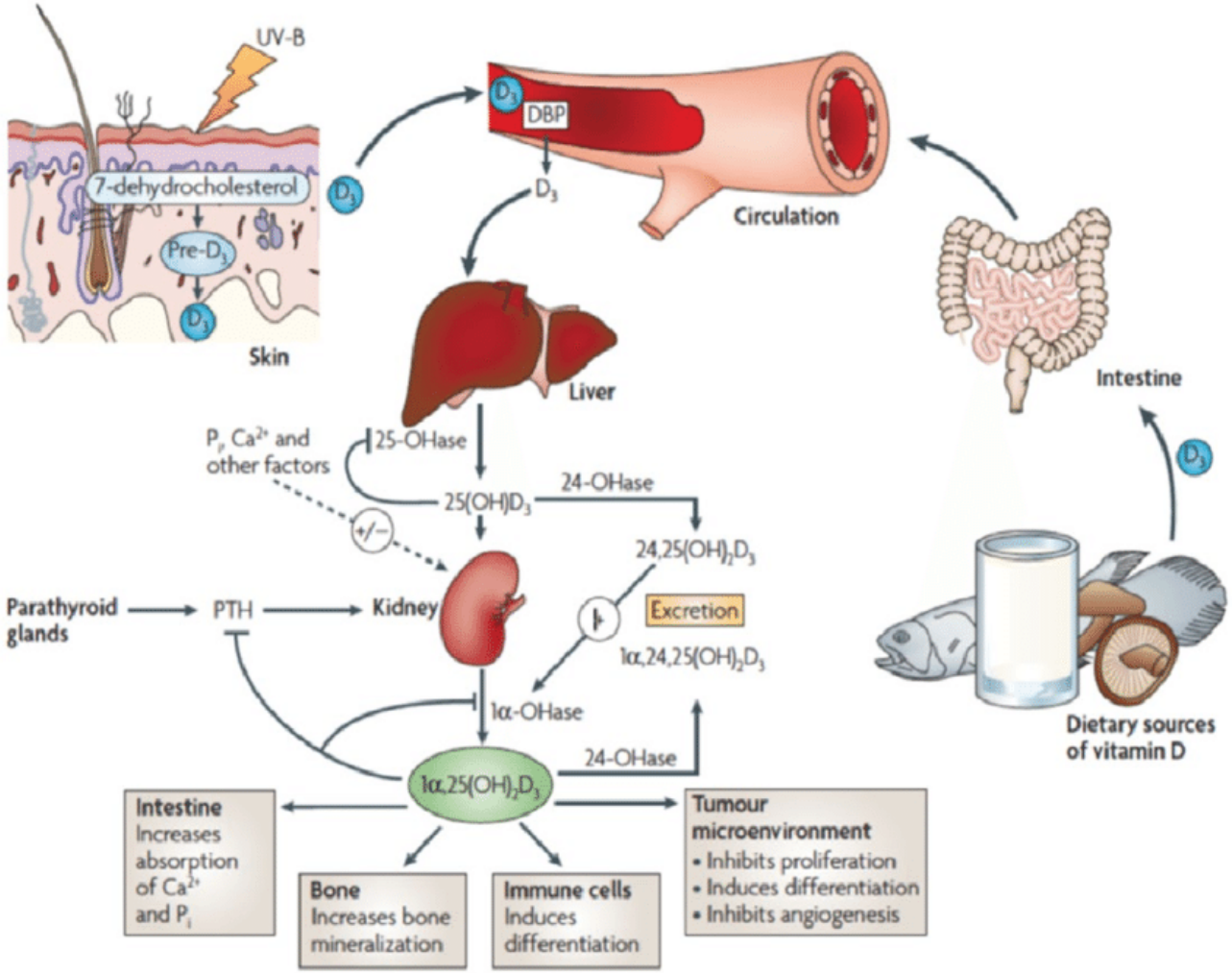
mg/dl = 2 X mmol/dl

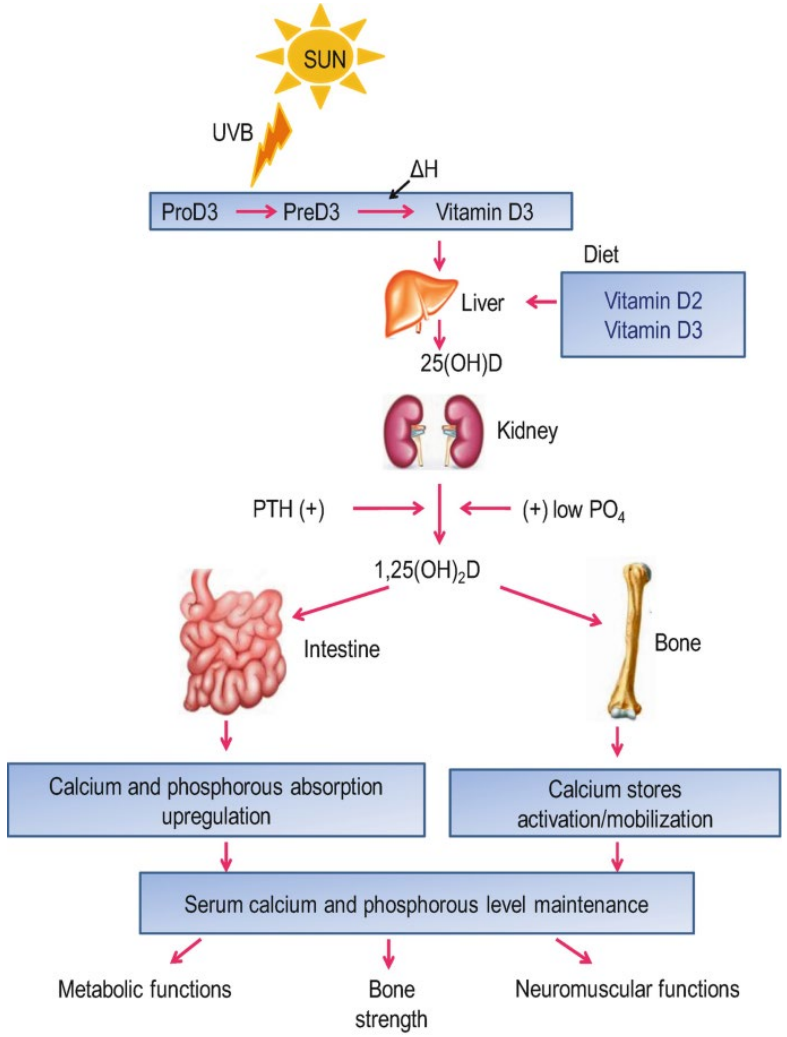
Calcium metabolism



Moor MB, Bonny O. Ways of calcium reabsorption in the kidney. Am J Physiol Renal Physiol. 2016 Jun 1;310(11)

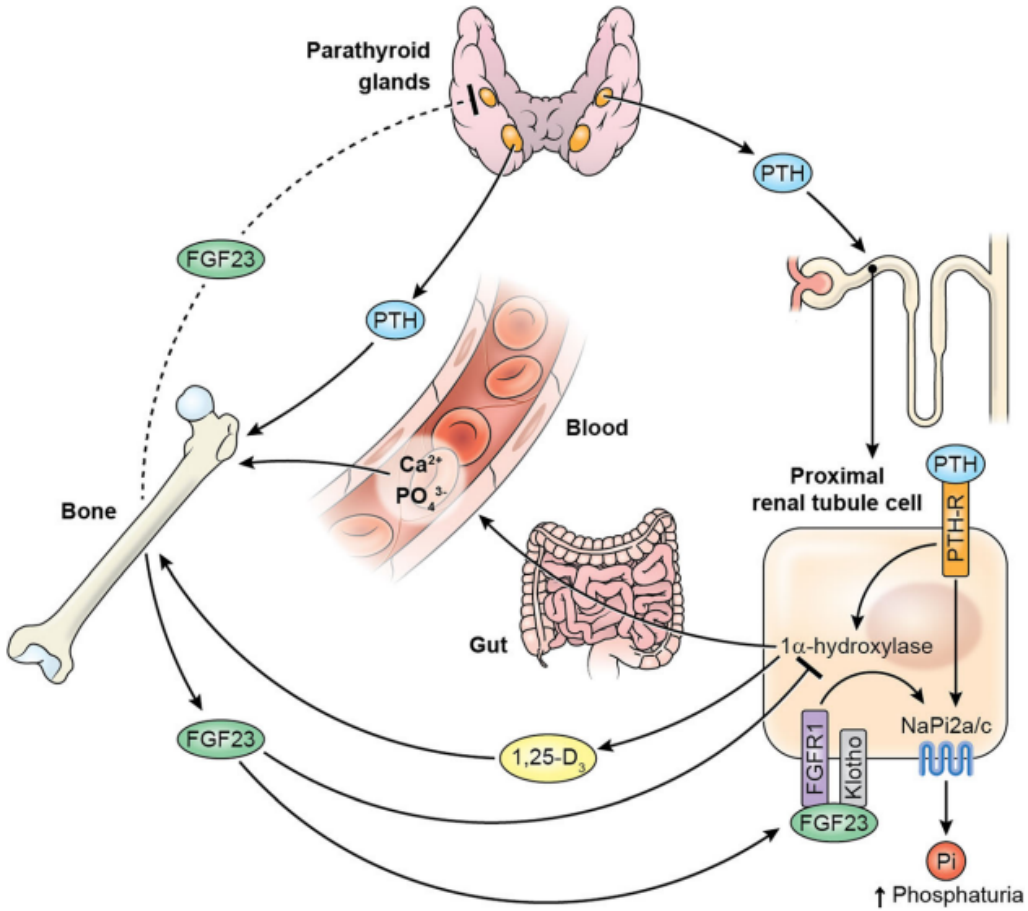
Vitamin D metabolism





Recap of calcium and phosphate homeostasis

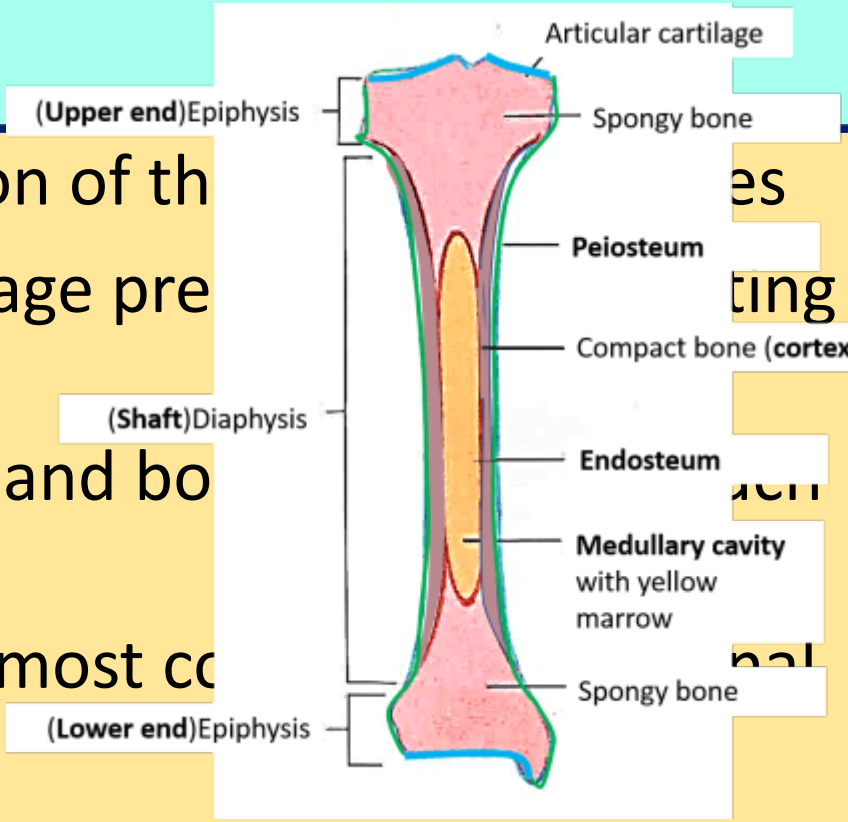
Fig. 3 The PTH-Vitamin D-FGF23 axis. FGF23 secretion from bone osteocytes acts on the kidney to induce phosphaturia via NaPi 2a/c transporters, similar to PTH, which acts via the PTH receptor. However, in contrast to the action of PTH to induce 1α hydroxylase, the enzyme that hydroxylates 25 vitamin D to 1,25-D, FGF23 acts to suppress 1α hydroxylase. 1,25-D is responsible for increased calcium and phosphate absorption from the gut and supports bone mineralization. The action of FGF23 on the parathyroid gland has been reported to suppress PTH secretion *in vitro* and in rodent models, but demonstration of a similar effect in humans is lacking



Blau JE, Collins MT. The PTH-Vitamin D-FGF23 axis. Rev Endocr Metab Disord. 2015 Jun;16(2):165-74.

Rickets overview

What is rickets?



- a condition characterized by a defect in mineralization of th es
- results from abnormalities of the growth plate cartilage pre ting longer bones
- leads to poor bone growth, defective mineralization, and bo uch as bow-legs and knock-knees
- usually secondary to deficiencies of calcium or vit D, most cc nal deficiency of vitamin D
- Osteomalacia = defective mineralization of the bony matrix, usually occurs concomitantly

Before bony epiphyseal fusion: rickets and osteomalacia
After bony epiphyseal fusion: osteomalacia

ickets. Statpearls

w of Rickets in Children. Kidney Int Rep. 2020 Apr 11;5(7):980-990.

Types of rickets

Calcipenic rickets

- **Vitamin D deficiency or resistance**
  - Dietary deficiency
  - Malabsorption
  - Lack of sunlight exposure
  - Defect in 25 hydroxylation of vitamin D (e.g., liver disease, medications such as phenytoin)
  - Failure of 1 hydroxylation of vitamin D due to inherent deficiency of 1 alpha hydroxylase secondary to defects in the 1 alpha hydroxylase gene (VDDR I)
  - End-organ resistance to vitamin D (VDDR II)
- **Calcium deficiency**
- **Renal rickets secondary to CKD**

Phosphopenic rickets

Renal tubular phosphate loss

- Isolated phosphate loss secondary to genetic mutations:
  - XLHR
  - ARHR
  - ADHR
  - Hypophosphatemic rickets with hypercalciuria
- Renal Fanconi syndrome
- Dietary phosphate deficiency
- Phosphate malabsorption

Ref: Chanchlani R, et al. An Overview of Rickets in Children. Kidney Int Rep. 2020 Apr 11;5(7):980-990.

Features	Calcipenic rickets	Phosphopenic rickets
Muscle weakness	Present	Absent*
Bony pain	Common	Uncommon
Extremities involved	All limbs equal	Predominantly lower limbs
Tetany	May be present	Absent
Enamel hypoplasia	May be present	Absent
Dental abscess	Absent	May be present
Serum calcium	Low/normal	Normal
Serum phosphorus	Low	Low
Alkaline phosphatase	Markedly elevated	Mild to moderately elevated
Parathyroid hormone	Elevated	Normal/minimally elevated
Osteopenia and osteitis fibrosa	Present	Absent

*Present in tumor-induced osteomalacia

Hypophosphatemia is a common denominator

Ref:Jagtap VS, et al. Hypophosphatemic rickets. Indian J Endocrinol Metab. 2012 Mar;16(2):177-82

What is refractory rickets?

- a group of rare diseases characterized by lack of response to vitamin D, administered in doses sufficient to manage patients with rickets caused by vitamin D deficiency

- Includes rickets secondary to hypophosphatemia, vitamin D dependence, renal tubular acidosis (RTA), liver disease, malabsorption and chronic kidney disease

Ref:
1. Grzanka K, Kucharz EJ. Vitamin D-resistant rickets. Wiad Lek. 2004;57:663–71.
2. Bajpai A, Bardia A, Mantan M, Hari P, Bagga A. Non-azotemic refractory rickets in Indian children. Indian Pediatr. 2005 Jan;42(1):23-30

The Indian experience

AIIMS, 2005

241 records, 110 with altered RFT excluded

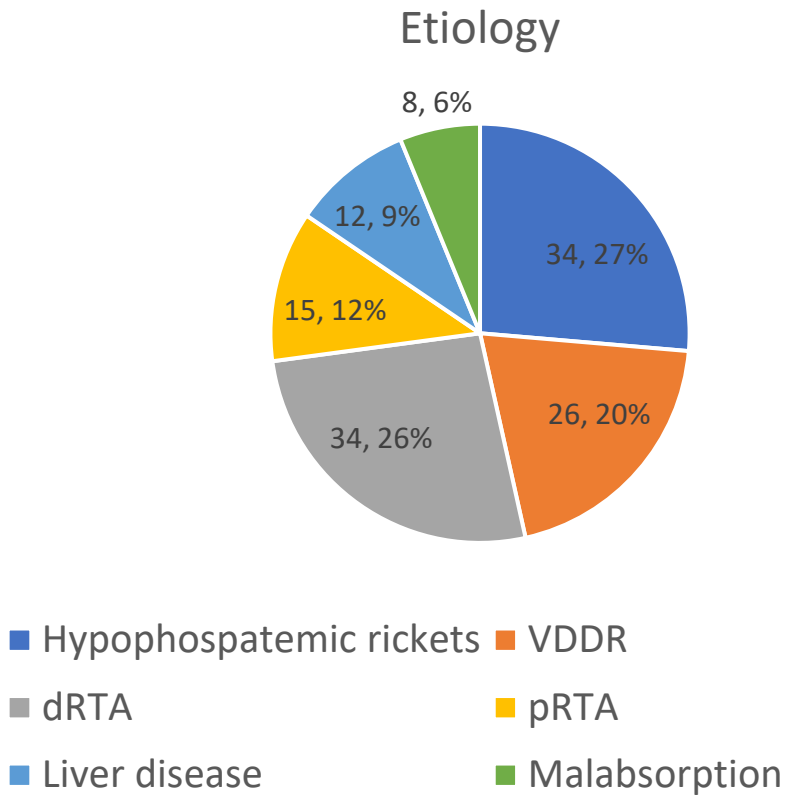


TABLE II–*Clinical Features in Chief Etiological Categories.*

	Distal RTA n = 34	Proximal RTA n = 15	Vitamin D dependent rickets n = 26	Hypophosphatemic rickets n = 34
Boys : Girls	19 : 15	13 : 2	11 : 15	15 : 19
Age at onset (yr)*	3 (2-4) [1 mo-10 yr]	2 (0.7-3.3) [1 mo-10 yr]	1.9 (1.1-2.7) [18 days-9 yr]	2.7 (2.1-3.3) [1-10 yr]
Onset <1 yr	12	7	13	3
Onset >1 yr	22	8	13	31
Clinical features				
Polyuria	34	12	–	–
Fractures	7	–	3	3
Enamel hypoplasia	3	–	7	3
Seizures	–	–	8	–
Families affected	6	2	1	4

1. Tetany was seen in 6 subjects and alopecia in 2 with vitamin D dependent rickets.
2. Hypokalemic muscle weakness was seen in 3 patients with distal RTA.

* Expressed as mean (95% confidence interval) [range].

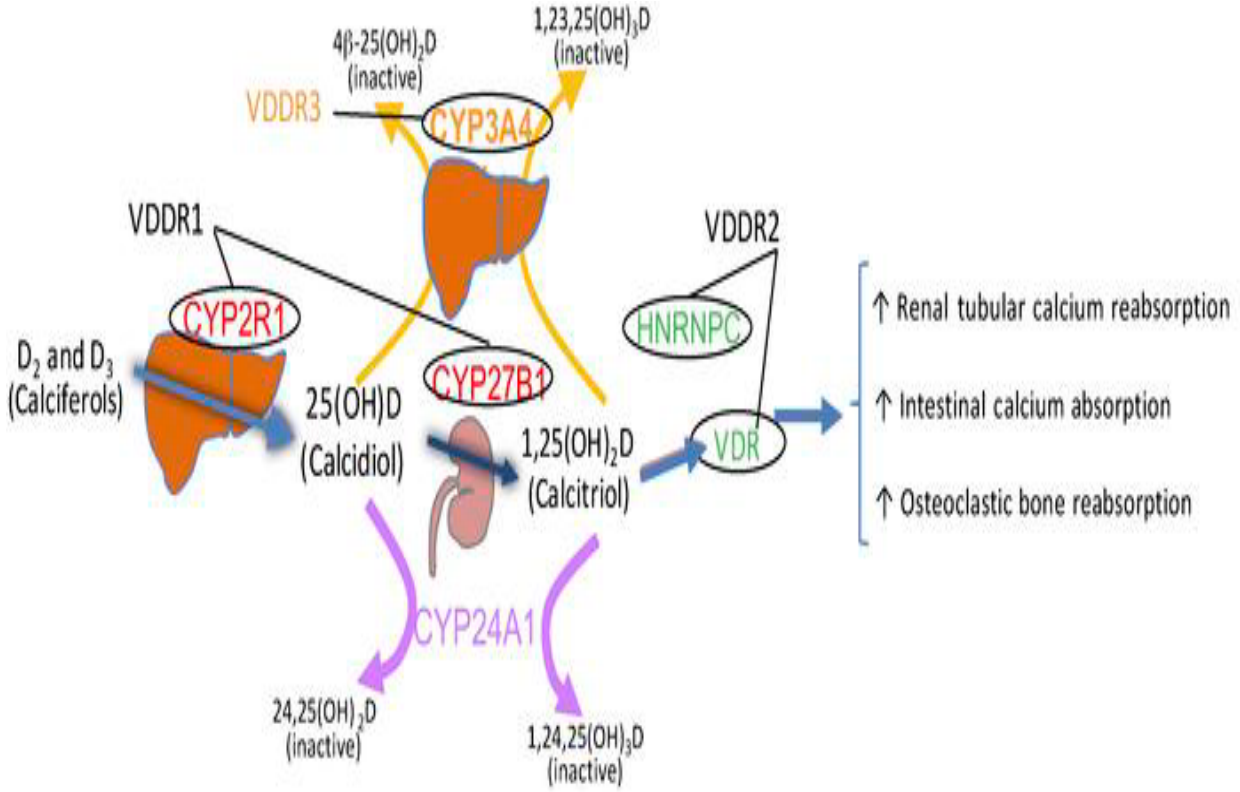
Bajpai A, Bardia A, Mantan M, Hari P, Bagga A. Non-azotemic refractory rickets in Indian children. Indian Pediatr. 2005 Jan;42(1):23-30

Vitamin D dependent rickets

Introduction

A group of genetic disorders

- characterized by early-onset rickets
- due to the inability to maintain adequate concentrations of active forms of vitamin D or a failure to respond fully to activated vitamin D



Levine MA. Diagnosis and Management of Vitamin D Dependent Rickets. Front Pediatr. 2020 Jun 12;8:315.

J Clin Invest DOI: 10.1172/JCI98680

Genetic/biochemical defect

Type	25(OH)D	$1,25(OH)_2D$	PTH	Inheritance	Gene defect (OMIM)
VDDR1A	N/I	D	I	A.R.	CYP27B1 (264700)
VDDR1B	D	D	I	A.R.	CYP2R1 (600081)
VDDR2A	N/I	N/I	I	A.R.	VDR (277440)
VDDR2B	N/I	N/I	I	A.R.	Unknown (600785)
VDDR3	D	D	I	A.D.	CYP3A4 (124010)

VDDR, vitamin D-dependent rickets, N, normal; I, increased, D, decreased; PTH, parathyroid hormone.

Levine MA. Diagnosis and Management of Vitamin D Dependent Rickets. Front Pediatr. 2020 Jun 12;8:315.

Clinical features

- Onset: age 2-4 months
- First manifestations: hypotonia, irritability, tetany or seizures, and failure to thrive
- Frontal bossing, long-bone deformities, and rib cage abnormalities
- Type I b: phenotype later becomes milder
- Type 2a: 50% have alopecia

Levine MA. Diagnosis and Management of Vitamin D Dependent Rickets. Front Pediatr. 2020 Jun 12;8:315.

Treatment

Suggested calciferol doses for maintenance treatment of patients with VDDR.

	VDDR1A (µg per day)	VDDR1B (µg per day)	VDDR2 (µg per day)	VDDR3 (µg per day)
Vitamin D3 or D2	NI	100–200	125–1,000?*	**1,000 to?**
Calcifediol	NI	**20–50**	20–200*	50 to?
Calcitriol	**0.3–2**	0.3–2	**5–60**‡	1 to?
1α (OH)D	**0.5–3**	0.5–3	**5–60**‡	2 to?

Dose requirements are uncorrected for body weight and are similar in children and adults. In all cases, supplemental calcium is recommended as described in text. The preferred form of calciferol is noted in bold for each disorder. NI, not indicated.

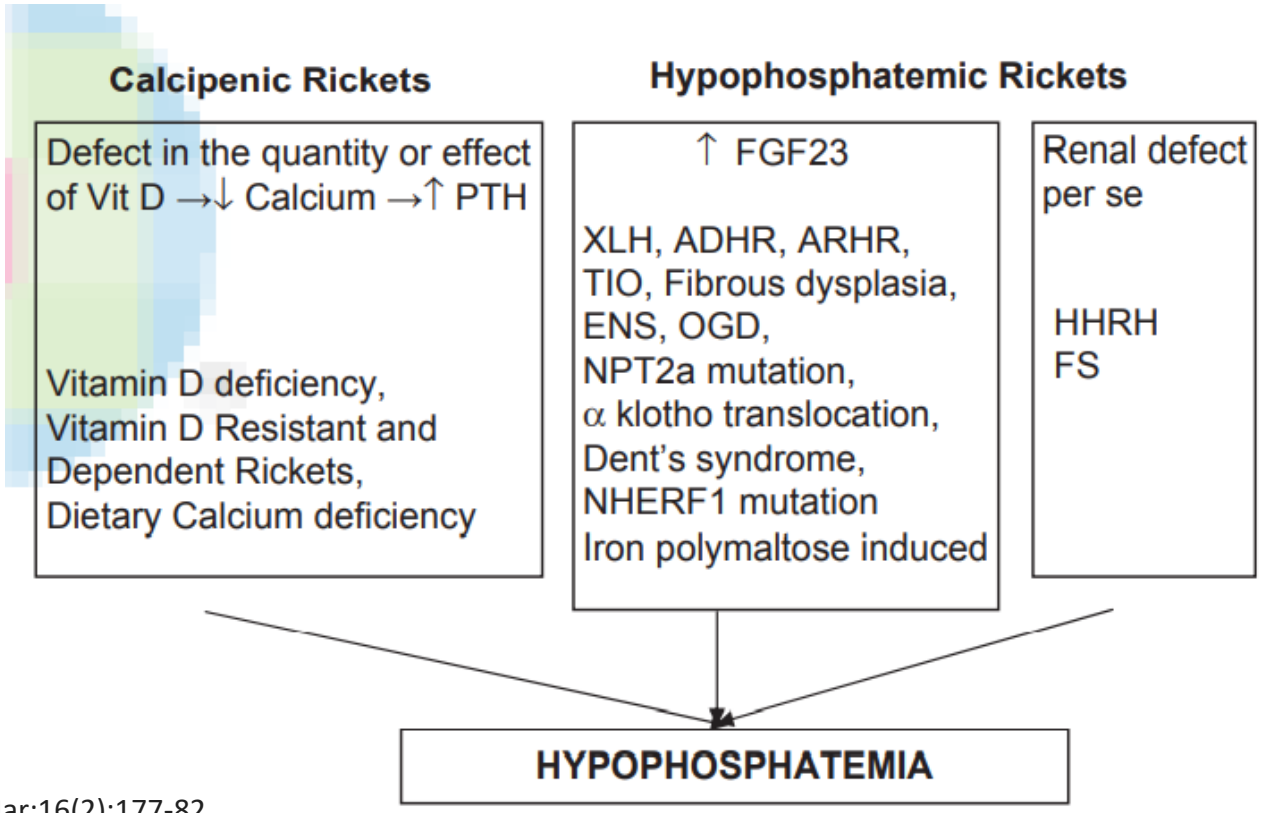
Calcium supplements: 50 mg/kg/day
Patients with VDDR 2 may need IV calcium

Levine MA. Diagnosis and Management of Vitamin D Dependent Rickets. Front Pediatr. 2020 Jun 12;8:315.

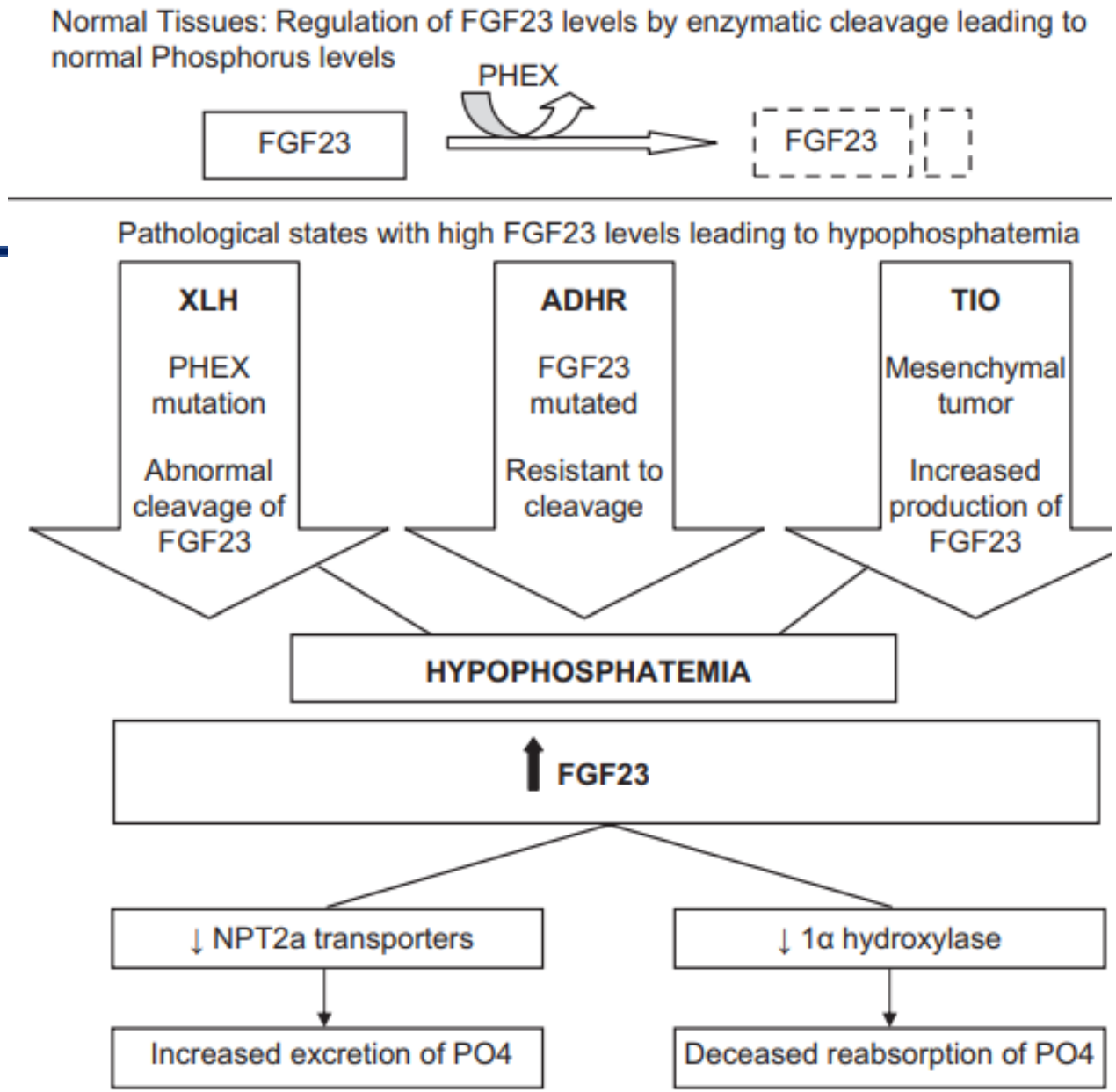
Hypophosphatemic rickets

Introduction

- Most common non-azotemic refractory rickets in Indian children
- Phosphate deficiency is the primary defect
- PTH is usually normal or slightly elevated



Ref:Jagtap VS, et al. Hypophosphatemic rickets. Indian J Endocrinol Metab. 2012 Mar;16(2):177-82



Ref:Jagtap VS, et al. Hypophosphatemic rickets. Indian J Endocrinol Metab. 2012 Mar;16(2):177-82

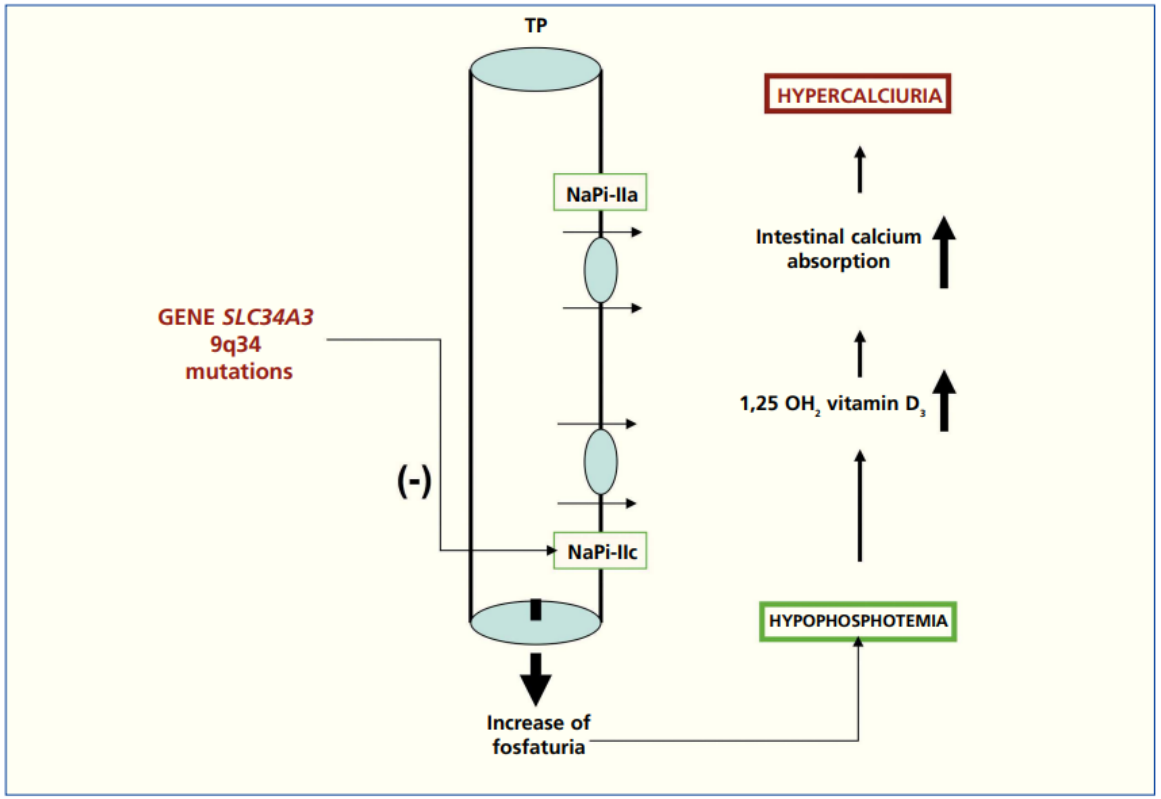
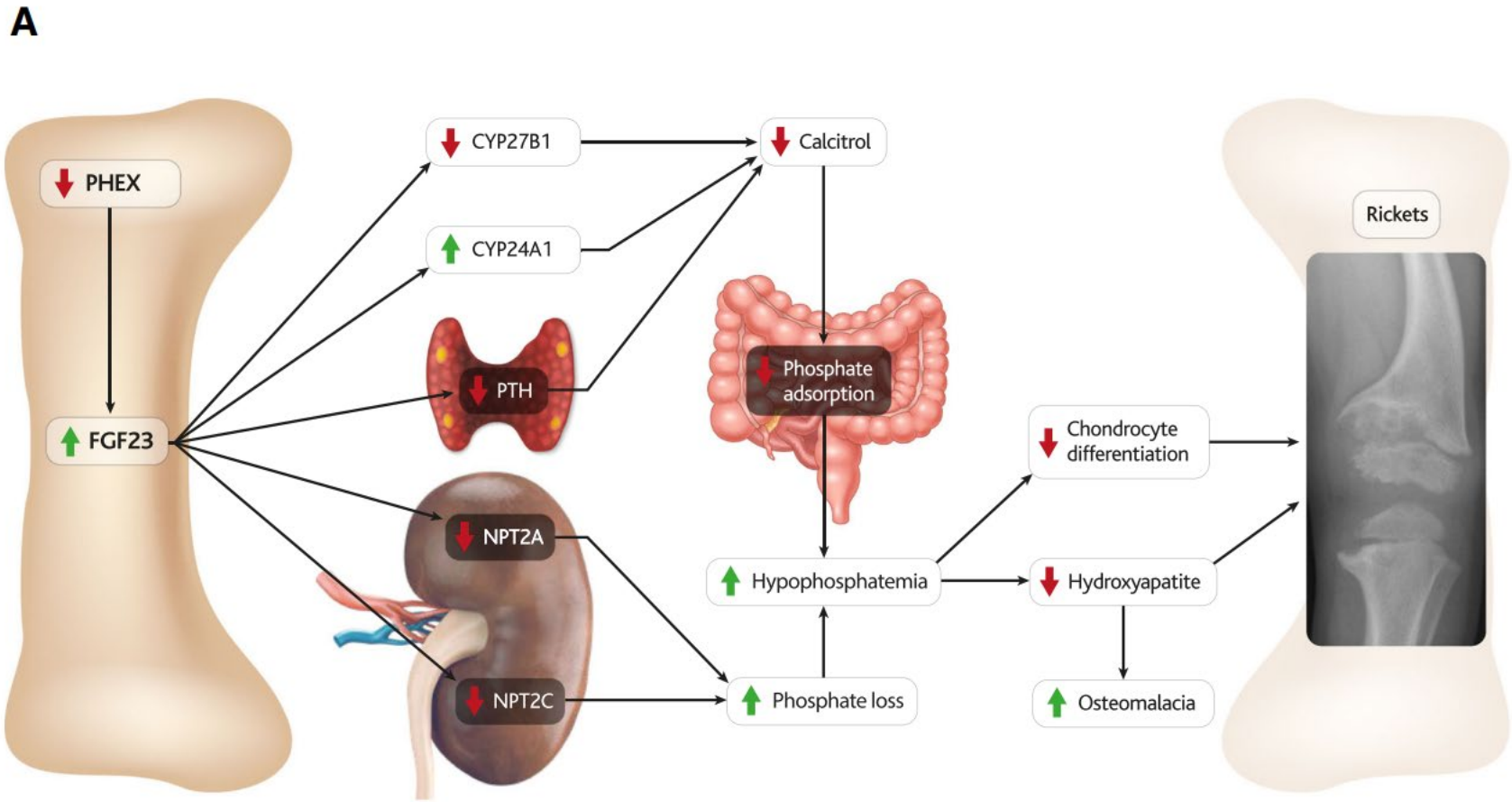


Figure 1. Schematic representation of the reabsorption of phosphorus in the apical membrane of proximal tubule and the biochemical consequences of the mutations with loss of function in the gene *SLC34A3*.

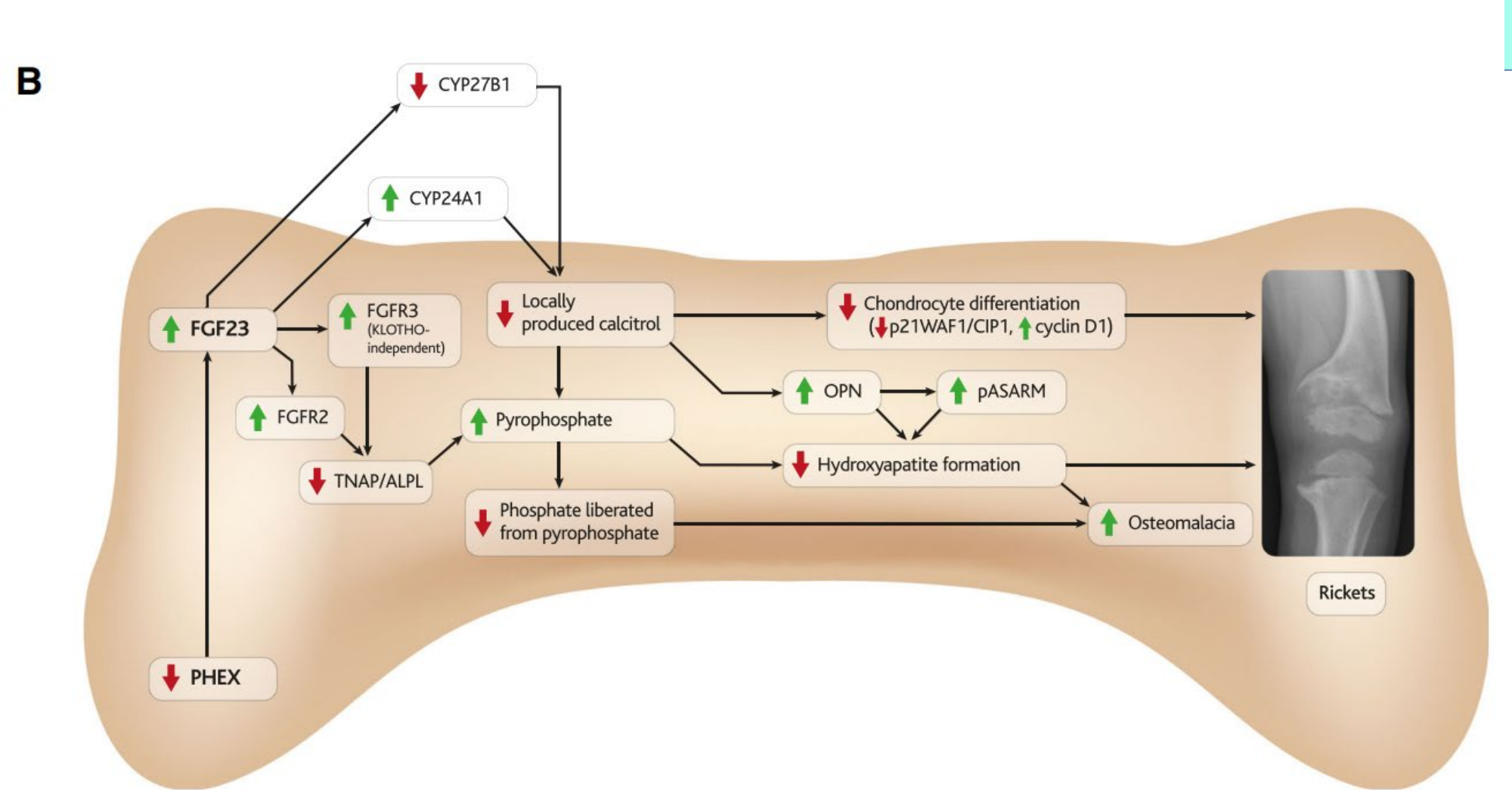
Nefrologia 2012;32(4):529-34

Pathophysiology



Beck-Nielsen et al. Orphanet Journal of Rare Diseases (2019) 14:58

Pathophysiology

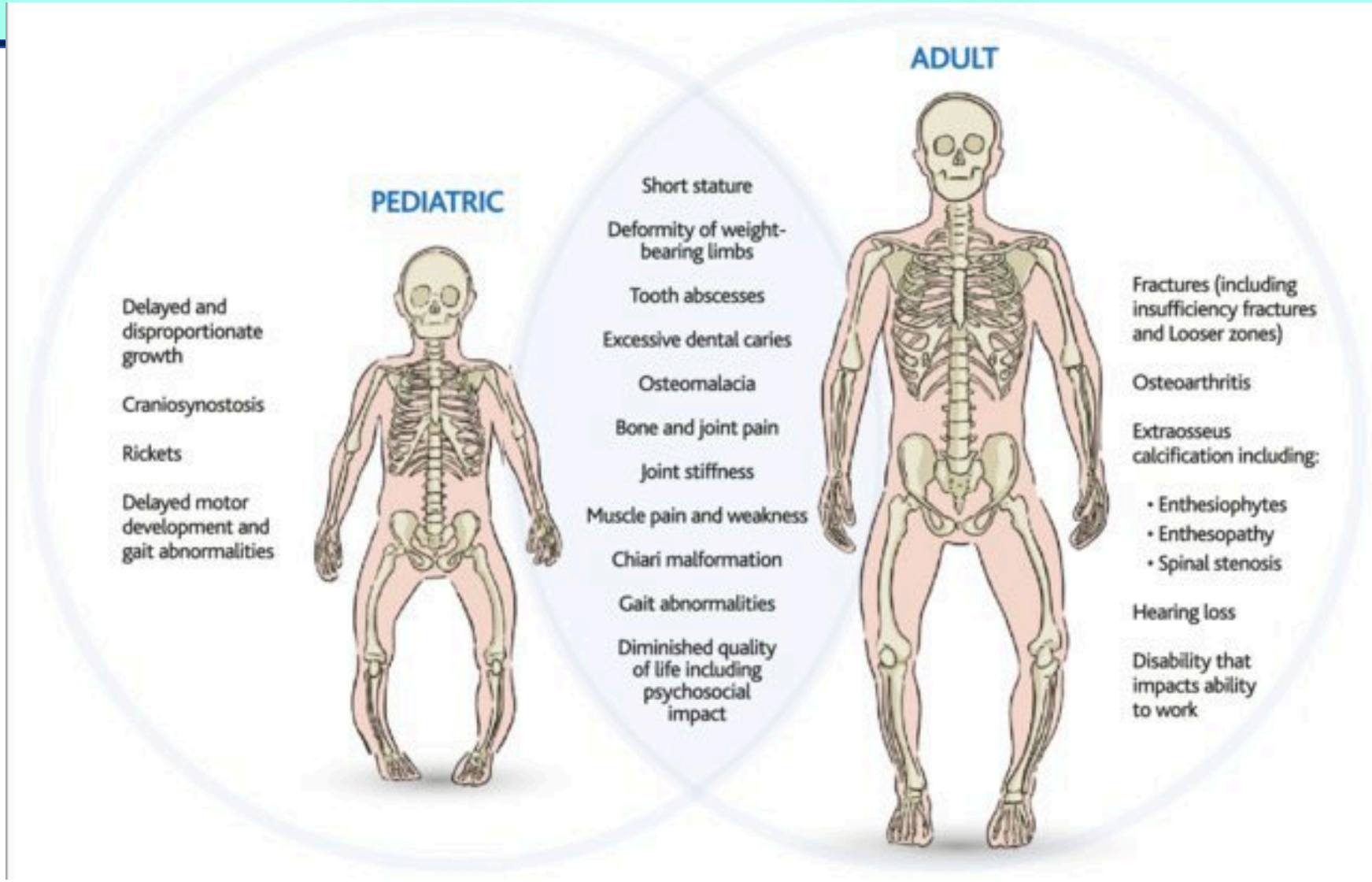


Beck-Nielsen et al. Orphanet Journal of Rare Diseases (2019) 14:58

Table 2: Etiology and biochemistry of hypophosphatemic rickets

	Gene	Mutation	Inheritance	Pathophysiology	FGF23	$1,25(OH)_2D$	Hypercalciuria
Inherited							
XLH	*PHEX*	Loss of fn	XD	*PHEX* normally causes downregulation of FGF23	↑	N or ↓	No
ADHR	*FGF23*	Gain of fn	AD	Mutant *FGF23* is proteolysis resistant	↑	N or ↓	No
ARHR	*DMP1*	Loss of fn	AR	Loss of *DMP1* impairs osteocyte maturation and increases FGF23	↑	N or ↓	No
	ENPP1	Loss of fn	AR				
Fibrous dysplasia	*GNAS*	Gain of fn	Somatic	Increased production of FGF23 by dysplastic bone	↑	N or ↓	No
OGD	*FGFR1*	Gain of fn	AD	Increased production of FGF23 by dysplastic bone	↑	N or ↓	No
ENS	*? FGF1*	Not known	Not known	Increased production of FGF23	↑	N or ↓	No
HHRH	*SLC34A3*	Loss of fn	AR	NaPi2C loss results in phosphaturia → stimulates $1,25(OH)_2D$	N or ↓	↑	Yes
NaPi2a Mutation	*NPT2*	Loss of fn	AD	Phosphaturia → stimulates $1,25(OH)_2D$	Not known	↑	Yes
Acquired							
FS	_	_	_	Proximal tubular defect due to multiple myeloma/lymphoma/drugs/heavy metals	Not known	N or ↓ or ↑	Yes/no
TIO	_	_	_	Mesenchymal tumors secrete phosphatonins	↑	↓	No

Clinical features



Clinical features

- 1st manifestation: usually frontal bossing at age 6 months
- Craniotabes & rachitic rosary are uncommon
- Progressive lower limb deformities as child starts walking
- Disproportionate short stature with short limbs
- Lower limbs: genu varum, genu valgum, coxa vara
- Dental: abscessed noncarious teeth, enamel defects, enlarged pulp chambers and taurodontium
- Adults: short stature, bone pains, pseudofractures, and enthesopathy
- Workup: low serum phosphorus, normal calcium, normal or slightly elevated PTH, and decreased TMP/GFR

TMP/GFR

1. Overnight fast
2. The first voided urine should be discarded.
3. Collect a 25 ml sample of the second void urine into a universal container for urine creatinine and phosphate
4. Send with serum electrolytes and phosphate

$$FePO_4 = \frac{U\ PO_4}{S\ PO_4} \times \frac{S\ creat}{U\ creat}$$

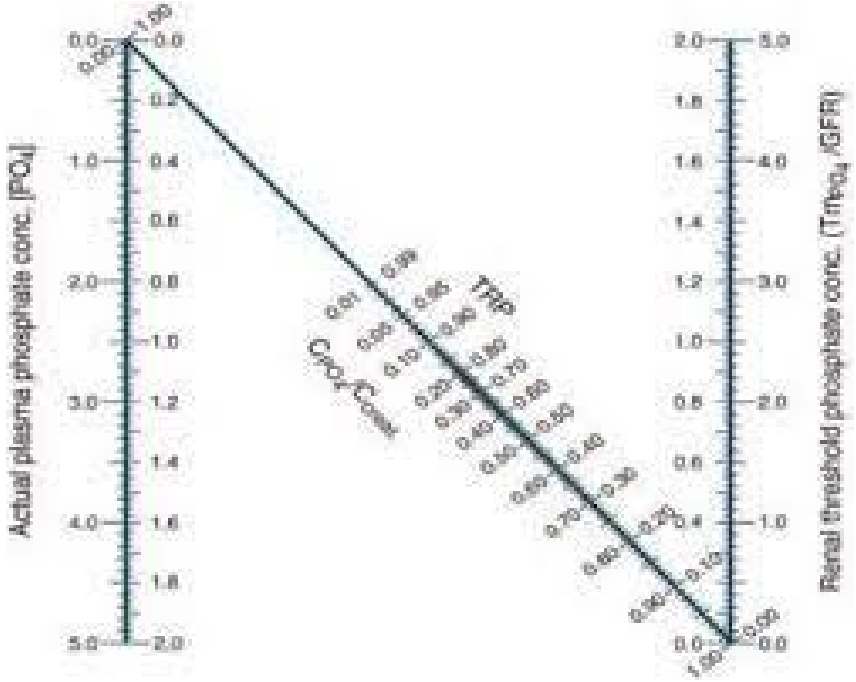
$$TRP = 1 - FePO_4$$

If TRP ≤ 0.86,
TMP/GFR = TRP X S PO_4

If TRP > 0.86
TMP/GFR = α X S PO_4

where

$$\alpha = \frac{0.3 \times TRP}{1 - (0.8 \times TRP)}$$



Management

- Requires therapy from diagnosis till growth is complete
- Calcitriol: 20-30 ng/kg/day in divided doses; may be increased
- Elemental phosphorus: 20-40 mg/kg/day (in 3-5 divided doses); titrated to effect
- Target serum PO_4: closer to lower end of normal – not to normalize
- Monitor Ca/PO4/alk PO4 ase/urine spot Ca/Cr ratio – 3 monthly, PTH & USG KUB– annually
- Correct iron deficiency since it increases FGF23 levels
- Monitor for skeletal abnormalities; may need corrective surgery
- Growth hormone therapy: once metabolic control is optimal

Burosumab

Mechanism of action

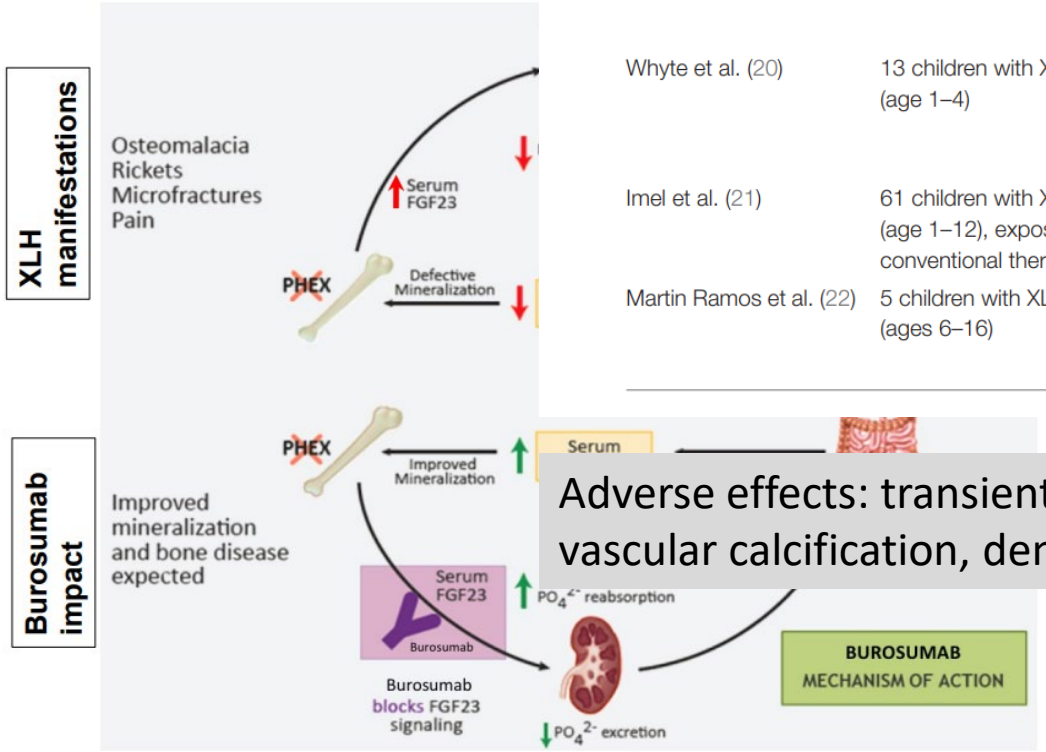


TABLE 2 | Pediatric clinical trials involving burosumab for XLH.

References	Cohort	Phase	Study design	Burosumab dose/administration	Outcomes
Carpenter et al. (19)	52 pediatric XLH patients	II	Open-label trial (dose frequency study)	Dose adjusted to achieve normal serum Pi, given	Therapy increased renal tubular phosphate reabsorption, serum Pi, linear
Whyte et al. (20)	13 children with XLH (age 1–4)	II	Open-label multicen trial (with extension)		
Imel et al. (21)	61 children with XLH (age 1–12), exposed to conventional therapy	III	Randomized trial vs. conventional therapy		
Martin Ramos et al. (22)	5 children with XLH (ages 6–16)	II	Case series		

Adverse effects: transient hypercalcemia, hyperc
vascular calcification, dental abscesses

- Highly recommended in children with XLH >1 year and in adolescents where overt bone disease is being refractory to conventional treatment and/or conventional treatment is causing complications and/or the patient is unable to adhere to the conventional treatment schedule
- Not recommended to be given in conjunction with conventional treatment, or initiated when fasting serum Pi is within the normal reference range, or where severe renal impairment exists

Schindeler A, Biggin A, Munns CF. Clinical Evidence for the Benefits of Burosumab Therapy for X-Linked Hypophosphatemia (XLH) and Other Conditions in Adults and Children. Front Endocrinol (Lausanne). 2020 May 28;11:338.

Other causes of “renal rickets”

Renal tubular acidosis/renal Fanconi syndrome

- Bone as a buffer for acidosis:

  leaching of mineral matrix

- Reduced tubular PO_4 absorption

- Reduced 1 α OH ase activity

Chronic kidney disease

- Nutritional deficiency: anorexia, malabsorption, lack of activity/exposure to sunlight

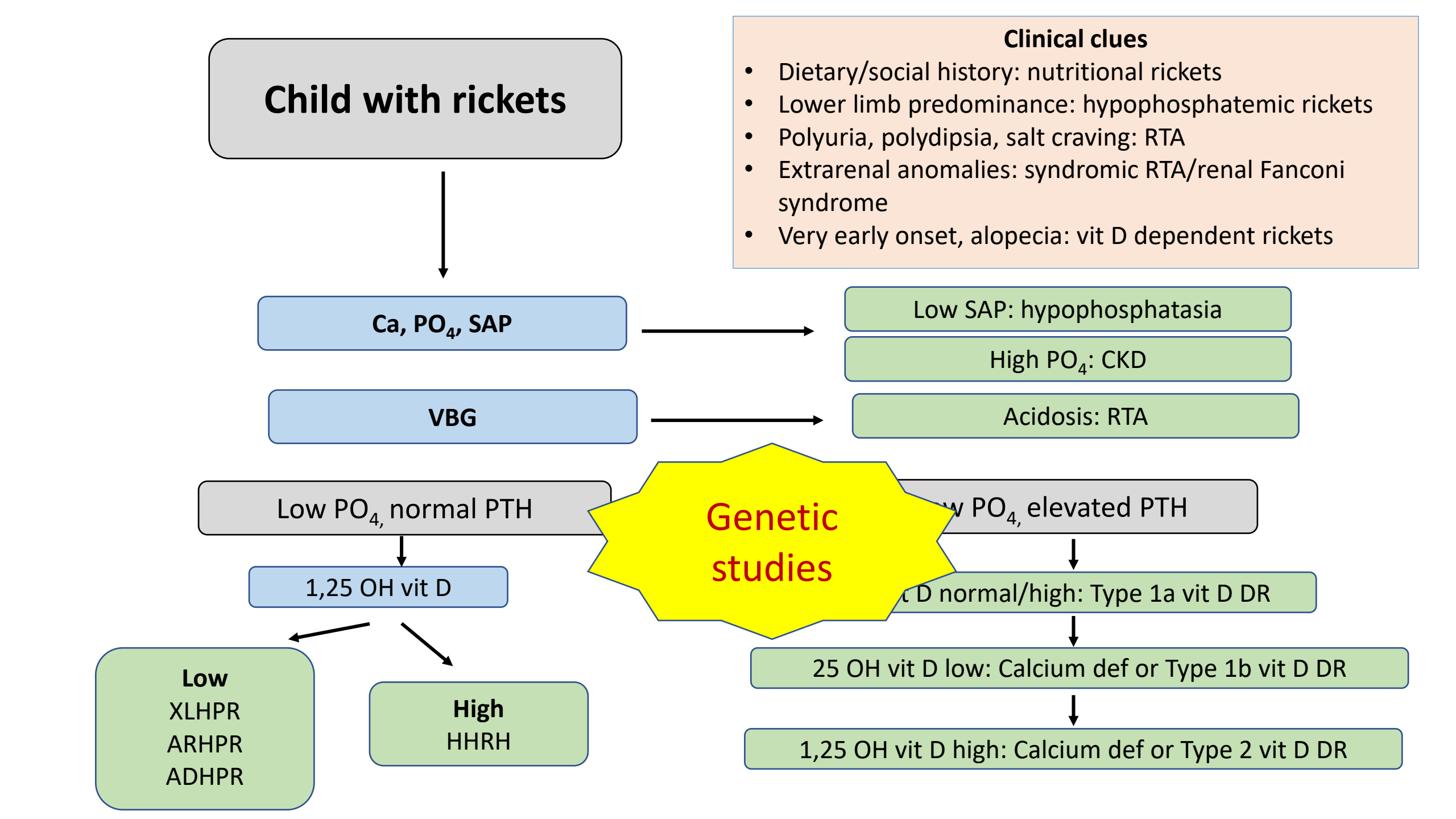
- Reduced 1 α OH ase activity

Salient biochemical features

Type	Calcium	Phosphorus	Alkaline phosphatase	PTH	25 (OH)D	1,25 $(OH)_2$ D
Calcipenic rickets						
Vitamin D deficiency	↓ or N	↓ or N	↑ or ↑↑	↑	↓	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	↓	↑ or ↑↑	↓ or N	N	↑
X-linked hypophosphatemic rickets	N	↓	↑	N or slightly ↑	N	N or ↓
Autosomal dominant hypophosphatemic rickets	N	↓	↑	N	N	↓
Autosomal recessive hypophosphatemic rickets	N	↓	↑	N	N	↓
Hereditary hypophosphatemic rickets with hypercalciuria	N	↓	↑	N or ↓	N	↑

25 (OH)D, 25-hydroxy vitamin D; 1,25 (OH)2 D, 1,25 dihydroxy vitamin D; N, normal levels; PTH, parathyroid hormone; ↑, increased levels; ↓, decreased levels.

Ref: Chanchlani R, et al. An Overview of Rickets in Children. Kidney Int Rep. 2020 Apr 11;5(7):980-990.


Child with rickets
Clinical clues
• Dietary/social history: nutritional rickets
• Lower limb predominance: hypophosphatemic rickets
• Polyuria, polydipsia, salt craving: RTA
• Extrarenal anomalies: syndromic RTA/renal Fanconi syndrome
• Very early onset, alopecia: vit D dependent rickets
Ca, PO4, SAP
Low SAP: hypophosphatasia
High PO4: CKD
VBG
Acidosis: RTA
Low PO4, normal PTH
Genetic studies
w PO4, elevated PTH
1,25 OH vit D
t D normal/high: Type 1a vit D DR
25 OH vit D low: Calcium def or Type 1b vit D DR
1,25 OH vit D high: Calcium def or Type 2 vit D DR
Low
XLHPR
ARHPR
ADHPR
High
HHRH

To sum up

- Rickets: a condition characterized by a defect in mineralization of the epiphyseal plates
- Diagnosis: clinical and lab findings; **confirmed on X Rays**
- Calcipenic vs phosphopenic – phosphopenia is a common factor
- Nutritional rickets: most common – diagnose and treat as per guidelines
- Refractory rickets: rule out CKD and RTA first
- Phosphopenic rickets: FGF23 overactivity vs HHRH based on 1,25 OH vit D; treatment – phosphate, active vit D & GH vs burosumab
- Calcipenic rickets: vit D def vs vit D dependent rickets

Thank you

Command Hospital (Eastern Command), Kolkata

Renal Tubular Acidosis

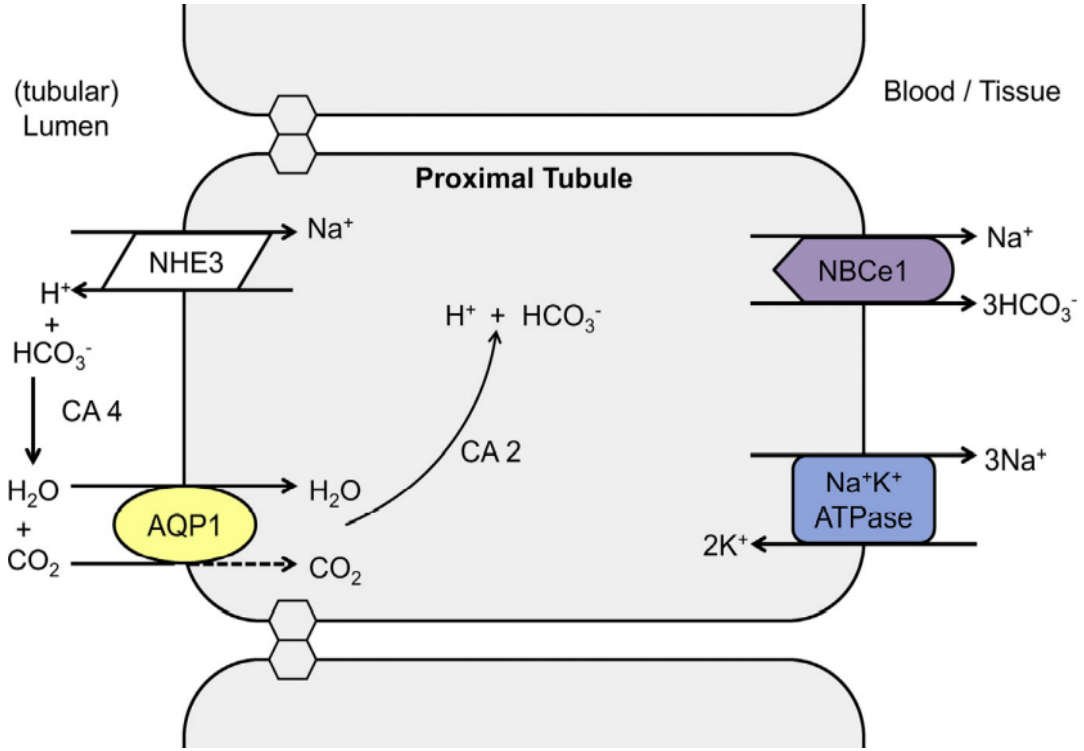
Dr Girish Chandra Bhatt, MD, FASN, FISN
Associate Professor, ISN-SRC, Pediatric Nephrology
Department of Pediatrics, AIIMS, Bhopal

Overview of the Talk

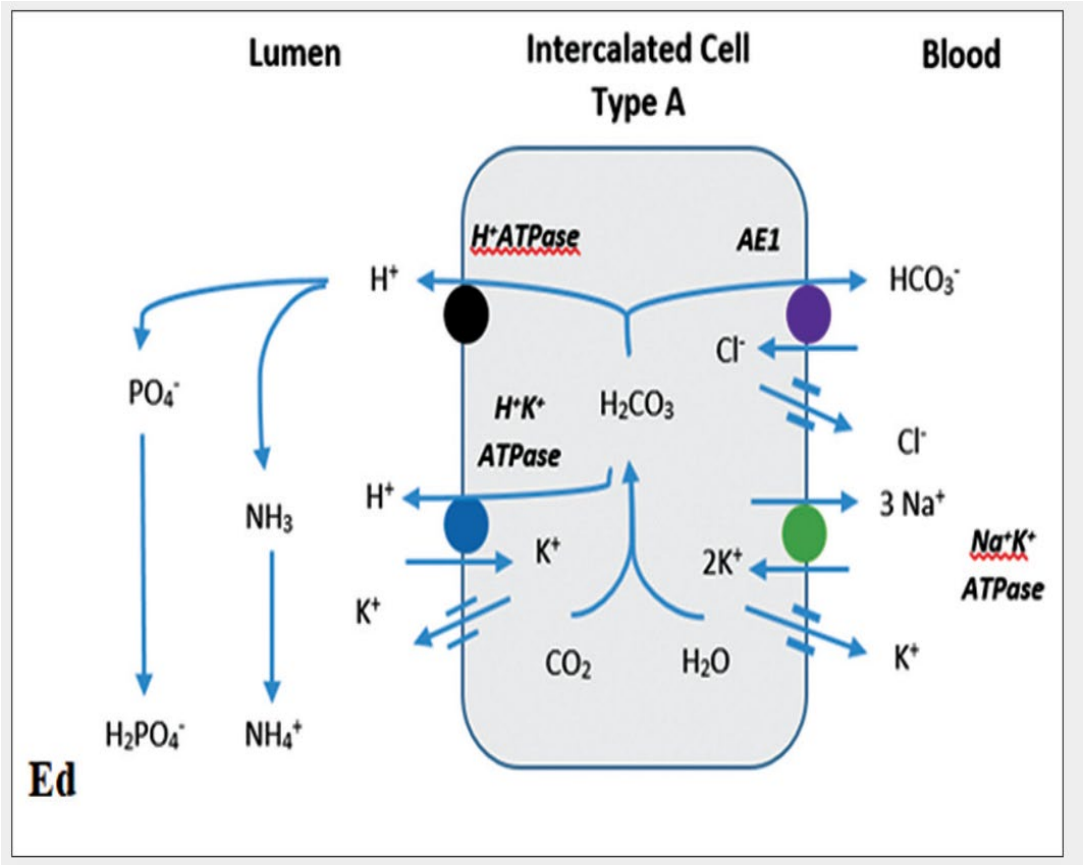
- Acid Base Homeostasis
- Classification and approach to renal tubular acidosis
- Functional tests & Genetics
- Interesting case discussions

Acid Base Homeostasis

Bicarbonate absorption in proximal tubule



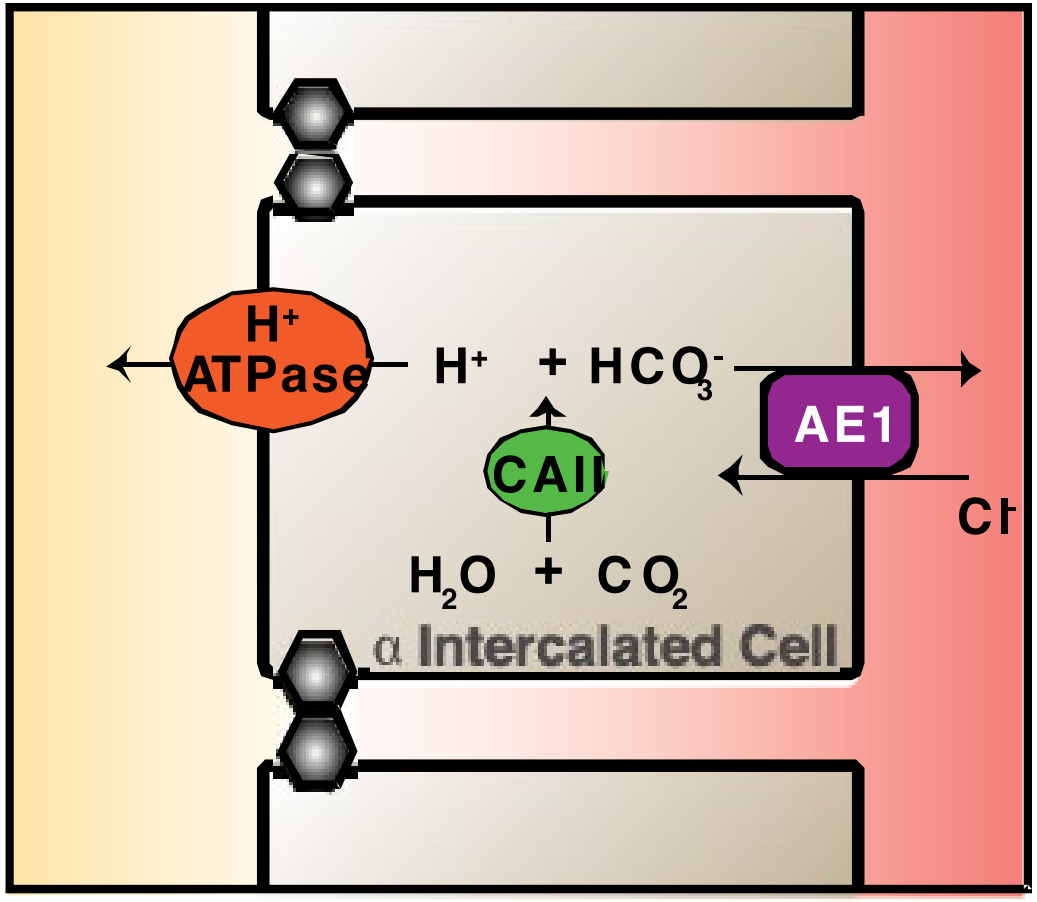
Distal urinary Acidification



Comprehensive Pediatric Nephrology 2016

Distal Renal Tubular Acidosis: Etiology – Genetic

Gene	Protein
ATPV0A4	H^+ATPase, a4 subunit
ATPV1B1	H^+ATPase, b1 subunit
SLC4A1	Anion exchanger 1 (AE1)
CA2	Carbonic anhydrase II (CAII)* but causes mixed RTA
WDR72	**Tryptophan-aspartate repeat domain 72**



Nomenclature

	Name	Segment Affected	Physiology
Type 1	Distal renal tubular acidosis (dRTA)	Distal nephron, predominantly collecting duct	Failure to secrete H^+
Type 2	Proximal renal tubular acidosis (pRTA)	Proximal tubule	Failure to reabsorb bicarbonate (HCO_3^-)
Type 3	Mixed (proximal & distal renal tubular acidosis)	Both proximal tubule and collecting duct	Failure to secrete H^+ and reabsorb HCO_3^-
Type 4	Hyperkalemic renal tubular acidosis	Collecting duct	Hypoaldosteronism

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Historical perspectives

Bruce etal
- Hetrogygous mutation SLC4A1

T Cohen: Nerve deafness and dRTA
- Autosomal recessive inheritance

Pins KL: RTA with osteomalacia (3 cases)
- Designated as dRTA

Lightwood R: Calcium infarction of kidney
- Autopsy of 6 infants
- Deposition of Ca salt in tubules
- FTT, constipation, anorexia

Aetiology of dRTA

- Primary dRTA
  - Genetic abnormalities of the apical H+ ATPase unit
  - Variants of the gene encoding the (basolateral) anion exchanger 1 (AE1)
  - Variants of the gene encoding the cytosolic carbonic anhydrase 2
- Autoimmune
- Nephrotoxic medications
- Hypercalciuria/nephrocalcinosis
- Tubular interstitial disease

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Distal Renal Tubular Acidosis:Etiology – nongenetic

Autoimmune	**Drug Induced**	**Miscellaneous**
Sjorgren syndrome	Amphotericin B	Sickle cell disease
Thyroiditis	Cyclamate	Marfan syndrome
HIV-nephropathy	Vanadate	Ehlers-Danlos syndrome
Chronic active hepatitis	Ifosphamide	
Polyarthritis nodosa	Toluene	
cryoglobulinemia	Mecury	
Primary Bilary cirrhosis	Lithium	
	Foscarnate	

Proximal Renal Tubular Acidosis - Etiology

Genetic	Drugs	Miscellaneous
Cystinosis	Nucleoside reverse transcriptase inhibitors: Tenofovir, adefovir	Amyloidosis
Dent's disease	Nucleoside analogs: Didanosine, lamivudine, stavudine	Heavy Metals (Pb, Hg, Cd)
Hereditary fructose intolerance	Chemotherapeutics: Ifosphamide, cisplatin	Post renal transplant
Lowe syndrome (OCRL1)	Anticonvulsants: valproic acid	Tubulointerstitial nephritis
Mitocondrial disease	Antibiotics: aminoglycosides	Vitamin D deficiency
Tyrosinemia	Antiparasitics: Sumarin	Membranous
Wilson's Disease	Antivirals: cidofovir	Multiple myloma
SLC4A4 (NBCe1) (Glaucoma, cataracts, band Keratopathy)	Other: fumaric acid, paraquat	Paroxysmal nocturia

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Clinical presentation & Biochemical tests

Clinical features

- Failure to thrive
- Polyuria/Polydipsia
- Vomiting
- Bony deformities
- Sensorineural hearing loss
- Paralysis
- Anaemia

Biochemical tests

- Blood gas
- Urinary anion gap
- Serum electrolytes
- Provocative tests
  - FeHCo3
  - NH4Cl test
  - Furosemide tests

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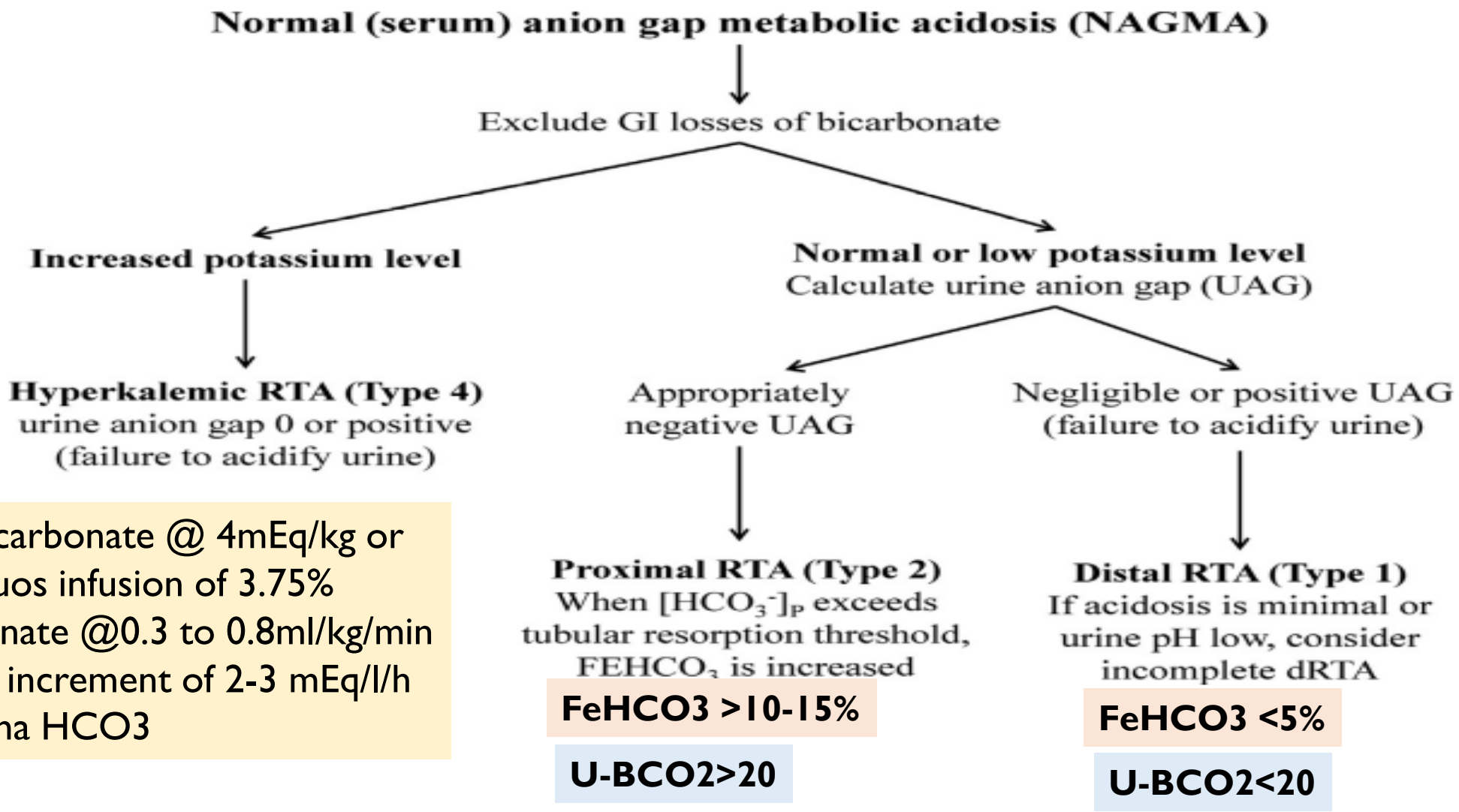
Biochemical tests for diagnosis of dRTA

- Hyperchloremic normal anion gap metabolic acidosis
- Urinary anion gap
  - Valid for NAGMA
  - $Na^+ + K^+ - Cl^-$
  - NH4+ constitutes the major urine cation, and its excretion is accompanied by chloride as $NH4^+Cl^-$
  - Distal RTA: Positive or negligible UAG
  - Proximal: Negative UAG

Alexander et al. Pediatr Clin North America 66 (2019) 135–157

Diagnostic Approach



Oral bicarbonate @ 4mEq/kg or
Continuos infusion of 3.75% bicarbonate @0.3 to 0.8ml/kg/min to have increment of 2-3 mEq/l/h of plasma HCO3

FeHCO3 >10-15%

U-BCO2>20

FeHCO3 <5%

U-BCO2<20

FeHCo3=(uHCO3 x sCr) / (sHCO3 x uCr)

Alexander et al. Pediatr Clin North America 66 (2019) 135–157

Test for phosphate Handling

- Plasma phosphate levels indicates proximal tubular function
- Fractional excretion of phosphate determined on a timed (6-h, 12-h, 24-h) urine specimen for phosphate wasting (Fanconi syndrome)
- Normally 5–12% of the ultrafiltered phosphate is excreted and the tubular reab- sorption is 88–95%.

$$FePO4=(uPO4 \times sCr) / (sPO4 \times uCr)$$

- Tubular reabsorption
  - Plasma phosphate and GFR
- Tubular maximum for phosphate, corrected for GFR (TmP/GFR) or

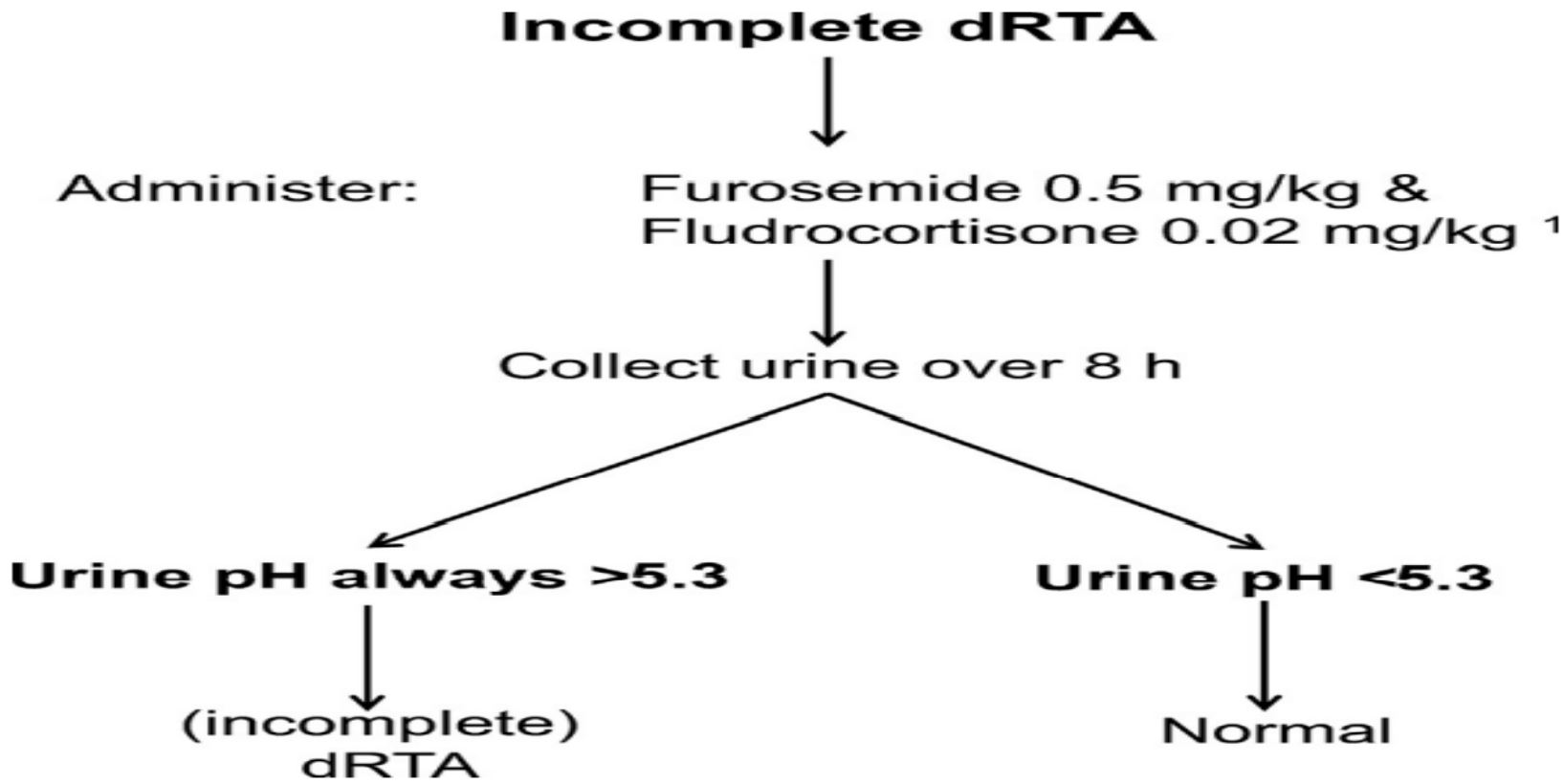
Bijvoet's index is used.

- The normal value of TmP/GFR is 2.8– 4.4 mg/dl, with lower values in older children.

Bagga A, Sinha A. Renal Tubular Acidosis. Indian J Pediatr. 2020 Sep;87(9):733-744

Diagnostic approach for incomplete dRTA

- Suspected when patient have mild metabolic acidosis and near normal $HCO3^-$



Alexander et al. Pediatr Clin North America 66 (2019) 135–157

Combined RTA /Type 3

- Rare form of autosomal recessive RTA
- Combines features of both type 1 and type 2 RTA
- Manifestations:
  - *Oteopetrosis, cerebral calcifications, nephrocalcinosis*
  - *Facial dysmorphism (hypertelorism, low set ears, and a depressed nasal bridge),*
  - *Conductive hearing loss and cognitive impairment*
- *Mutation in CA2*

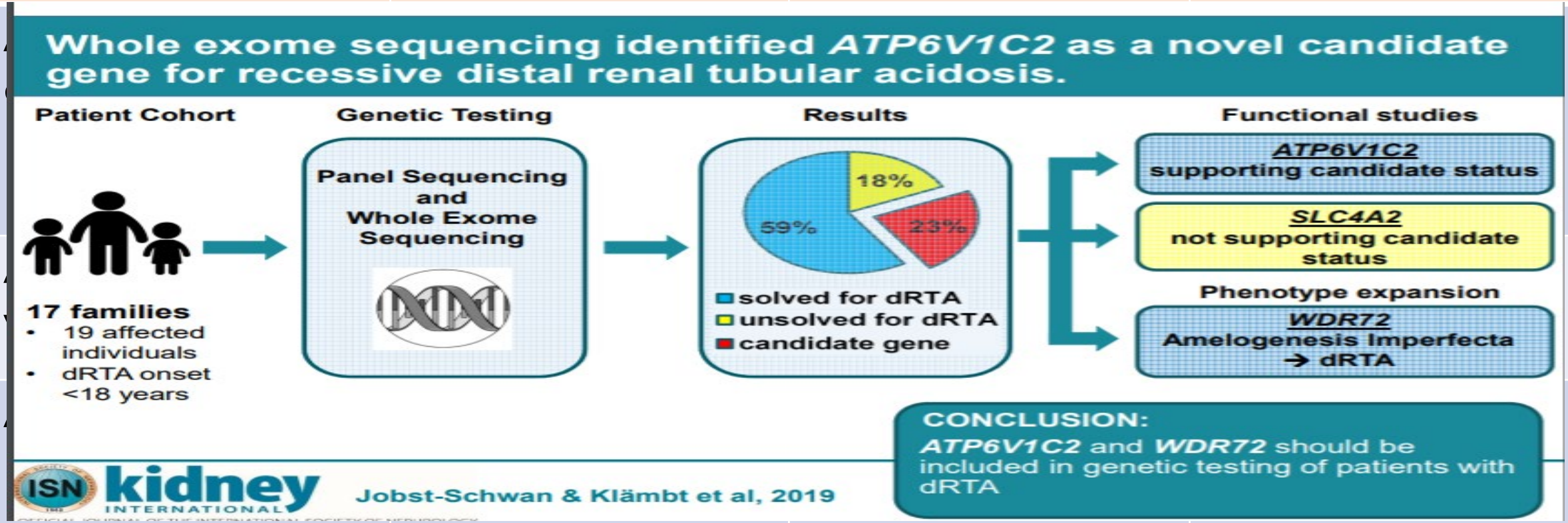
Renal tubular acidosis with hyperkalemia/Type 4

- High normal potassium with NAGMA
- The primary abnormality is actual or effective hypoaldosteronism resulting in sodium loss from the collecting duct
- Hyperkalemia occurs because *potassium and proton secretion in the collecting duct is coupled in this part of the nephron to sodium reabsorption*
- Genetic forms of hyperkalemic (type 4) RTA are known as pseudo-hypoaldosteronism

J Am Soc Nephrol 2009;20(2):251-4.

Genetics

Syndrome	Clinical features	Locus Symbol	Gene Product



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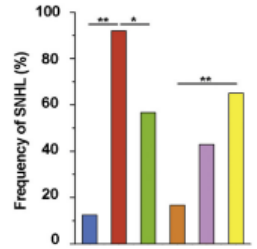
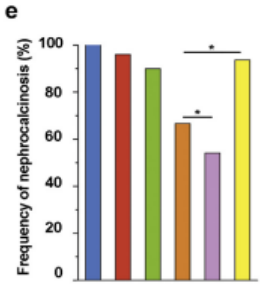
Genotype-phenotype correlation

a

c



e



	SLC4A1	*ATP6V1B1*	*ATP6V0A4*	Variants of unknown clinical significance	Negative	Mutated
M/F, no. (%)	4/9 (44.4)	13/25 (52)	14/30 (46.6)	5/7 (71.4)	7/18 (38.9)	31/64 (48.4)
Age at onset of dRTA, mo	153.2	13.9	28.6	47.6	131.1	65.2
SNHL, no. (%)	1/8 (12.5)	23/25 (92)	17/30 (56.7)	3/7 (42.9)	3/18 (16.7)	41/63 (65)
Age at onset of SNHL, mo	240	41.8	183.5	168	198.7	155.1
Nephrocalcinosis, no. (%)	8/8 (100)	24/25 (96)	27/30 (90)	4/7 (57.1)	12/18 (66.6)	59/63 (93.6)
FTT, no. (%)	4/8(50)	19/24 (79.1)	23/30 (76.6)	5/6 (83.3)	2/21 (9.5)	46/62(74.2)
Hypokalemia, no. (%)	3/9 (33.3)	15/25 (60)	15/25 (60)	3/6(50)	3/17(17.6)	33/59 (55.9)
CKD		16/51 (31.3)		2/7 (28.6)	5/14 (35.7)	16/51 (31.3)

Pallazio et al Kidney International (2017) 91, 1243-1255

Observations from cohort

- Most cases of dRTA are "sporadic" (>70%), although genetically transmitted, deriving from homozygous or compound heterozygous mutations, with a single family member affected
- Mutations in the ATP6V0A4 gene are quite as frequent as mutations in the ATP6V1B1 gene in patients with AR dRTA
- The association of dRTA with early SNHL is not an absolute indicator of the underlying causal gene
- CKD is more frequent than reported thus far and can occur in patients with a long history of the disease.

Pallazio et al Kidney International (2017) 91, 1243-1255

Original Article | Published: 10 January 2022

Whole-exome sequencing and variant spectrum in children with suspected inherited renal tubular disorder: the East India Tubulopathy Gene Study

Rajiv Sinha, Subal Pradhan, Sushmita Banerjee, Afsana Jahan, Shakil Akhtar, Amitava Pahari, Sumantra Raut, Prince Parakh, Surupa Basu, Priyanka Srivastava, Snehamayee Nayak, S. G. Thenral, V. Ramprasad, Emma Ashton, Detlef Bockenhauer & Kausik Mandal

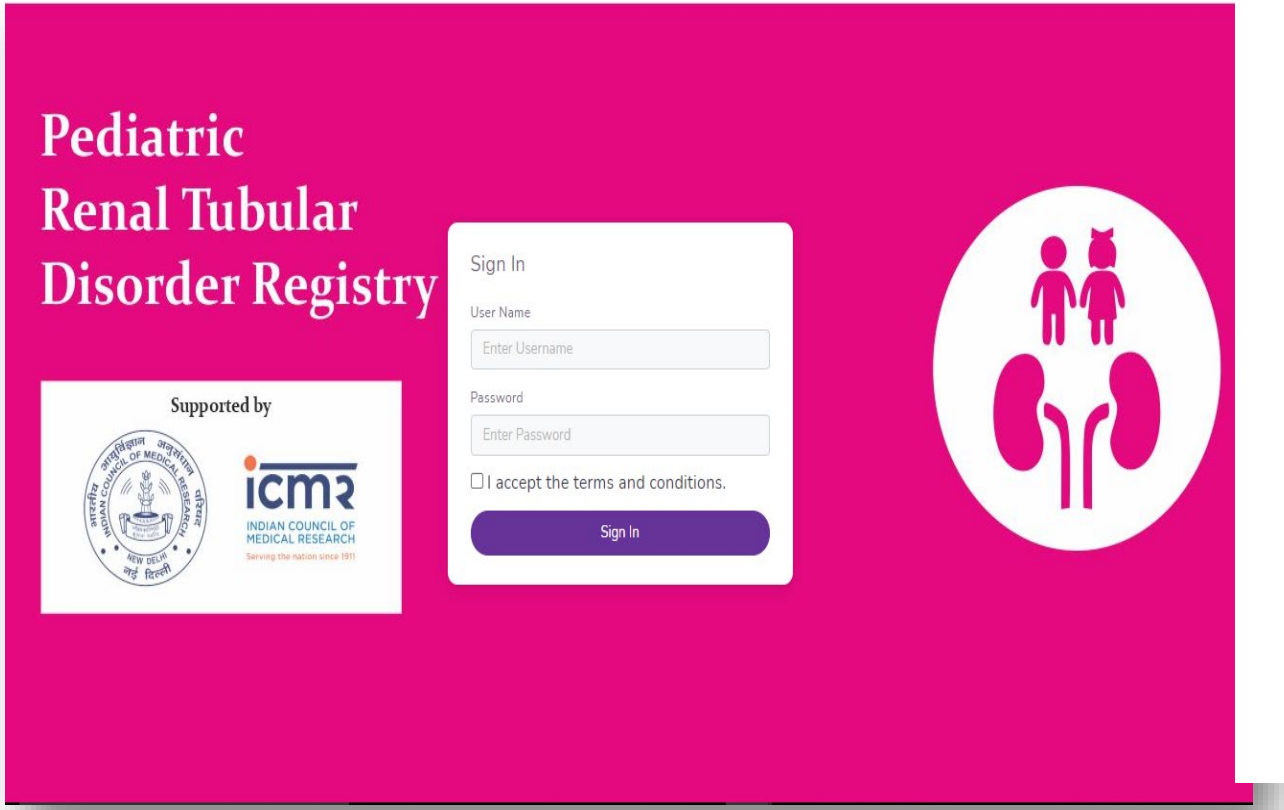
Pediatric Nephrology 37, 1811–1836 (2022) | Cite this article
624 Accesses | 3 Citations | 8 Altmetric | Metrics

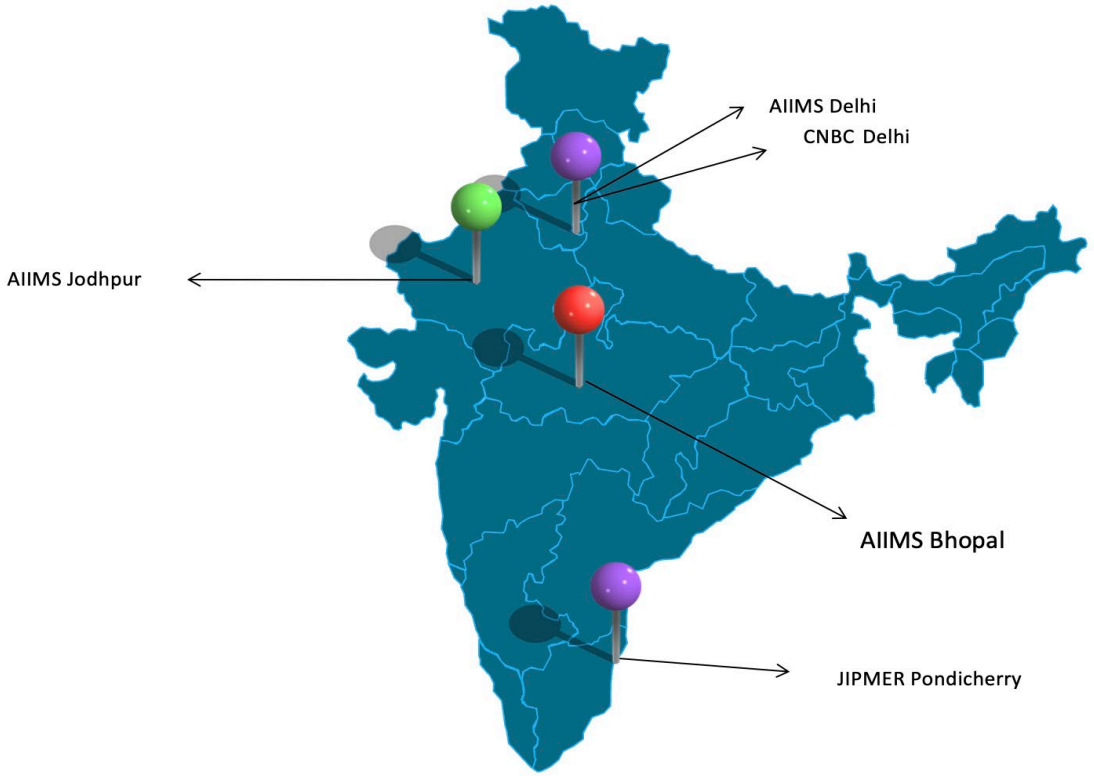
Distal RTA (n=25; yield 64%)		Proximal RTA / Fanconi syndrome (n=12; yield 75%)	
Genes	**No of pathogenic variants**	**Genes**	**No of pathogenic variants**
ATP6V1B1	4	OCRL	1 (Lowe's)
ATP6V0A4	5	SLC2A2	2(Fanconi Bickel syndrome)
WDR72	1	CTNS	4 (Nephropathic cystinosis)
SLC4A1	6	FAH	2(Tyrosinemia type I)

ICMR Task Force On Rare Disease
(Renal Tubular Disorders)

For Login In Indian Pediatrics Renal Tubular Disorders Registry link are given below:-
http://indiantubulopathyregistry.com

Online registry portal was developed for data entry from all centers across India





Variations found on genetic analysis

Distal RTA (n=51; yield:63%)		Proximal RTA / Fanconi (n=14; yield:64%)	
Genes	**No of pathogenic variants**	**Genes**	**No of pathogenic variants**
ATP6V1B1	8 (3 hearing impairment; 2 nephrocalcinosis)	OCRL	2 (Lowe's)
ATP6V0A4	6 (5 hearing loss; 2 nephrocalcinosis)	ABHD5	1 (Chanarin-Dorfman syndrome)
WDR72	6 (6 with ameliogenesis imperfecta; 2 nephrocalcinosis)	CTNS	6 (Nephropathic cystinosis)
SLC4A1	18 (15 nephrocal-cinosis and 3 with ovalocytosis)	FAH	1(Tyrosinemia type I)

International Pediatric nephrology Congress 2022

Summary of genetic **causes**

Protein	Gene	Inheritance	Typical clinical features	Type of RTA
NBCe1	SLC4A4	AR	Glaucoma, cataracts, band keratopathy	pRTA
AE1	*SLC4A1*	AD/AR	Nephrocalcinosis, osteomalacia, rarely hemolytic anemia	dRTA
b1 subunit of the H1ATPase	ATP6V1B1	AR	Sensorineural hearing loss, nephrocalcinosis or nephrolithiasis	dRTA
a4 subunit of the H1ATPase	ATP6V0A4	AR	Late-onset sensorineural hearing loss, nephrocalcinosis or nephrolithiasis	dRTA
CA2	CA2	AR	Osteopetrosis	*Combined RTA (type 3)*

Alexander et al. Pediatr Clin North America 66 (2019) 135-157

Treatment

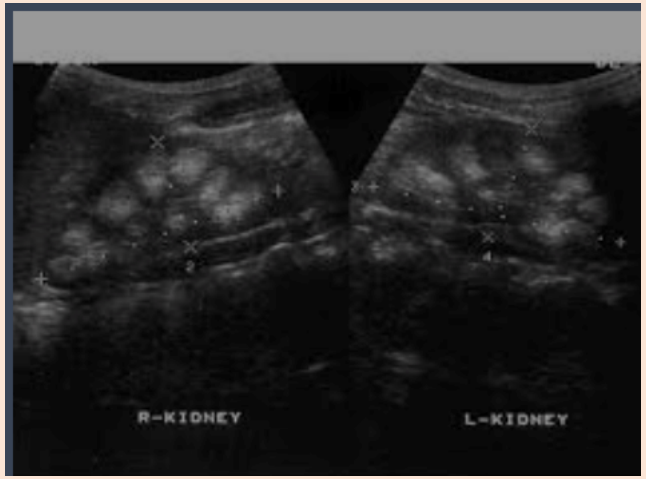
- Alkali supplementation to target HCO3 of >20 mEq/ L in infants; >22 mEq/L in older children
- Potassium-citrate based alkalizers are preferred
- Infants@5-6 meq/day; 3-4 meq/ day @5-6 years and 1-2meq/day in adults for dRTA
- Proximal RTA/Fanconi syndrome
  - Requires high dosage of alkali@5-20meq/day and potassium suppplemenation@2-5 meq/day
  - Fanconi syndrome: Phosphate (40–80 mg/kg/d) sachets or tablets containing 250 or 500 mg phosphorus.

Bagga A, Sinha A. Renal Tubular Acidosis. Indian J Pediatr. 2020 Sep;87(9):733-744

Case 1

- 7 years old male child presented with rickets and failure to thrive
- He was found to have polyuria/polydipsia and bony deformities
- The blood gas showed pH-7.2; HCO3 of 12; K+=3.1; AG=12; PTH:458(increased); Cl-=117

- UAG=10; FeHCO3=3%;
- Ultrasonography?
- Diagnosis?



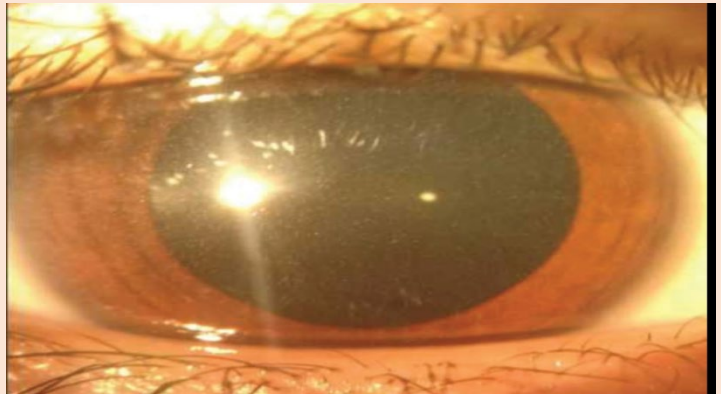
- Distal Renal tubular disorder
- Genetic testing: ATP6V1B1
- Alkalizer @2 meq/day (Always correct potassium before initiating bicarbonate to decrease the reflex hypokalemia)
- SNHL hearing loss: reverse phenotyping

Case 2

- A 3-year-old male child presented with complaints of poor weight gain, delayed motor milestones since 1 year of age and features suggestive of rickets (wrist widening, bowing of legs and Harrison's sulcus
- He was third born of a third degree consanguineous marriage
- PH=7.19; HCO3=8; K+=2.1; UAG=8; Cl-=112; PO4=2.1; Ca=8.2
- FeHO3=30%; TRP=15%; FePO4=85%; TMP/GFR=1.4

The next step would be

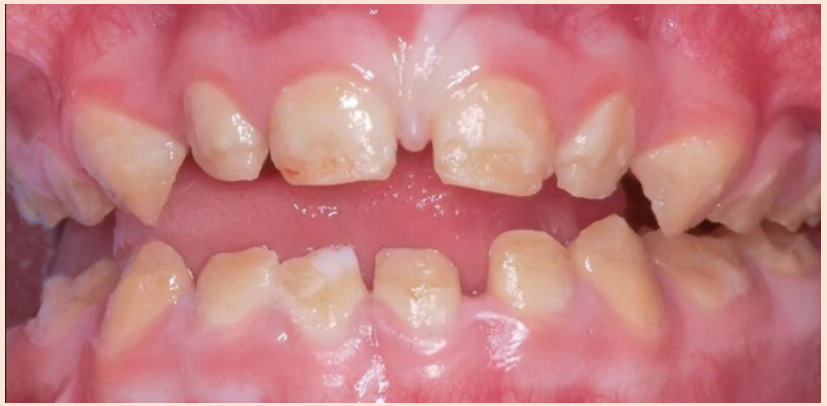
- Aminoaciduria; glucosuria was present
- Eye evaluation?



- Fanconi syndrome
- Genetic testing: Compound heterozygous mutation in CTNS gene
- Segregation analysis confirmed pathogenic variation
- Alkalizer @10 meq/day (Always correct sodium before initiating bicarbonate to decrease the reflex hypokalemia); Cysteamine

Case 3

- 4 year old female child presented with short stature,rickets, polyuria and polydipsia
- PH=7.23; HCO3=13; UAG=16; K+=2.9;
- PO4-=2.1; FeCHO3=6%; FePO4=81%
- Dental issues?
- Type of RTA?



- Amelogenesis imperfecta
- dRTA with proximal dysfunction with amelogenesis imperfecta
- Mutation analysis: WDR72 mutation
- WDR72 mutation typically causes dRTA (2013)

Summary

- Suspected in child with FTT wit NAGMA
- Provocative tests
  - Bicarbonate loading
  - Furosemide/Fludrocortisone tests
- Urinary anion gap may help to differentiate type of RTA; Not very useful
- Molecular genetics
  - To establish diagnosis or for picking up the co-morbid conditions (reverse phenotyping)
  - Genetic counselling

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All India Institute of Medical Sciences Bhopal

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Thank You!
Questions??

UTI in children: New ISPN guidelines 2023

Pankaj Hari, MD

Professor, Pediatric Nephrology AIIMS, Delhi

Chair, Best Practices & Standards Committee, International Pediatric Nephrology Association

Overview

- **Guidelines**
  - methodology
- **Diagnosis & therapy of UTI**
- **Imaging after UTI**
- **Recurrent UTI, bladder bowel dysfunction**
- **Vesicoureteric reflux, renal scarring**
    - Surgery/endoscopic treatment
    - Antibiotics prophylaxis, duration
    - Non antimicrobial intervention
- **VUR and ESKD**

Clinical Practice Guidelines

"Systematically developed statements to assist practitioners, patient decision-makers in appropriate healthcare for specific clinical circumstances"

Consensus-based

GOBSAT (*Good old boys sitting around a table*) model

Evidence-based

Systematic search, synthesis of evidence, grading of evidence

Why should guideline change?

Revised Statement on Management of Urinary Tract Infections

INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY Indian Pediatrics 2011

Scheduled review

Changes in evidence

- **Benefit and harms:** **antibiotic prophylaxis**
- **Values and preferences:** **surgery vs. medical treatment of VUR**
- **Resource availability:** **IVP replaced by DMSA scan**

Emergence of new interventions

ISPN guideline on UTI & VUR

Excluded UTI in complex abnormalities (obstructive uropathy, neurogenic bladder)

PROCESS

Appoint Work Groups, Evidence Review Team (ERT)

– Discuss process, Refine topics/questions

Assign topics to systematic review or narrative review

– Perform new or update existing

Create evidence profile

Rate **quality of evidence** for each outcome and overall

GRADE and formulate recommendation

Clinical practice points *vs.* recommendations

Clinical practice points

- No systematic review conducted
- Insufficient evidence
- Evidence inconclusive
- Guidance not actionable
- Guidance as table/figures/algorithm

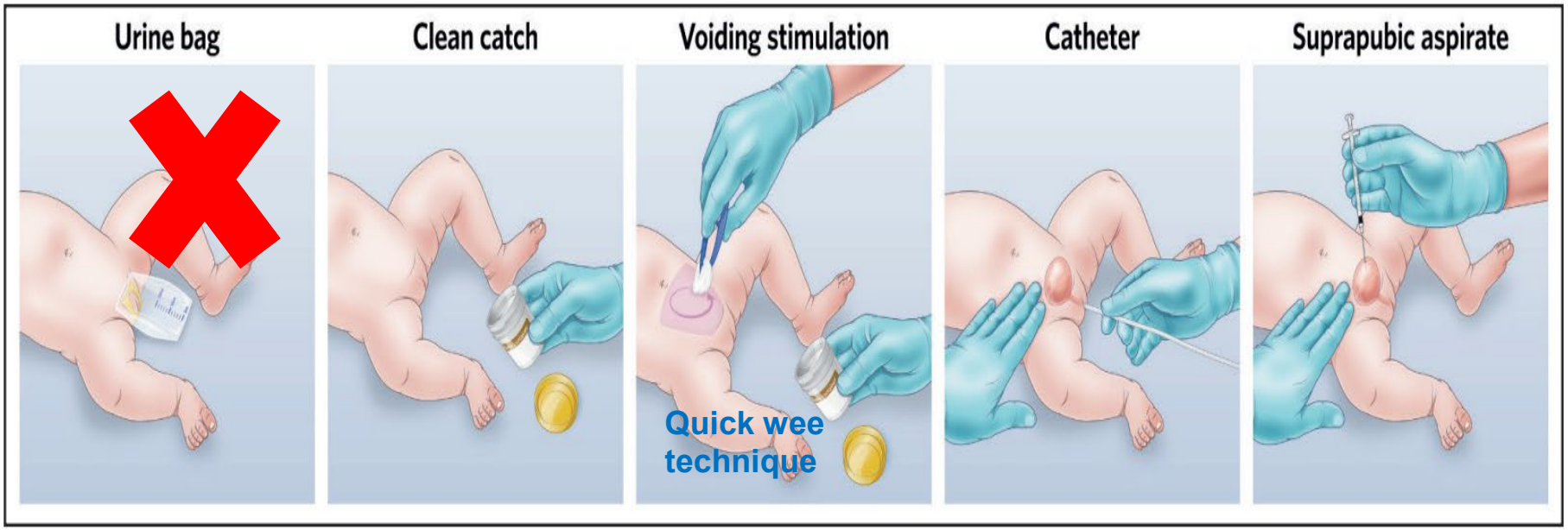
Recommendations

- 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

Adapted from KDIGO Guidelines on glomerular diseases 2020

Method of urine collection

PRECONTINENT CHILDREN :



Clinical practice point: suggest using clean-catch in toilet-trained

- Non-toiled trained stable children: clean-catch should be attempted initially, if unsuccessful catheterization or suprapubic aspiration (SPA) can be used
- Sick infants: catheterization or SPA preferred

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

ISPN guidelines, 2022

Screening test for UTI

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

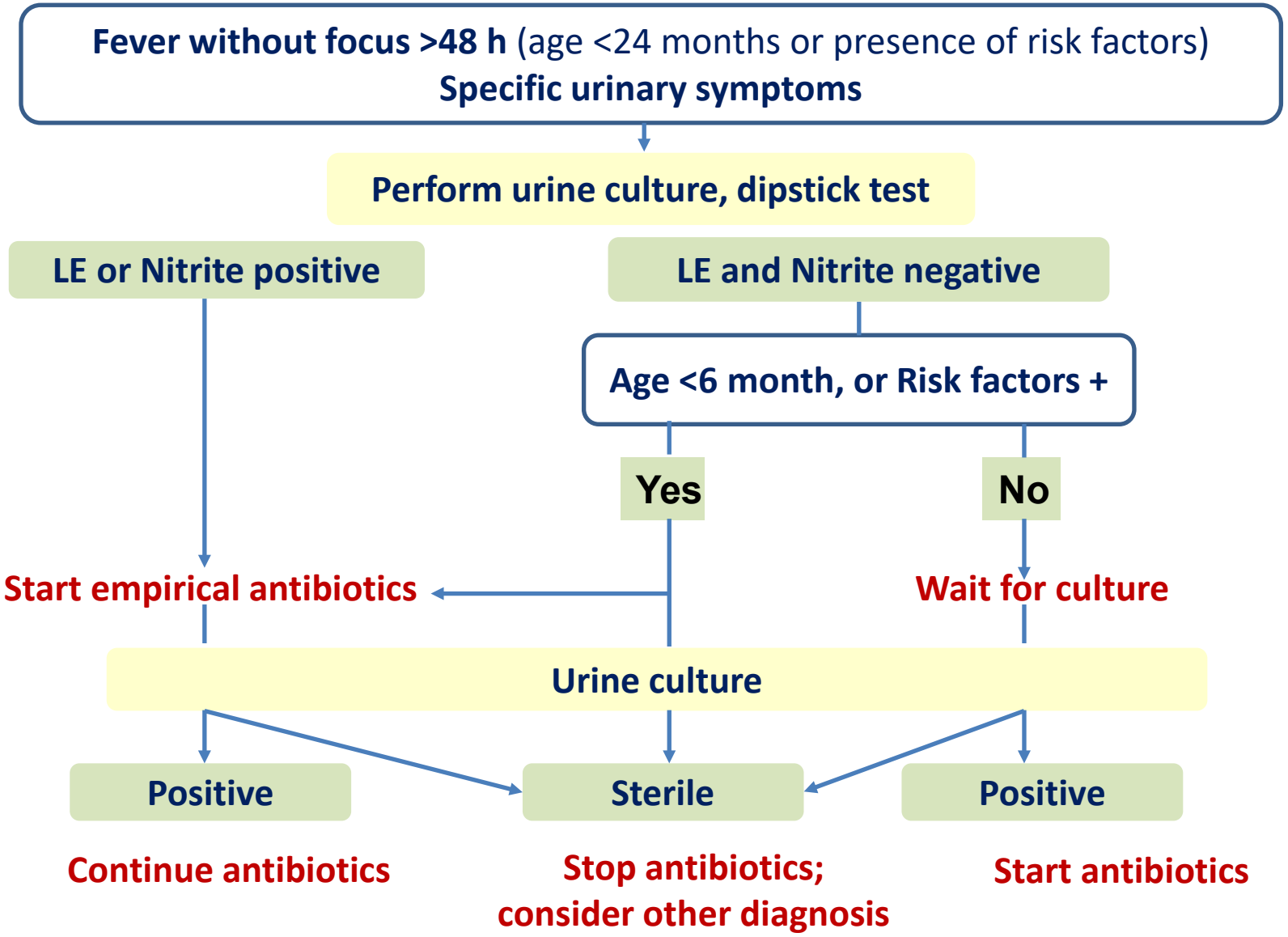
Microscopy for bacteria and Gram stain has excellent accuracy; microscopy for WBC can be replaced by leukocyte esterase; **Dipstick negative in 10%; cannot replace urine culture** *Williams, Lancet 2010*

Recommendation:

- Suggest using urine dipstick (leukocyte esterase + nitrite combination) as a screening test
- When feasible urine microscopy, (for bacteriuria and pyuria) in a freshly voided sample, can be used as an alternative for screening of UTI (2⊕⊕⊕◯)

ISPN guidelines, 2022

Approach to Diagnosis of UTI



Risk factors: Bladder-bowel dysfunction, primary vesicoureteric reflux, previous history of UTI

UTI: diagnosis

Clinical practice point:

- Suggest diagnosis of UTI be based on the significant growth of a single bacterial species in presence of symptoms
- Growth of single uropathogenic bacteria $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4\text{-}5}$ (CFU/ml) by suprapubic aspiration, catheterization, and clean-catch, are highly suggestive of UTI

Asymptomatic bacteriuria

- *Clinical practice point:* Suggest **NOT** to perform routine culture or repeat urine culture after treatment if there is clinical response
- Not to treat asymptomatic bacteriuria

ISPN guidelines, 2022

UTI: treatment guidelines

- **Recommendation:** Use oral antibiotics for acute pyelonephritis except

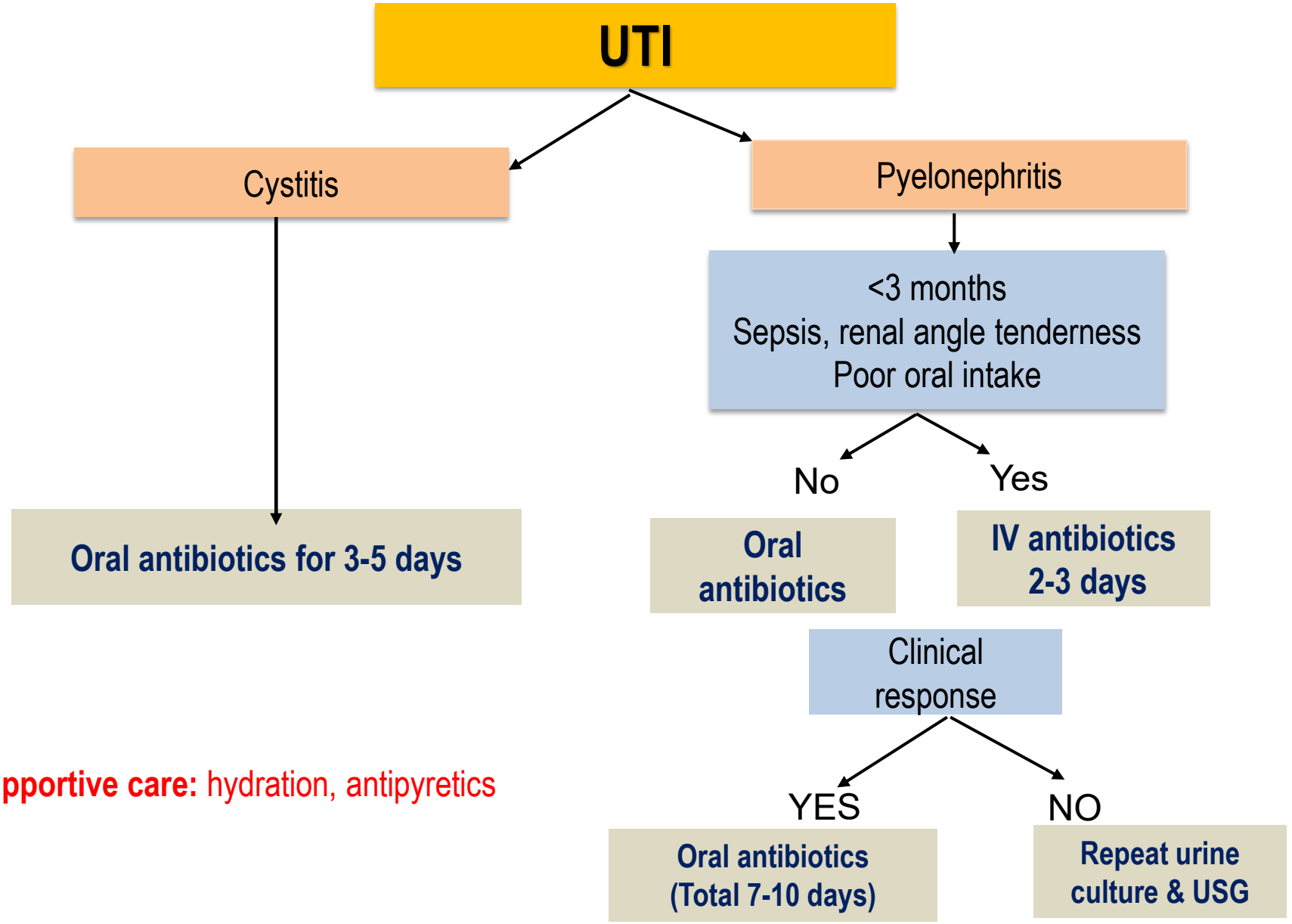
  i) infants aged <1 month ii) children with bacteremia/sepsis iii) children unable to ingest (1⊕⊕⊕◯)

  Suggest IV for initial 3-4 days or till defervescence, followed by oral

- *Clinical practice point:* Suggest initial intravenous antibiotic to treat acute pyelonephritis in children aged 1-3 month
- **Recommendation:** suggest using 3rd generation cephalosporins or amoxicillin-clavulanic acid as empirical antibiotic in febrile UTI (2⊕◯◯◯)
- **Recommendation:** short course (3-5 days) of oral antibiotic for lower UTI (1⊕⊕⊕◯)
- *Clinical practice point:* 7-10 days of antibiotic treatment for acute pyelonephritis in children aged >6 month

ISPN guidelines, 2022

Treatment of Urinary Tract Infection



Supportive care: hydration, antipyretics

BBD & Recurrent UTI

Bladder bowel dysfunction (BBD): combined bladder and bowel dysfunction in the absence of neurological abnormality *(ICCS, 2017)*

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

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

Clinical practice point

Suggest all children with UTI should be evaluated for BBD

Prophylaxis should be given in recurrent febrile UTI and BBD irrespective of presence or absence of VUR

ISPN guidelines, 2022

Imaging after UTI

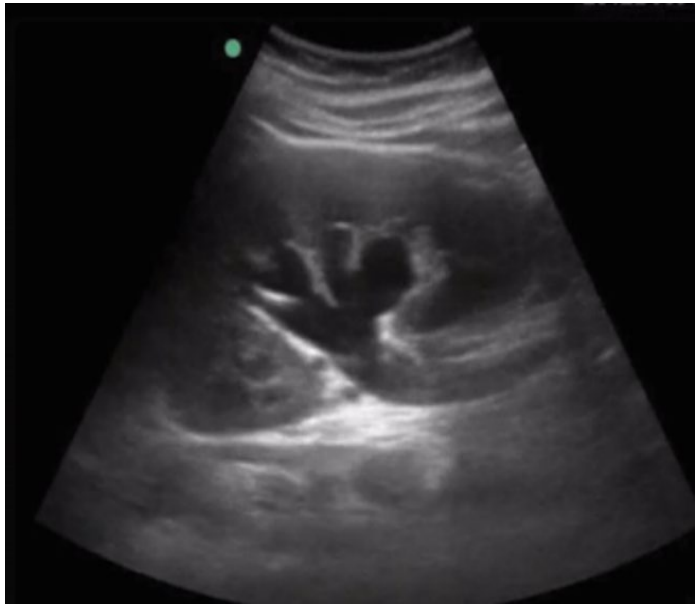
Imaging in selected children after first UTI

Findings suggestive of VUR

- Renal hypoplasia (B/L or U/L)
- Abnormal echogenicity
- Hydronephrosis
- Ureteric dilatation
- Uroepithelial thickening
- Bladder abnormality

Perform after 4-6 weeks; during UTI if

- urosepsis, non response, renal dysfunction



Clinical practice point

Ultrasound scan of the urinary tract should be performed after an episode of UTI in children

ISPN guidelines, 2022

Dimercaptosuccinic acid (DMSA) scan

Early DMSA (within 2 wk)

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

Late DMSA (4-6 mo after acute infection)

Clinical practice point

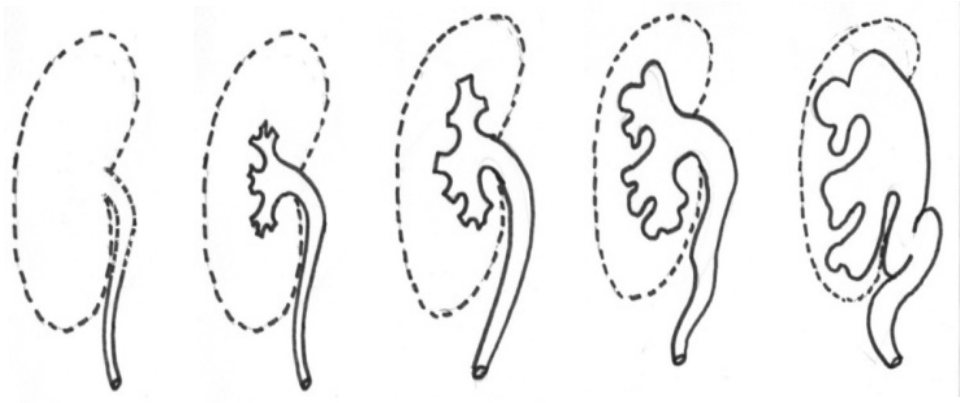
suggest performing a late-phase DMSA scan to assess kidney scarring in children with recurrent UTI or high-grade VUR

More relevant, since it detects damage!

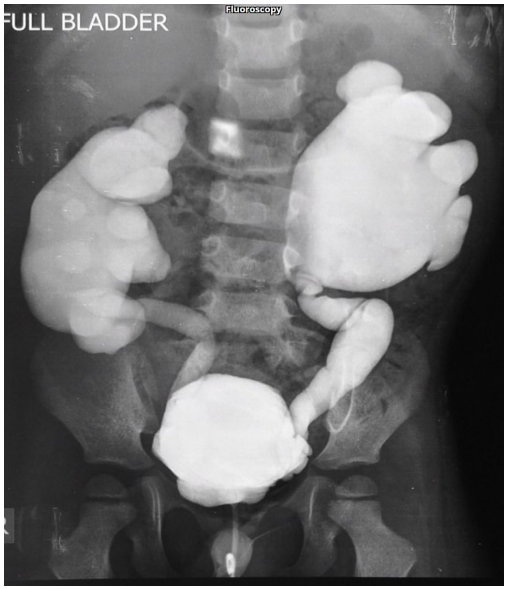
ISPN guidelines, 2022

Micturating cystourethrography

- Gold standard for VUR; provides anatomy of urinary tract
- Invasive & radiation



Grade I Grade II Grade III Grade IV Grade V

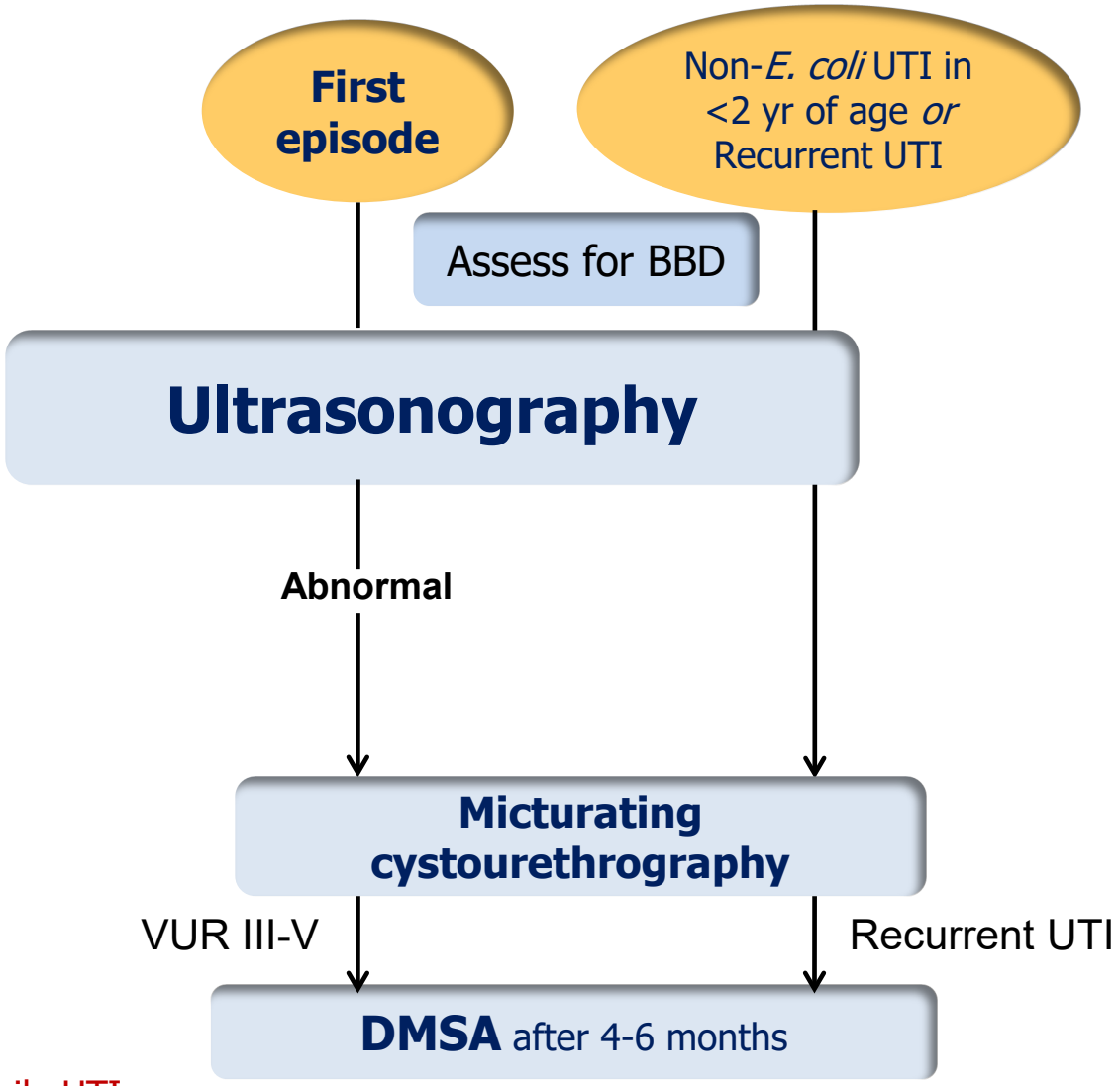


Clinical practice point

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

ISPN guidelines, 2022

Approach to imaging after UTI



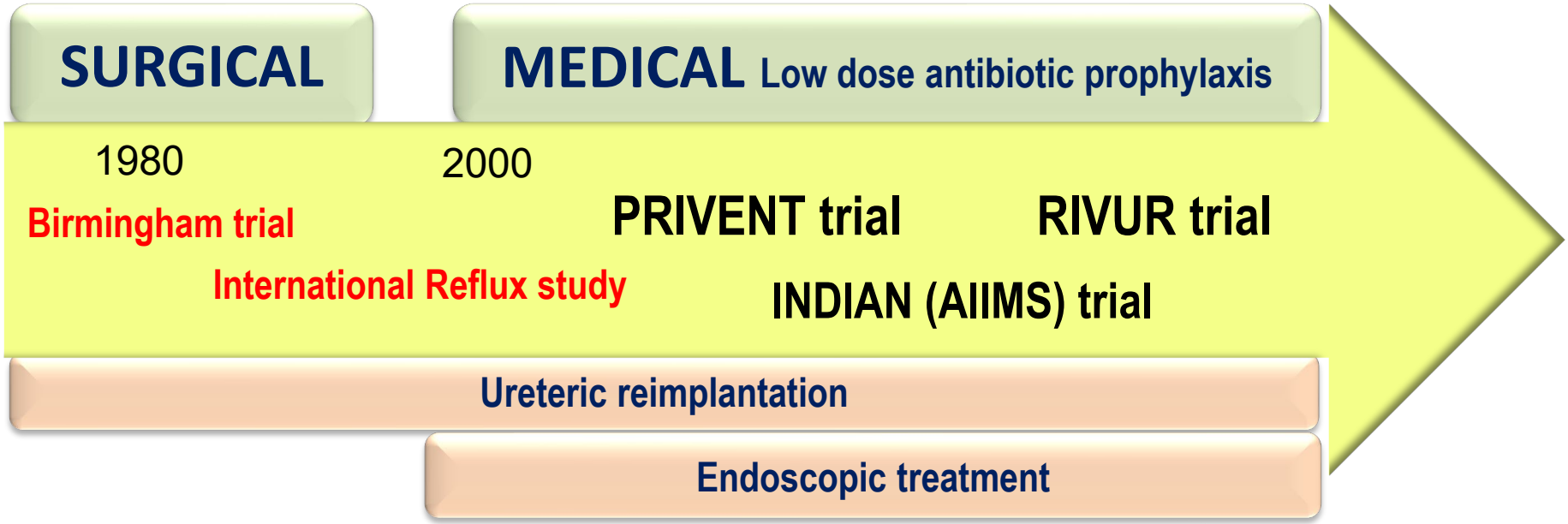
Recurrent UTI: 2 episodes of febrile UTI

BBD; bladder bowel dysfunction, DMSA; Dimercaptosuccinic acid VUR; vesicoureteric reflux

Primary VUR: how therapy changed

Most commonly diagnosed after UTI; 30-40% of UTI have VUR

Association with ESKD



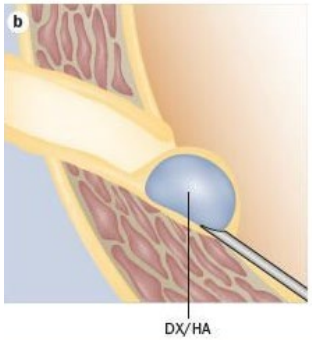
Antibiotic versus surgery/endoscopic injection

Meta-analysis: recurrence of symptomatic UTI similar after surgery & antibiotic prophylaxis; less febrile UTI

No difference in renal scarring at 5, 10 years

Surgery does not prevent progression to ESRD

% change of GFR similar at 5 and 10 yr; majority of reflux improve



Endoscopic treatment

- Success 60-95%; improves with second injection, depends on grade of reflux, expertise
- Recurrence 11-26% over 3-12 mo, ureteral obstruction 0.6%
- NO benefit over prophylaxis

Cochrane database of systematic reviews, 2019

Antibiotic Prophylaxis

Normal urinary tract

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

ISPN guidelines, 2022

Vesicoureteric reflux

- 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

Prophylaxis in high grade VUR

Recommendations

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

We suggest using co-trimoxazole or nitrofurantoin as the first-line antibiotic for prophylaxis in children older than 6 months. (2⊕⊕◯◯)

Clinical practice point

- Consider using prophylaxis in low-grade VUR in infants with febrile UTI
- Suggest discontinuation of prophylaxis in older than 2 years if: i) toilet trained, ii) absence of BBD, iii) no febrile UTI in last 1 yr

ISPN guidelines, 2022

VUR: treatment guidelines

Recommendation

- Suggest prophylaxis should be the first line of management in high grade VUR (2⊕⊕⊕◯)
- Suggest surgical reimplantation be considered in high grade VUR with recurrent breakthrough febrile UTI on prophylaxis (2⊕⊕⊕◯)

Clinical practice point:

- Suggest open reimplantation be preferred over endoscopic treatment
- Patients may be given option of endoscopy as initial treatment with guidance from physician about its minimally invasive nature and lower success rate
- In high-grade VUR, surgical intervention may be an alternative for parenteral hesitancy to use antibiotics

ISPN guidelines, 2022

Prevention of UTI

Cranberry

Large polymeric compound (pro-anthocyanidin) inhibits bacterial adherence

Not better than antibiotic prophylaxis

Quantity of active ingredient (36-72 g/d), availibility

Recommendation

Suggest using cranberry products for the prevention of UTI in children with recurrent UTI and normal urinary tract. (2⊕⊕◯◯)

Circumcision

Recommendation

Suggest circumcision should be offered for prevention of UTI only in children at risk of recurrence (2⊕⊕⊕◯)

ISPN guidelines, 2022

Follow up of VUR

Clinical Practice Points

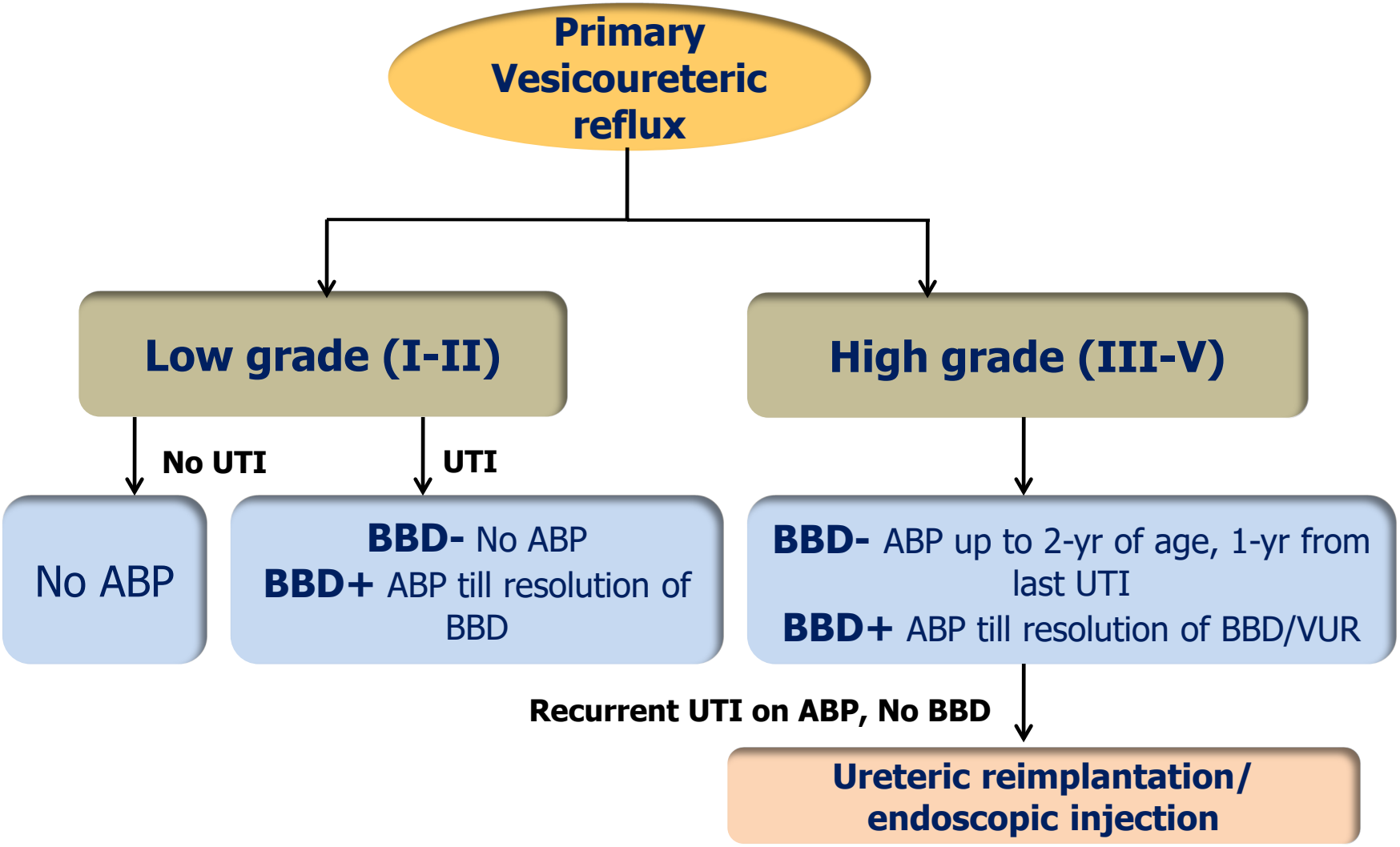
VUR need periodic follow up till considered clinically insignificant; reflux nephropathy need long term follow-up

Suggest

- Screening siblings (aged less than 3 years) of the children with primary VUR with an ultrasound scan
- Renal USG to monitor renal growth in high-grade reflux & those with scarred kidney
- DMSA be repeated during follow up, only in recurrent febrile UTI
- In high-grade reflux, repeat MCU be performed only if surgical intervention is planned
- DRCG may be done for documenting for resolution of reflux at 4-8 yr of age, in high-grade reflux

ISPN guidelines, 2022

Treatment of primary VUR



Recurrent UTI:2 episodes of febrile UTI

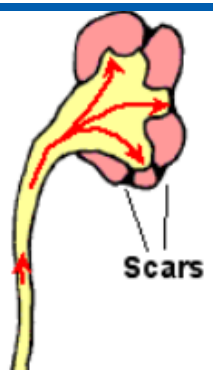
ABP; antibiotic prophylaxis, BBD; bladder-bowel dysfunction

VUR: risk of ESKD

Reflux nephropathy

- About 5% ESKD

Annual Report NAPRTCS 2014



Retrospective study of 735 children with VUR (1970 -2004)

- Mean follow-up 76 mo
- 3% developed hypertension
- Probability of CKD & ESRD at 10 yr was 15% & 5%
- **No CKD if normal DMSA at diagnosis**

Silva et al Ped Nephrol 2006

Prevalence of VUR: 1 to 17% or 100000 per million

Reflux ESRD: 0.7 per million population

USRDS 2007

Important changes in new guideline

		2011	2022
1	**Methodology**	Evidence not graded, recommendations not as statements	Evidence graded; statements as recommendations or practice points; conforms to AGREE /IOM checklist
2	**Urine culture**	>10^5 CFU/ml clean catch	>10^4-10^5 CFU/ml (infants)
3	**Complicated UTI/pyelonephritis**	Treat for 10-14 days	7-10 days
4	**Acute DMSA**	-	Not recommended
	Late DMSA	<5 yr old after first UTI, recurrent UTI, all VUR	Recurrent UTI, Grade 3-5 VUR

Important changes in new guideline

		2011	2022
5	**MCU**	Age <1 yr, abnormal US, recurrent UTI	Non *E coli* UTI in <2 yr old; abnormal US, recurrent UTI
6	**Antibiotic Prophylaxis**	<1 yr awaiting evaluation, Frequent UTI, All VUR	No prophylaxis in normal tracts Yes if BBD High grade VUR (3-5)
	Stop prophylaxis	Grade 1-2 @ 1yr of age Grade 3-5 @ 5 yr of age	Till toilet trained or 2-3 yr old, no breakthrough UTI in last 1 yr, absence of BBD
7	**Surgical intervention**	Recurrent breakthrough UTI, parental preference Deterioration in renal function	Recurrent breakthrough UTI, parental preference

Key Points

New guidelines have followed rigorous methodology

- Post UTI imaging is selective, less aggressive
- Emphasis on BBD; associated with recurrence
- **Surgery as good as prophylaxis** for VUR; indications limited
- Prophylaxis
  - **Recurrent UTI, BBD, high grades of VUR;** risk of antimicrobial resistance

Non-antibiotic interventions should be explored

Acknowledgements

Group coordinators

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A Iyengar
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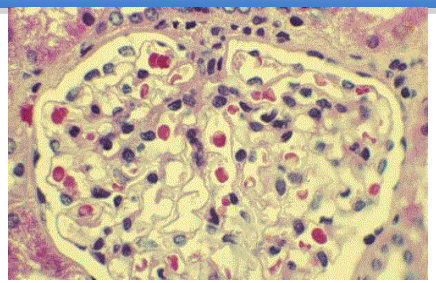
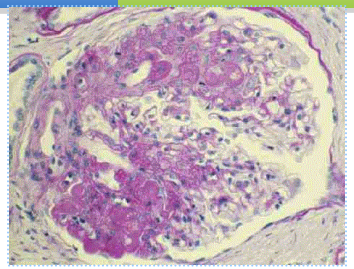
U Ali

Thank you!

Nephrotic syndrome
Current management





Management guidelines, definitions

	ISPN	KDIGO	
Steroid sensitive NS	2000 2008 **2021**	2012 **2021**	**2022**
Steroid resistant NS	2009 **2021**	2012 **2021**	**2020**

Steroid sensitive	Complete remission within **6**-weeks' treatment with prednisone
Frequent relapses	Relapses ≥2 in ***first*** 6-months, ≥***3*** in any 12-months
Dependence	≥2 consecutive relapses on/in <2-wk of discontinuing prednisone

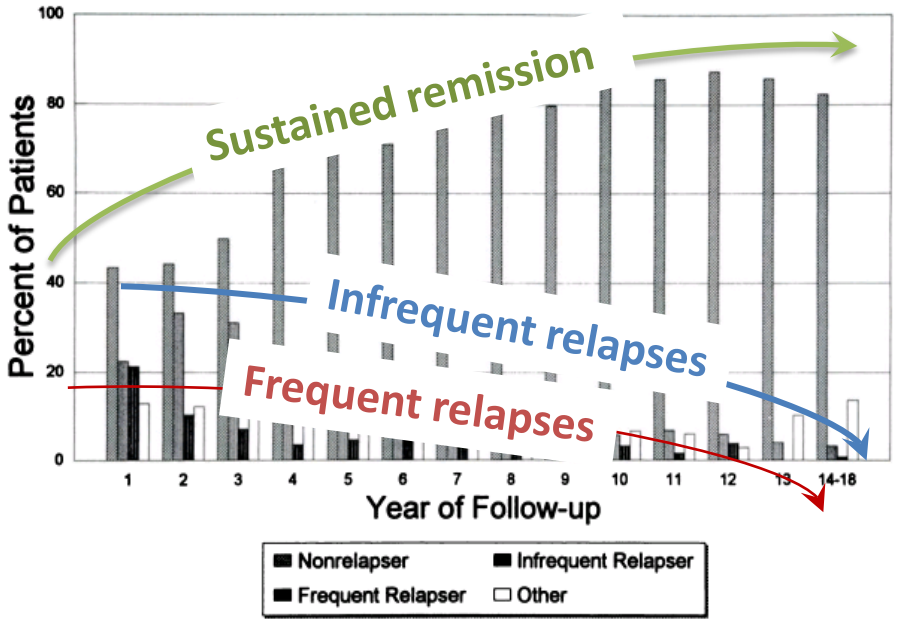
Significant toxicity	Hyperglycemia; obesity; short stature; glaucoma, cataract; myopathy; psychosis
Difficult-to-treat	**Frequent relapses; significant toxicity; failing ≥2 strategies**

Nephrotic syndrome: Proteinuria >1 g/m^2; albumin <3.0 g/dl; edema

Steroid sensitive nephrotic syndrome

Incidence 2-9/100000 children/yr

Prevalence 12-16 per 100000 children



Steroid resistance 2–4/million/yr

Evaluation at onset; follow up

At onset

Urinalysis; urine protein to creatinine ratio

Blood counts

Urea, creatinine, electrolytes, albumin, cholesterol

Tuberculin test

Additional: At onset; relapse

Chest radiography	Positive tuberculin test or history of contact Suspected pneumonia
Renal ultrasonography	If planned kidney biopsy Gross hematuria; suspected renal vein thrombosis
Complete blood counts	Suspected infection, hypovolemia
Urea, creatinine, albumin, electrolytes	Anasarca; hypovolemia/dehydration Oliguria/anuria; prolonged (>48-hr) diuretic therapy
C3, C4, ANA, antistreptolysin O	Gross, persistent microscopic hematuria; secondary cause (systemic lupus, IgA vasculitis)
Serum transaminases; HBsAg; anti-HCV	History of jaundice or liver disease

Indications for kidney biopsy

At onset , if

Gross hematuria or persistent microscopic hematuria

Sustained hypertension

Acute kidney injury not attributed to hypovolemia

Systemic features: fever, rash, arthralgia, low complement C3

Initial or late corticosteroid resistance

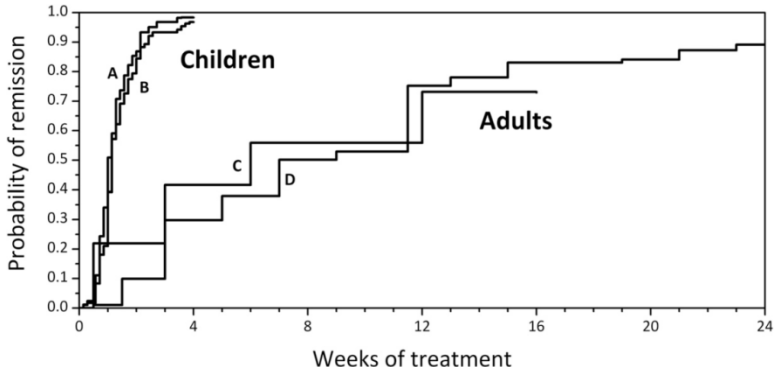
Therapy with calcineurin inhibitors

Prolonged (>30-36 months)

Reduced kidney function

Prior to initiating therapy

Initial Prednisolone Therapy



ISKDC: **60** mg/m^2/d x 4-wk; **40** mg/m^2/alternate day x 4-wk

1A

Initial Therapy with Prednisolone

2 mg/kg x 6-wk; 1.5 mg/kg/alternate day x 6-wk

No legacy of 'prolonged steroids' for preventing frequent relapses

Similar duration of therapy in young

CTRI/2015/06/005939 (**174**)

NCT04536181 (**154; China)**

Relapses in 70%; frequent in 50%

Prednisolone 60 mg/m^2/d till remission;
40 mg/m^2/alt. day for 4 wk

1B

No benefit of prolonged taper
PROPINE; AIIMS; *RESTERN*

CJASN 2020; KI 2020
Pediatr Nephrol 2021

Lower daily dose may work as well….

Once daily therapy

No role of antacids, calcium, thyroxine

Frequent relapses: Alternate-day prednisone is first line [concerns of steroid toxicity…]

1B **Prednisone @ 0.5-0.7 mg/kg AD for 9-12 months**

Satisfactory remission (remission; infrequent relapses): 43-92%

Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial

Pediatr Nephrol 2019;34:829-35

Intervention 0.26±0.02 mg/kg/d **Control** 0.5±0.1 mg/kg alt. day

Daily prednisone during infections…?

Author, yr	Study	Category	N
Mattoo 2000	Non-randomized, prospective	Frequent relapses	36
Abeyagunawardena 2008	Placebo-controlled cross-over	Infrequent	40
Abeyagunawardena 2017	Placebo-controlled cross-over	≥2 relapses per yr	48
AIIMS, 2011	Open label RCT	Frequent relapses	100
***PREDNOS 2**, 2021	**Placebo-controlled, multicenter**	≥2 relapses per yr	**365**

Prednisolone 15 mg/m^2 x 6 d during URTI

***Adjusted risk difference: -0.024, 95% CI -0.14 to 0.095; *P*=0.7

Alkylating agents reduce relapses by ~56%

Cochrane 2020: RR 0.44; 0.32-0.60

Caution in peri-pubertal boys **Avoid >1 course**

Better in FR & children >5-8 yr

Levamisole: Steroid sparing; safe..

Cochrane 2020: 8 RCT [n=474]; **RR 0.52 (95% CI 0.33, 0.82)**

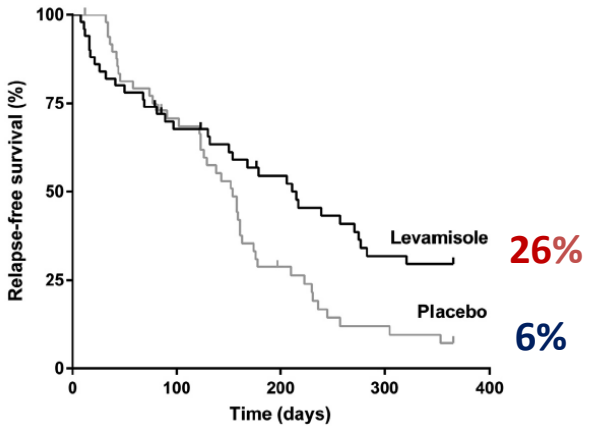
A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome

Kidney Int 2018

Placebo-controlled RCT (n=99)

Sustained remission & reduced relapses

Better in frequent relapsers



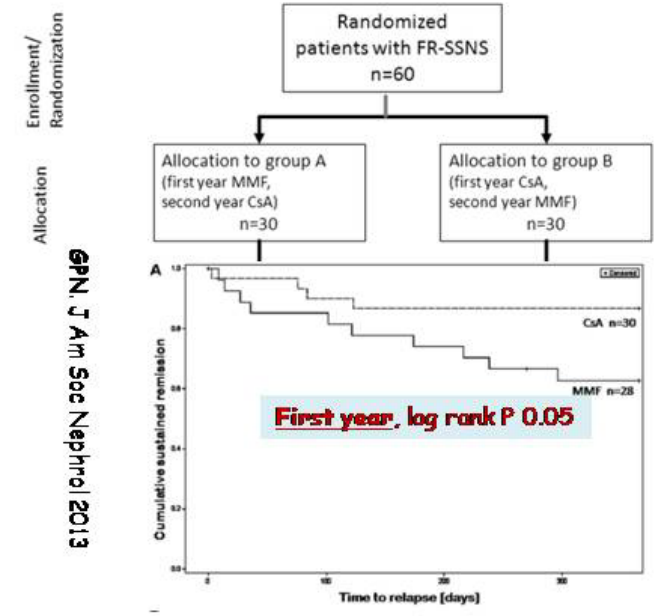
N=1391; 33 reports		KI 2018
Leukopenia	**3.7%**	**6%**
GI upset	2.4%	
Arthritis	-	**2%**
Other	5.7%	**10%**

Leukopenia; Vasculopathy

P-ANCA **+** : neutrophil elastase

MMF: Steroid sparing; use right dose

MMF inferior to CsA



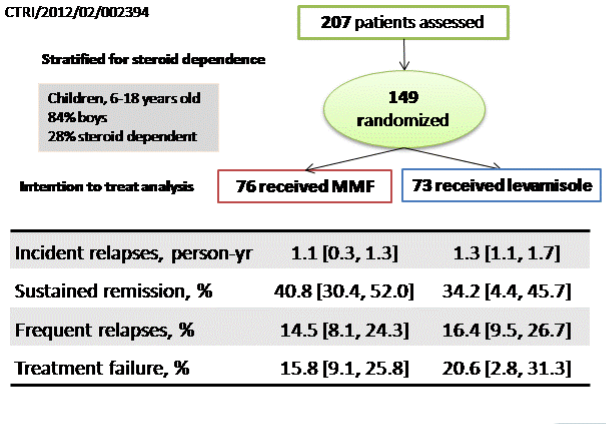
CsA sustained remission 85%

MMF remission 64% (P=0.06)

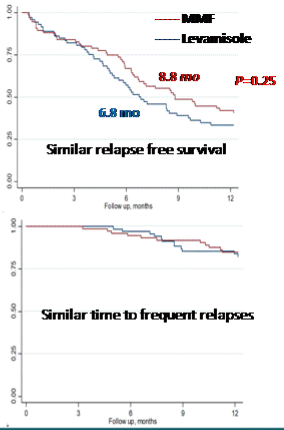
High MPA levels better

eGFR better with MMF

MMF not superior to levamisole



Incident relapses, person-yr	1.1 [0.3, 1.3]	1.3 [1.1, 1.7]
Sustained remission, %	40.8 [30.4, 52.0]	34.2 [4.4, 45.7]
Frequent relapses, %	14.5 [8.1, 24.3]	16.4 [9.5, 26.7]
Treatment failure, %	15.8 [9.1, 25.8]	20.6 [2.8, 31.3]



Relative relapse rates similar in subgroups for sex, age & disease severity

CONCLUSION:
MMF not superior to levamisole in reducing frequency of relapses or likelihood of remission in children with frequent relapses

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
KI (2019) https://doi.org/10.1016/j.kint.2018.08.039

KI 2019; 95: 210-18

Cochrane Library

Relapse on MMF *vs.* Cyclosporine
82 children; RR 1.90 [95% CI 0.7-5.5]

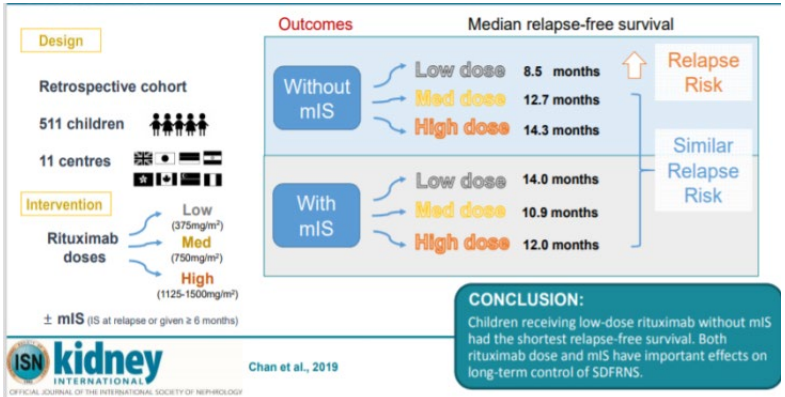
Relapse on MMF *vs.* Levamisole
RR 0.90 [0.7-1.2]

Rituximab: Frequent relapses, CNI dependence

5 RCT; N=269

Risk of relapse	Relative risk [95% CI]	Studies (N)
At 3-months	0.32 [0.14-0.70]	3 (132)
At 6-months	**0.23 [0.12-0.43]**	**5 (269)**
At 1-year	0.63 [0.42-0.93]	3 (198)

Likelihood of relapse at 6-24 months



I. Add MMF — JSKDC07; RITURNS II; RITUXIVIG

II. Re-dose @ relapse

III. Sequential therapy

Risk of infusion reactions: RR 5.8 [1.3-25.3] (4 studies; n=252)

Hypo IgG: 11-40%; <8-yr, low baseline IgG, use of MMF, >5-7 doses

Frequently relapsing nephrotic syndrome

ISPN Guidelines 2021

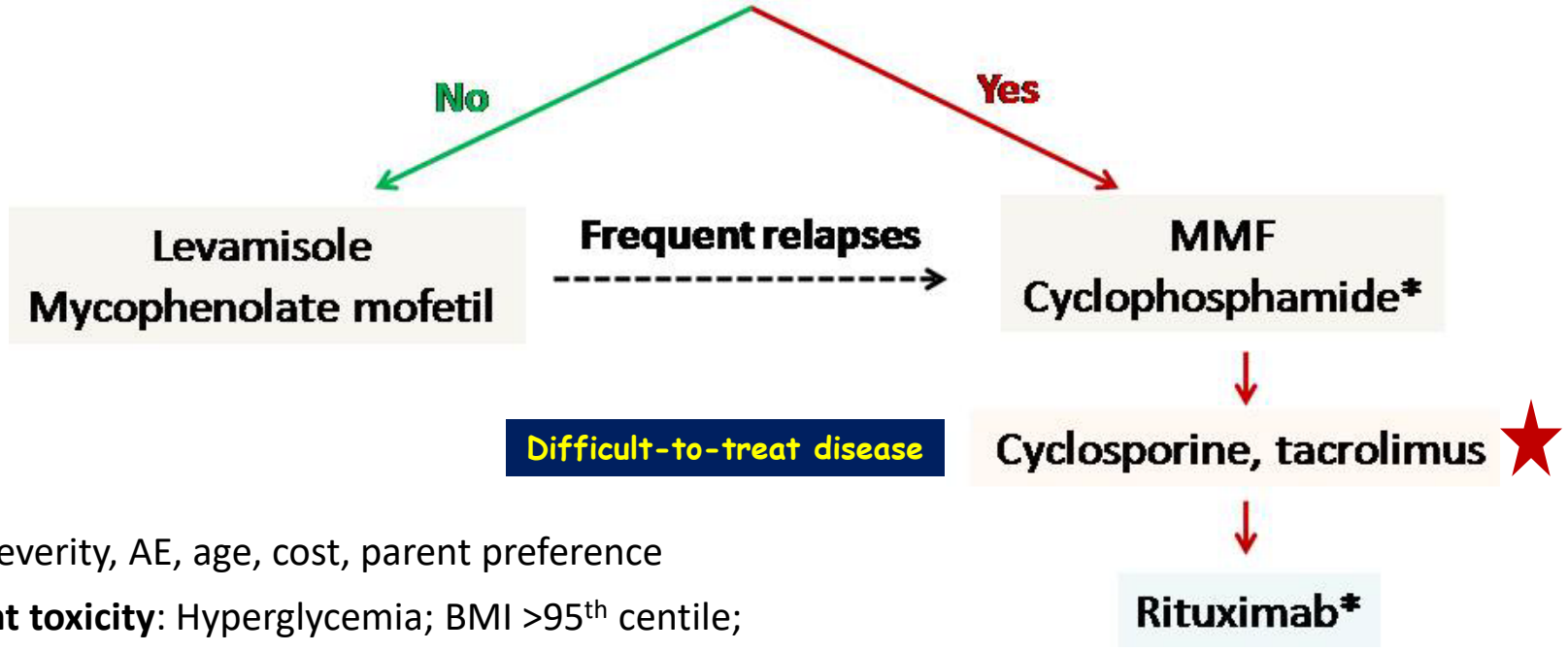
Prednisone alternate day; daily during infections

Frequent relapses, steroid dependence

Relapse threshold >1 mg/kg AD

Significant steroid toxicity

>1 severe relapse



Choice: Severity, AE, age, cost, parent preference

Significant toxicity: Hyperglycemia; BMI >95th centile; short stature; raised IOP; cataract; myopathy; psychosis

***Avoid cyclophosphamide:** <5-7 yr; peri-pubertal boys

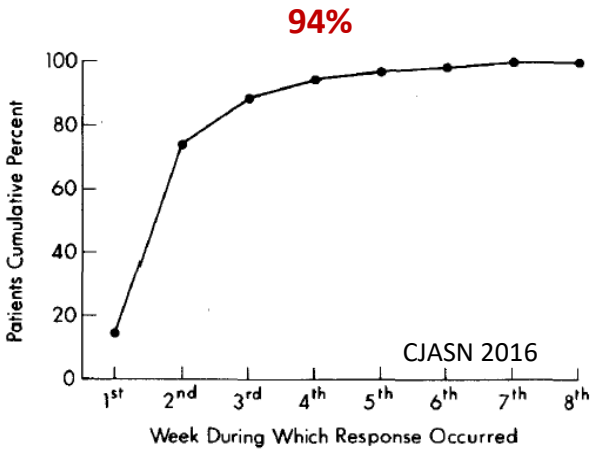
***Avoid RTX in the young**

Adverse effect monitoring

Steroid Resistance: Lack of complete remission despite 6-wk daily steroid therapy

ISPN, **IPNA, KDIGO**: Lack of remission by 4-**6** wk

+ 3 IV methylprednisolone pulses ?



Adults: No response to prednisolone 1 mg/kg/day *or* 2 mg/kg on alternate days, within 16 wk

Prevalence of steroid resistance 5-20%

China. **KI Reports 2021**

Late steroid resistance 1-5%; minimal change often; **85% 10-yr renal survival**
No response to immunosuppression predicts progressive kidney failure

Quantify proteinuria; eGFR; Biopsy

Urinalysis, including microscopy

Spot urine protein to creatinine ratio; or 24-hr urine protein excretion

Complete blood counts

Blood creatinine, albumin, electrolytes, fasting glucose, glycosylated hemoglobin (HbA1c)

Total, low density and high-density cholesterol; triglycerides

Calcium, phosphate, alkaline phosphatase

Hepatitis B surface antigen; hepatitis C and human immunodeficiency virusantibodies

Ultrasonography of kidneys

Kidney biopsy (light, immunofluorescence, electron microscopy); avoid in selected patients*

All SRNS should undergo biopsy

FSGS ~40%, minimal change 30-35%

*Biopsy may be avoided in patients with familial steroid-resistance or with extrarenal features, where genetic diagnosis is preferred

Tubulointerstitial changes determine outcome

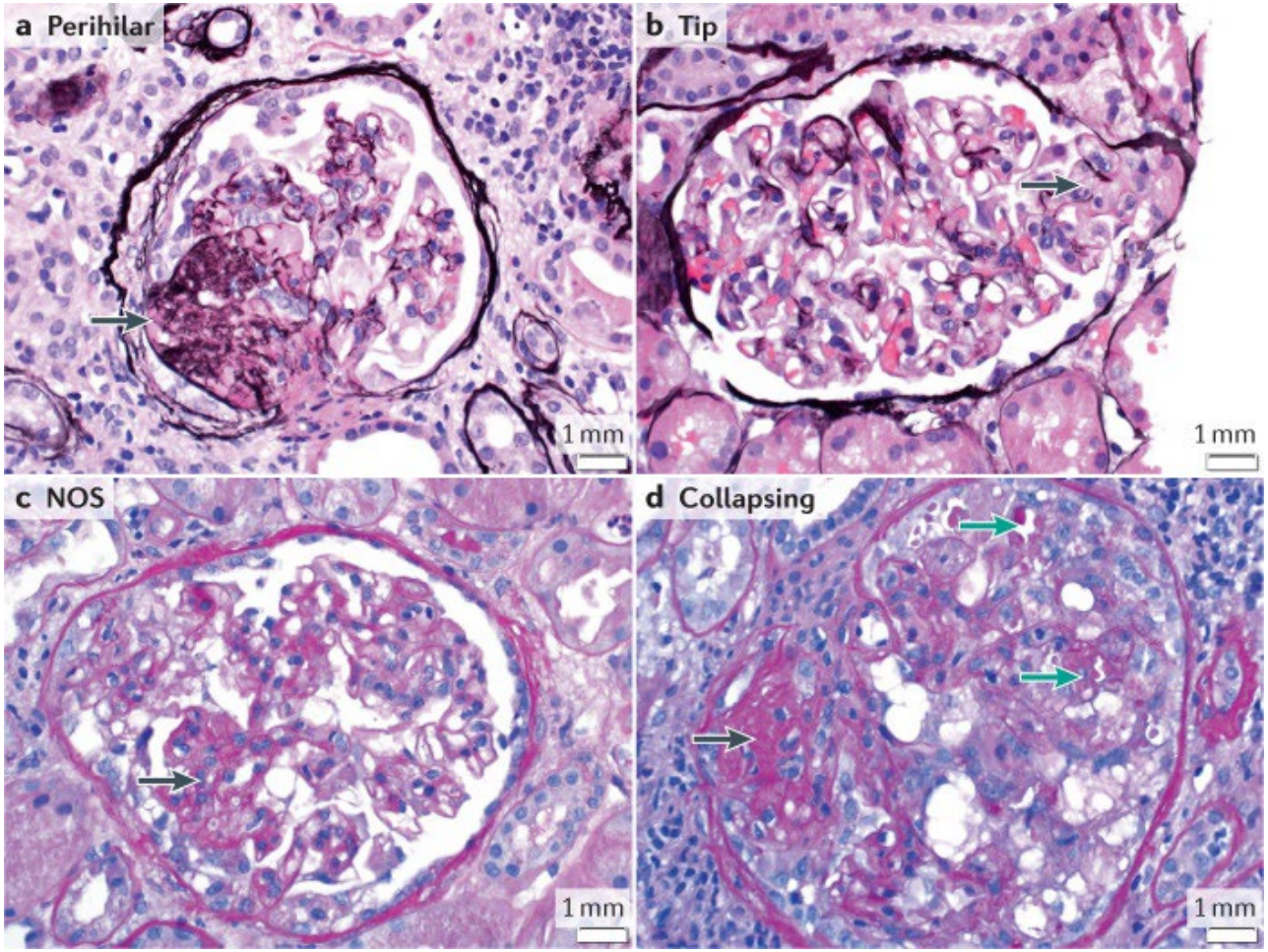
Use of nephrotoxic agents

~15-20%: Secondary; IgA nephropathy, C3G; amyloidosis

FSGS Subtypes

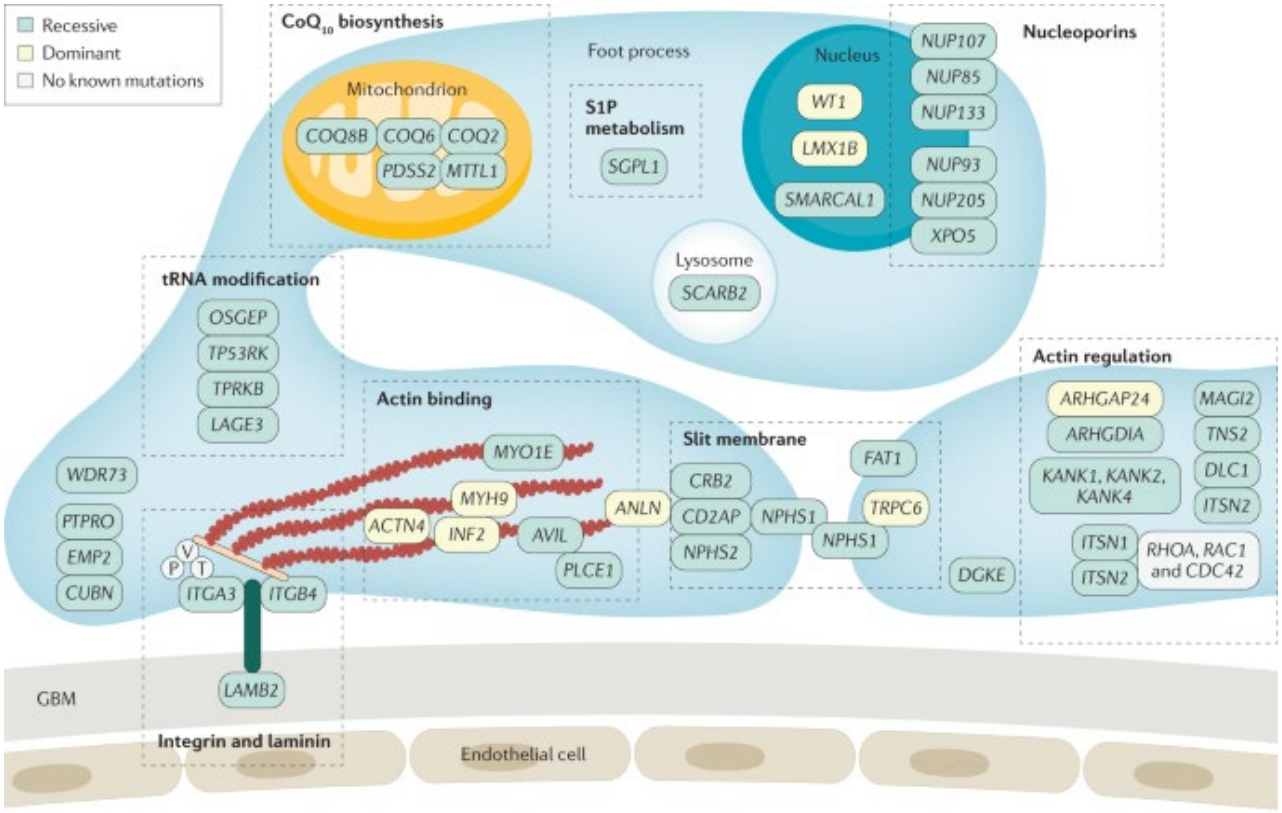
	Permeability factor assoc.	Secondary FSGS	Genetic FSGS	Undetermined
Onset	Sudden	Insidious	Variable	Insidious
Proteinuria	Nephrotic	Variable; high	High in children	Variable
Podocyte effacement	Generalized (>80%)	Mild, segmental	Segmental, diffuse	Mild, segmental
Allograft recurrence	High (>70%)	Low	Nil	Low
RAS inhibitors	Poor	Excellent	Good	Good
Steroids, CNI	Induce remission	Ineffective	Ineffective	Ineffective
Genetics	None	None	*Mutations*: Filtration barrier structure & function	None
Underlying cause	None	Causative factor **++**		Not established

FSGS: Columbia classification



- Prognostic significance
- Not specific for the etiology of FSGS

Monogenic steroid resistance ~25% Nat Rev Dis Primers 2020



Phenocopies : *COL4A, CLCN5*, *CTNS, GLA, LAMB2, WDR19, AGXT, FN1, PAX2, LMX1B*

Genetic abnormalities not seen with late resistance….

Genetics for steroid resistance

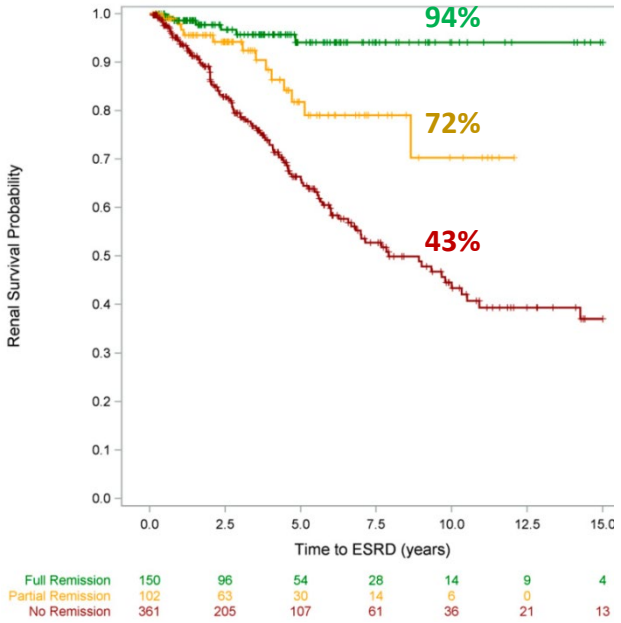
Similar features, histology
Limited response to CNI
Progressive kidney failure
Low recurrence <5%
No immunosuppression; need genetic counseling

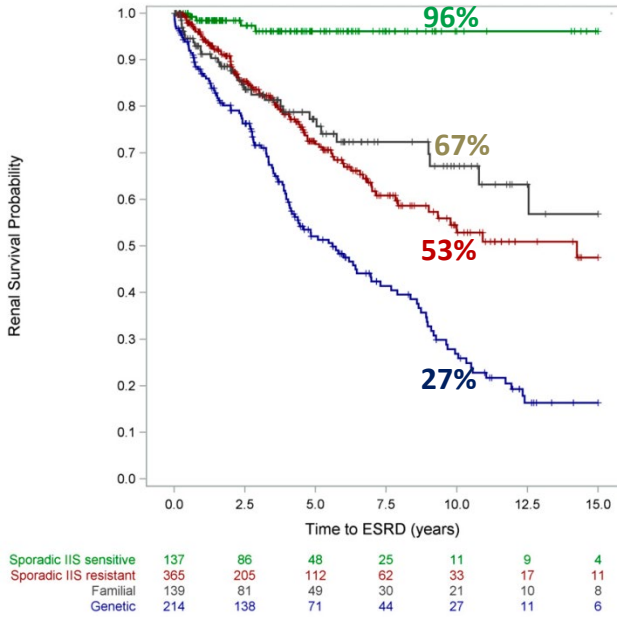
Congenital nephrotic syndrome
Onset during infancy
Syndromic features
Family history of resistance
Non-response to CNI
Prior to transplantation

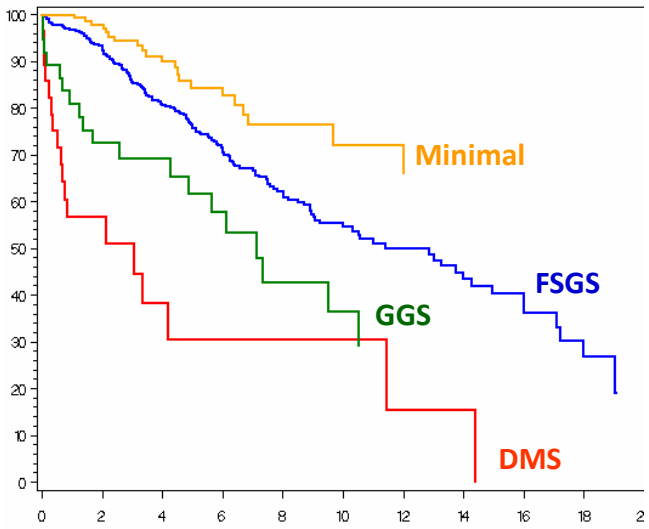
IPNA guidelines: All patients with initial SRNS

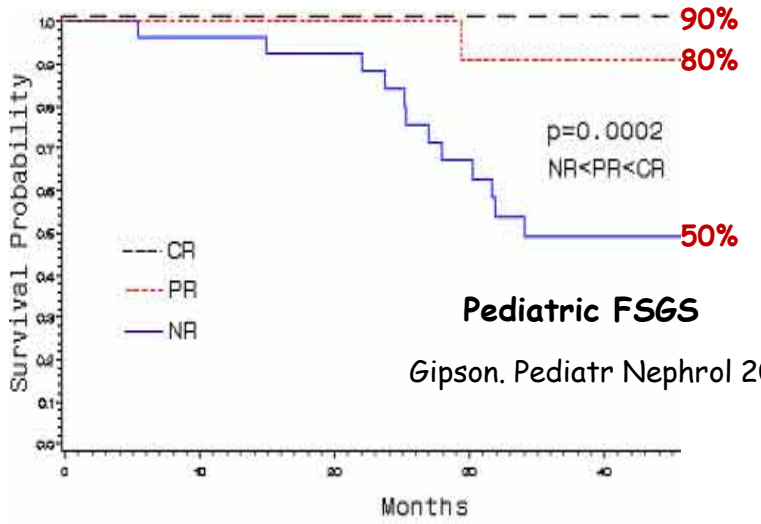
Importance of achieving remission

Poor kidney survival in genetic forms.... PodoNet, N=1354. JASN 2017









CNI: 50-70% complete, partial remission

Response by **8-12** weeks

Relapses ~70% on stopping therapy

Interventions for FSGS

Cochrane 2022: CD003233

Cyclosporin ± prednisone: Complete remission (RR 2.3; 95% CI 1.1, 4.7); remission (RR 1.6; 1.1, 2.4) [4 studies; n=231]

Cyclosporin: No difference in CKD outcomes; hypertension; infection

Efficacy CsA ~ tacrolimus

KDIGO: Assess response @ 6-months; stop if **no response**

Minimum 12-months if response; usually 2-3 years

Steroid resistance: Role for MMF (1)

 # NIH-FSGS trial **KI 2011**

Cyclosporine (n=72) *vs.* oral DEX/MMF (n=66) for 12 months

Remission: 33% MMF/DEX & 46% CsA (OR 0.59; 0.30, 1.18)

PODONET MMF monotherapy effective ~15% **JASN 2017**

Interventions for FSGS Cochrane 2022: CD003233

No benefit with MMF

Indications for MMF (i) eGFR <30; (ii) CNI therapy for **1-yr**; (iii) steroid sensitive relapses

(i) CNI therapy for **2-3 yr**; *(ii)* steroid sensitive relapses

Non-response to calcineurin inhibitors

First do genetic studies….

- **CNI with MMF** x 3-6 months ~25% efficacy
- **Rituximab** ~40% partial, complete remission

Initial resistance 54/123 (44%); late 45/78 (58%)

FSGS 54/130 (42%); minimal change 49/77 (64%)

Author (publication year)	Number of patients	Patients of remission[a]	Patients of CR	Patients of PR
Case reports[b] [17–29]	13	10 (76.9%)	10 (76.9%)	0 (0.0%)
Bagga et al. (2007) [30]	33	16 (48.5%)	9 (27.3%)	7 (21.2%)
Gulati et al. (2010) [31]				
Prytula et al. (2010) [32]	27	18 (66.7%)	6 (22.2%)	12 (44.4%)
Kari et al. (2011) [33]	4	1 (25.0%)	1 (25.0%)	0 (0.0%)
Ito et al. (2013) [34]	19	12 (63.2%)	6 (31.6%)	6 (31.6%)
Kamei et al. (2014) [35]	10	8 (80.0%)	7 (70.0%)	10 (10.0%)
Sinha et al. (2015) [36]	58	17 (29.3%)	7 (12.1%)	10 (17.2%)
Basu et al. (2015) [37]	24	16 (66.7%)	5 (20.8%)	11 (45.8%)
Hoseini et al. (2018) [38]	30	17 (56.7%)	14 (46.7%)	3 (10.0%)
Magnasco et al. (2012) [39]	16	3 (18.8%)	NA	NA
Total	234	118 (50.4%)	65 (29.8%)[c]	50 (22.9%)[c]

Kamei et al. Ped Nephrol 2020

Prompt CoQ10 therapy for specific SRNS….

PODONET KI Sep 2022

Defects in genes involved in CoQ_{10} biosynthesis & SRNS

Supplements of CoQ_{10} for 2-yr

Efficacy in 41 patients compared to a matched untreated cohort

Reduced proteinuria by 88% @ 12-months; preserved kidney function @ 5-yr (62% *vs.* 19%); fewer neurological issues

COHORT

116 individuals with defects in *COQ2*, *COQ6* and *COQ8B* genes treated with oral CoQ_{10} supplementation

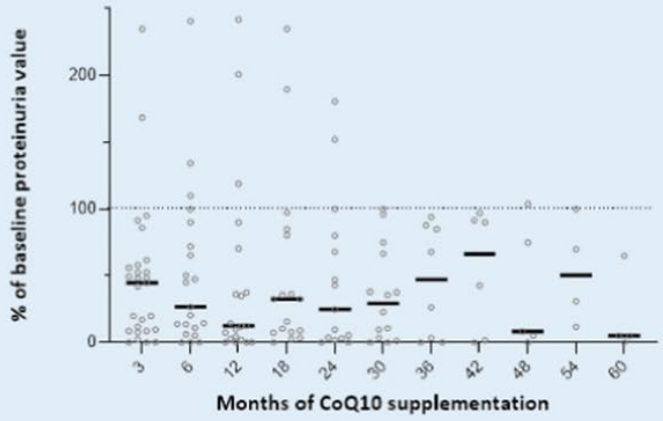
METHODS

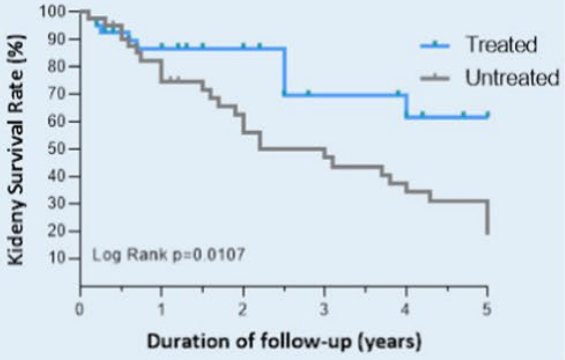
Short- and long-term efficacy and safety:

- Proteinuria responsiveness
- Genotype-responsiveness associations
- Kidney survival (matched CoQ_{10} Deficiency cohorts)

Treated vs Utreated

- Neurological and general clinical condition
- Side effects





- Substantial and sustained proteinuria reduction (by 88%, IQR 20;98 % at 12 months,p<0.0001)
- No significant differences in responsiveness among genotypes
- Better preservation of kidney function (5-year ESKD-free survival 61.8% vs. 18.7%)
- Potential improvement of the neurological and general clinical conditions
- Uncommon and mild side effects

ACEi or **ARB:** Reduce proteinuria ~30-40%

Dual RAAS blockade: Significant adverse events

Losartan *vs.* enalapril comparable Kidney Int Oct 2012

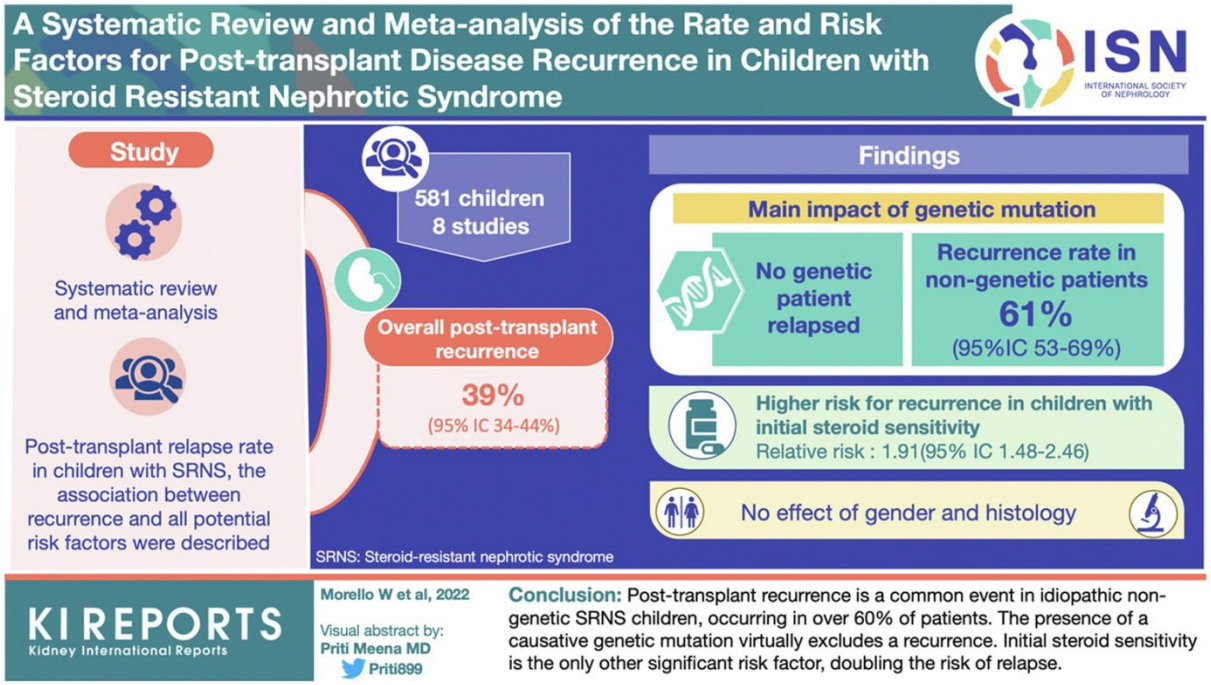
Sparsentan (blocks angiotensin II & endothelin 1) **DUET, DUPLEX**

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors:
Reduce albuminuria in proteinuric CKD, delay progression

Dapagliflozin & empagliflozin; safe use in children…. KI Reports 2022

CTRI/2022/04/042032

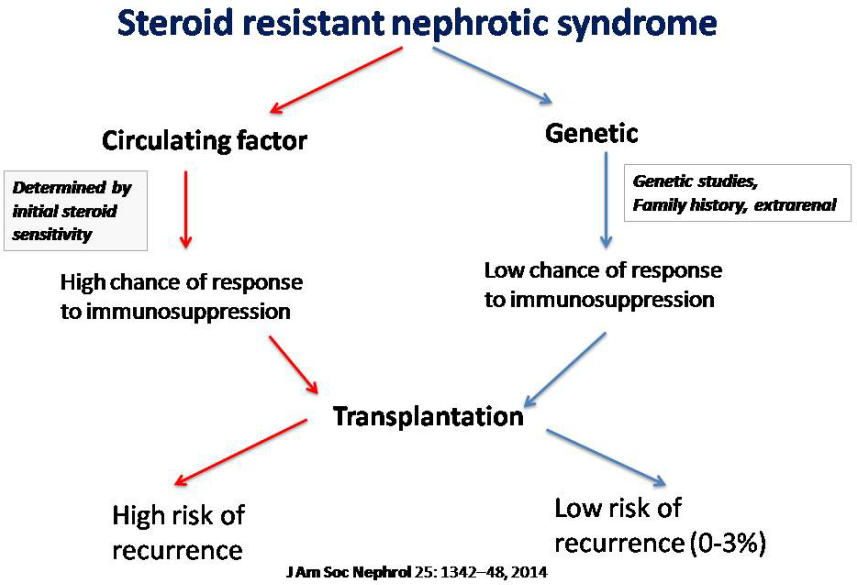
Effect of oral dapagliflozin, @ 5-10 mg/d for 12 weeks, on proteinuria in children receiving therapy with RAAS-blockers



Recurrent FSGS ~35%

First 2-yr of transplant

Predicts outcome

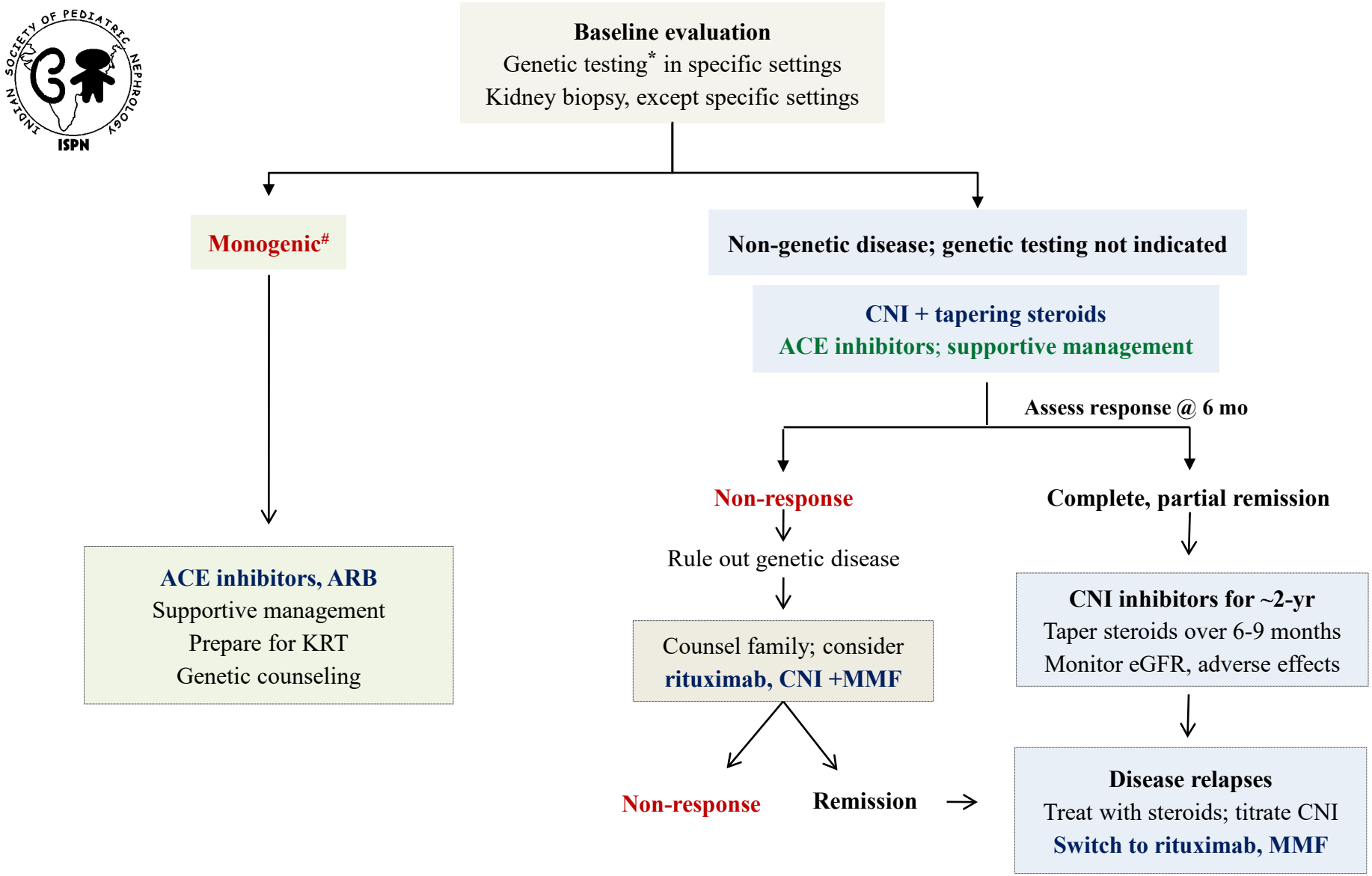


Initial steroid sensitivity in steroid-resistance predicts post-transplant recurrence

<20-yr-old; **non-genetic;** rapid progress ESRD; **prior recurrence**

Live-related *vs.* cadaveric

Steroid resistant nephrotic syndrome 2021



Evaluation and Management of Renal Stones

Moderator: Dr Aliza Mittal
Panellists: Prof. AS Sandhu, Prof. Arvind Sinha, Prof. Ranjeet W Thergaonkar, Dr. Girish Bhatt, Dr Rajesh Jhorawat

Introduction

- Incidence in children 5-10% of that in adults
- western countries (Europe 5–9%, North America 12–15%)/East (5%)

- Endemic areas-Near/Middle East and North Africa (Turkey, Saudi Arabia, Egypt, and Pakistan) (10–20%)
- Reasons can vary

- Consanguinity
- Hot dry climate and high ambient temperatures
- High prevalence of renal tubular acidosis (Thailand, South India)/
- North India- the absence of *Oxalobacter formigenes*, an intestinal oxalate degrading bacterium- absorptive hyperoxaluria

Epidemiology

- Increasing incidence of approx.- 4%/calendar year

Temporal trends in incidence of kidney stones among children. J Urol (2012)

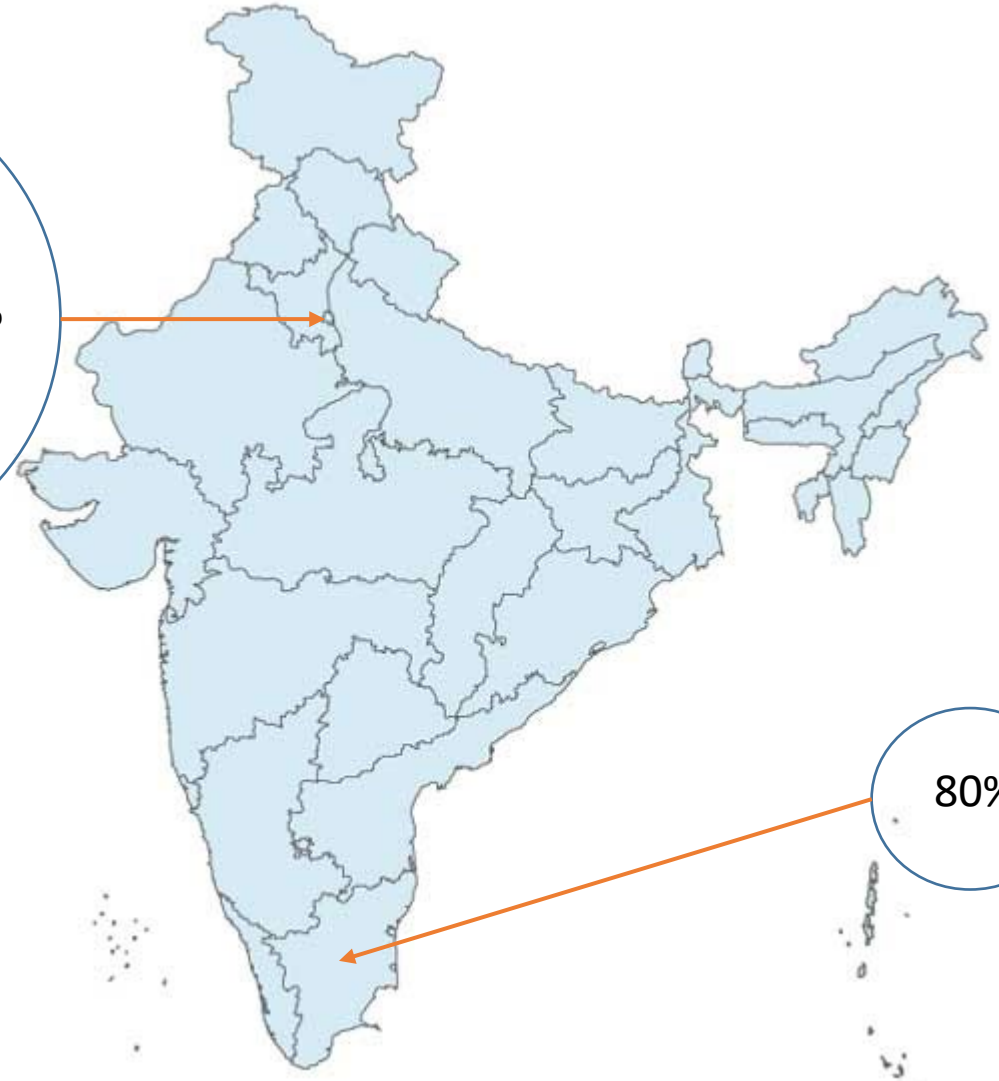
In economically developed countries- kidney or ureter, and are composed predominantly
of calcium oxalate (60–90%) or calcium phosphate (10–20%).
On the contrary, in low-income countries- bladder stones are more common and are formed by uric
acid or ammonium

López M, Hoppe B (2010) History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol

Higher in boys in first decade and in girls in second decade….males in adulthood..

Tasian GE Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin. J Am Soc Nephrol. 2016

Monogenic- 11%
Hypercalciuria-35.1%
Hyperoxaluria-24%
Both-11%
Metabolic cause-56%



80%

Overall-33-91%

Mandal A, Indian J Pediatr Jan 2023
Ramya K , Indian J Pediatr 2021

Why is it important to evaluate children for metabolic causes of renal stones/ What are the Risk factors for renal stones in children

- Idiopathic hypercalciuria, hyperoxaluria, hyperuricosuria, hypercalcemia,
- Vitamin D excess, Dent's disease, cystinuria and
- Familial hypomagnesemia with hypercalciuria (FHHNC) might contribute to pediatric UL
- Initiation of specific therapies

The high recurrence rate is considered a major issue in pediatric urolithiasis.
Lack of treatment results in a 50% recurrence rate within 7 years after the first colic episode

Lande MB. Role of urinary supersaturation in the evaluation of children with urolithiasis. Pediatr Nephrol 2005

Risk Factors

- Urinary tract Malformations,
- Obesity, dehydration, high salt intake, high intake of proteins, low urine citrate, high urate, lower urine pH
- Preterm birth, low birth weight, and admission to neonatal care units, as renal immaturity and exposure to nephrotoxic drugs, as well as the use of diuretics
- Chronic bowel diseases leading to malabsorption which causes an increased intestinal absorption of oxalate.
- Neurological diseases, associated with reduced fluid intake.
- Use of drugs such as diuretics, anticonvulsants, antibiotics, and vitamin D supplementation.

N=72

Metabolic risk factors

S. No.	Etiology	n (%)
1.	Hyperoxaluria*	25 (34.7)
2.	Idiopathic hypercalciuria	21 (29.2)
3.	Idiopathic hyperuricosuria#	3 (4.2)
4.	Cystinuria	3 (4.2)
5.	Magnesium ammonium phosphate with calcium carbonate apatite (staghorn calculus)	2 (2.8)
6.	Urate transporter defect	2 (2.8)
7.	Ammonium urate stone (vesical stone)	1 (1.4)
8.	Vitamin D toxicity	1 (1.4)
9.	Idiopathic hypercalcemia of infancy	1 (1.4)
10.	Mixed stones$	9 (12.5)
11.	Idiopathic	4 (5.5)

Ramya K. Indian J Pediatr (April 2021)

Why do renal stones form/physiology of stone formation

Age, Profession, Nutrition, Climate, Inheritance, Sex, Mentality, Constitutions, Race

⇩

Abnormal renal morphology, Disturbed urine flow, Urinary tract infection, Metabolic abnormalities, Genetic factors

⇩

Increased excretion stone forming constituents, Decreased excretion of inhibitors of crystallizations

⇩

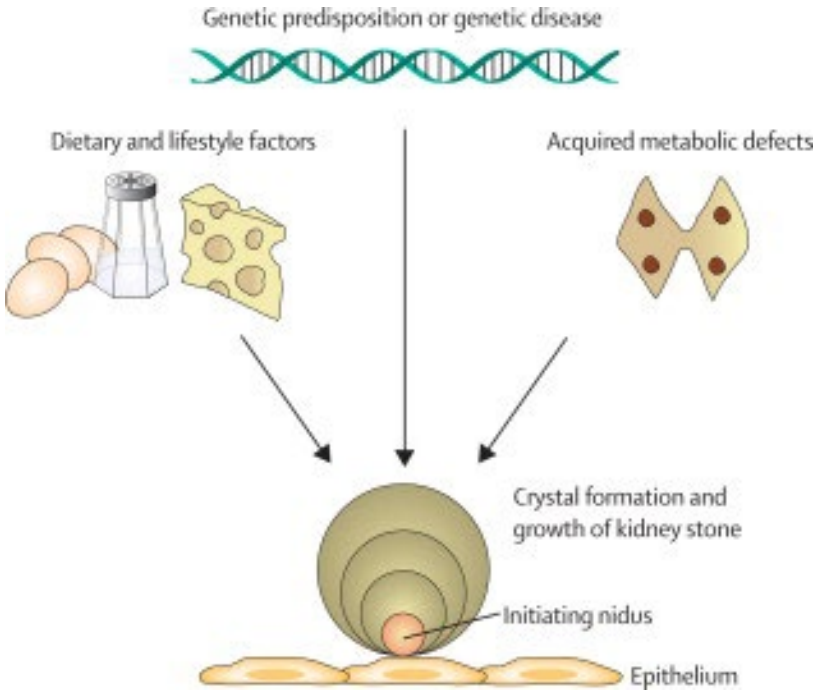
Physico–chemical change in the state of supersaturation

⇩

Abnormal crystalluria, Crystal's aggregations, Crystal's growth

⇩

Formation of stone[20]



Types of Renal stones

	Percentage of stones	Characteristics
Crystal		
Calcium oxalate-monohydrate	40–60%	Radio-opaque Well circumscribed
Calcium oxalate-dehydrate	40–60%	
Calcium phosphate (apatite; $Ca_{10}[PO_4]_6[OH]_2$)	20–60%	
Calcium phosphate (brushite; $CaHPO_4 \cdot 2H_2O$)	2–4%	
Uric acid Rarely staghorn	5–10%	Radiolucent
Struvite (magnesium ammonium phosphate) Can be staghorn	5–15%	
Cystine	1·0–2·5%	Mildly opaque
Ammonium urate	0·5–1·0%	
Mixed stones		
Mixed calcium oxalate-phosphate	35–40%	
Mixed uric acid-calcium oxalate	5%	

Kidney stones: pathophysiology and medical management Lancet 2006

Mixed stones
Calcium oxalate+ calcium phosphate+ uric acid

Calcium oxalate +calcium phosphate stones

Struvite stones: Magnesium ammonium phosphate with other solutes

Kirejczyk JK. An association between kidney stone composition and urinary metabolic disturbances in children. J Pediatr Urol. (2014)

What are the signs and symptoms of presentation of renal stones in children and in adults

- May remain asymptomatic
- Infant: Inconsolable crying, Abdominal pain, Irritability
- School age children and Adolescents: Renal Colic
- Non glomeru[illegible]ria
- Recurrent UT[illegible]
- Acute Renal [illegible]ention: Rarely

Abdominal pain-87%
Gross Hematuria- 26%
Dysuria- 20%
Passage of calculus per urethra- 7/54
UTI-5/54

Mandal A, Indian J Pediatr Jan 2023

Clinical features [n (%)]	
a) Flank pain/renal colic	41 (56.9%)
b) UTI	29 (40.3%)
c) Hematuria	29 (40.3%)
d) Vomiting	11 (15.3%)
e) Passage of stone in urine	5 (6.9%)
f) Post renal AKI (obstructive hydronephrosis)	4 (5.6%)
g) Recurrent calculi	2 (2.8%)
h) Hypertension	2 (2.8%)
i) Hydronephrosis (stone detected on CT scan)	1 (1.4%)
j) Incidental	1 (1.4%)

Naseri MM. Urolithiasis in the first 2 months of life. Iran J Kidney Dis. 2015;9:379-385.

Ramya K. Indian J Pediatr (April 2021)

What are the metabolic factors that need evaluation in stone formers. In other words how do we proceed with evaluation in a child with stone

1. F
2. L

Item	Frequency	Substrates
24 hr Urine collection	Once	Oxalate and amino acids
	3 times	Creatinine, proteins, beta 2 microglobulin, Na, K, Cl, Ca, P, Mg, uric acid, citrate
Urine microscopic examination	3 times	Crystals and urine sediment
Blood test	Once	Urea, creatinine, uric acid, Na, K, Cl, Ca, P, Mg, EAB
Timing of collection …should be kept in mind- Avoid acute infections, dehydration, paired samples Preferably a month after the acute event has been resolved and child is on normal diet and fluid intake		

Random and 24 hr urine corrected for creatinine for metabolites

	24-h urine	Random urine corrected by creatinine		Random urine factored for GFR
Volume	⩾ 1.0 mL/kg per hour			
Creatinine	2 to 3 yr: 6 to 22 mg/kg > 3 yr: 12 to 30 mg/kg			
Calcium	< 4.0 mg/kg (0.10 mmol/kg)	Age	mg/mg; mmol/mmol	< 0.10
		0-6 mo	< 0.80; < 2.24	
		6-12 mo	< 0.60; < 1.68	
		1-2 yr	< 0.40; < 1.12	
		2-18 yr	< 0.21; < 0.56	
Citrate	⩾ 400 mg/g creatinine	⩾ 0.28 (mmol/L/mmol/L)		> 0.18 (mg/L/mg/L)
Calcium/Citrate	< 0.33	< 0.33		
Na/K	⩽ 3.5	⩽ 3.5		
Uric acid	< 815 mg/1.73 m^2 BS	< 0.65		< 0.56 mg < 0.03 mmol
Cystine	< 60 mg/1.73 m^2 BS	< 0.02 (mg/mg) < 0.01 (mmol/mmol)		
Magnesium	> 88 mg/1.73 m^2 BS			
Oxalate	< 50 mg/1.73 m^2 BS < 0.49 mmol/1.73 m^2 BS	Age	(mg/mg)	
		0-6 mo	< 0.30	
		7 mo-4 yr	< 0.15	
		> 4 yr	< 0.10	
Phosphate		TP/GFR: > 2.8 and < 4.4 mg/dL[1]		

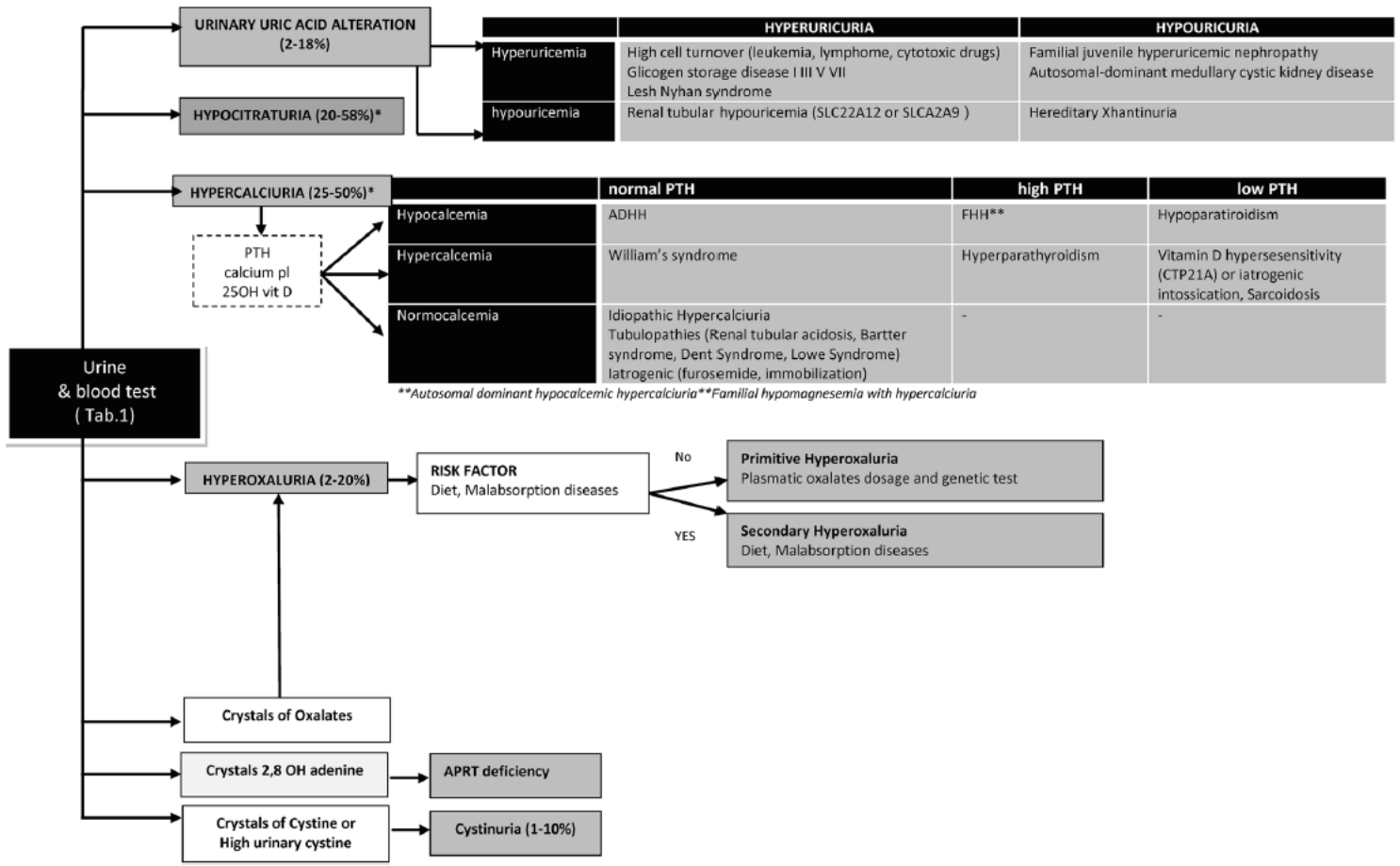


Fig. 2 Diagnostic algorithm for diagnostic evaluation of pediatric urolithiasis. Urine and blood test are described in Table 1. * Hypercalciuria and hypocitraturia can be associated with hyperoxaluria

In acute cases ….

- Urine routine, bacterioscopy of uncentrifuged urine, urine culture and antibiogram
- plain abdominal radiography (Rx) and kidney and urinary tract USG.

- Suspected acute pyelonephritis,
- a complete biochemical evaluation should be performed to appropriate patient monitoring and evaluation of the severity of this clinical condition.

Genetic conditions that may be relevant/actionable in pediatric nephrolithiasis

Pediatric Nephrology (2023) 38:625–634
https://doi.org/10.1007/s00467-022-05613-2

REVIEW

Genetic assessment in primary hyperoxaluria: why it matters

Giorgia Mandrile[1] · Bodo Beck[2] · Cecile Acquaviva[3] · Gill Rumsby[4] · Lisa Deesker[5] · Sander Garrelfs[5] · Asheeta Gupta[6] · Justine Bacchetta[7] · Jaap Groothoff[5] on behalf of the OxalEurope Consortium/Erknet Guideline Workgroup On Hyperoxaluria

Some mutations are signifcantly linked to **pyridoxine-sensitivity in PH1, such as homozygosity** for p.G170R and p.F152I combined with a common polymorphism- better outcomes

Indian Journal of Pediatrics
https://doi.org/10.1007/s12098-022-04234-9

ORIGINAL ARTICLE

Metabolic and Genetic Evaluation in Children with Nephrolithiasis

Anita Mandal[1] · Priyanka Khandelwal[1] · Thenral S. Geetha[2] · Sakthivel Murugan[2] · Jitendra Meena[1] · Manisha Jana[3] · Aditi Sinha[1] · Rajeev Kumar[4] · Amlesh Seth[4] · Pankaj Hari[1] · Arvind Bagga[1]

Mandal et al – Genetic etiology -11%

What imaging is needed in children presenting with renal stones: A Sandhu

- Ultrasound KUB
- Plain X-Ray (after adequate bowel preparation)
- CT- Non contrast, highly sensitive and specific,

Calculi migration may be followed by US

Pediatric age: radiation/ sedation

- Ultra-low dose non-contrast CT scans - US is non-diagnostic or for which the knowledge of anatomical details can be useful for the surgical strategy

What are the non pharmacological measures you advise to patients with stones

- Adequate hydration- 70-100 ml/kg/day
- Ensure a urine flow of at least 1 ml/kg- ideally 2-3 ml/kg/day
- Fluid intake be distributed throughout the day and half being water

Word of caution: Beverages

Pro-lithogenic:Apple and Grapefruit

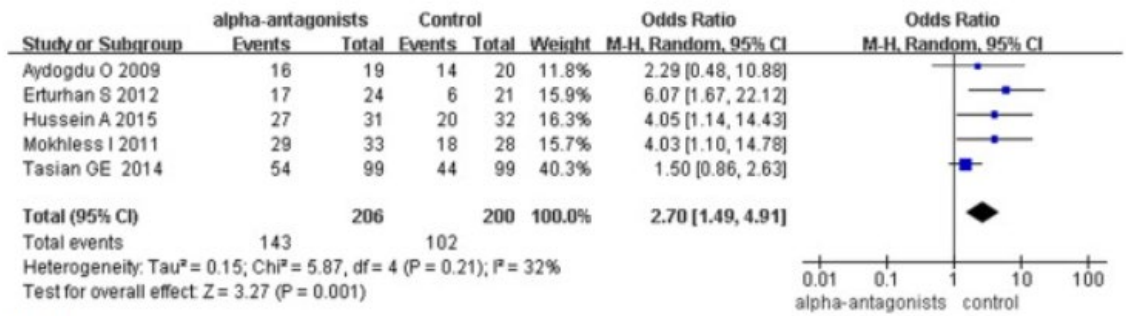
Phosphoric acid containing bevarages

Anti-lithogenic: Coffee , Tea, Alcohol

When do we need to start medications in stone disease and what medications

Medical Expulsive therapy (MET)

- Alpha-blockers or calcium channel blockers has been
- Relax ureteral smooth muscle and enlarge the distal third of the ureter.



Study or Subgroup	alpha-antagonists Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Aydogdu O 2009	16	19	14	20	11.8%	2.29 [0.48, 10.88]
Erturhan S 2012	17	24	6	21	15.9%	6.07 [1.67, 22.12]
Hussein A 2015	27	31	20	32	16.3%	4.05 [1.14, 14.43]
Mokhless I 2011	29	33	18	28	15.7%	4.03 [1.10, 14.78]
Tasian GE 2014	54	99	44	99	40.3%	1.50 [0.86, 2.63]
Total (95% CI)		**206**		**200**	**100.0%**	**2.70 [1.49, 4.91]**
Total events	143		102			

Heterogeneity: Tau² = 0.15; Chi² = 5.87, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 3.27 (P = 0.001)

Fig. 4

Alpha-antagonists stone expulsion rate.

Indication of MET: Non obstructive, small <10 mm and in distal part of ureter (2 mm from ureterovesical junction)

MET is safe and effective choice for ureteral stones in children

Tian D (2017) The efficacy and safety of adrenergic alpha-antagonists in treatment of distal ureteral stones in pediatric patients: a systematic review and metaanalysis. J Pediatr Surg

Velázquez N, Zapata D et al (2015) Medical expulsive therapy for pediatric urolithiasis: systematic review and meta-analysis. J Pediatr Urol

Medications effective..

- Acute setting; NSAID'S

Alleviates: ureteral oedema/increased peristalsis/Pelvic pressure

Monitor Renal function

- Increase Hydration
- Urine flow >1 ml/kg protects
- Do not exceed 2 litres

Instruct the patient to look for passage of stone (60-70% pass spontaneously)

Other drugs effective in setting of acute renal colic

n-scopolamine butylbromide, amitriptyline, calcium channel blockers, steroids, morphine and analogues used in cases of intractable pain and alpha-1 blockers (*e.g.*, tamsulosin)

Specific Medications for specific conditions

Condition	Medical management options
Hypercalciuria	High fluid intake, RDA intake of Protein and calcium, citrate and thiazides
Hypocitraturia	Potassium citrate(0.25-0.5 meq/kg/day) Adequate hydration Urine PH not> 6.5
Hyperoxaluria	
Uric Acid stones	
Cysteine stones	Potassium citrate (1.0-3.0 mEq/kg) is recommended to raise pH up to 7.0 D Penicillamine, Tiopronin (alpha-mercaptopropionylglycine_alpha-MPG)

Benefits on BMD with use of Thiazides and/or potassium citrate

Schwaderer AL, Cronin R, Mahan JD, Bates CM. Low bone density in children with hypercalciuria and/or nephrolithiasis. Pediatr Nephrol 2008; 23: 2209-2214

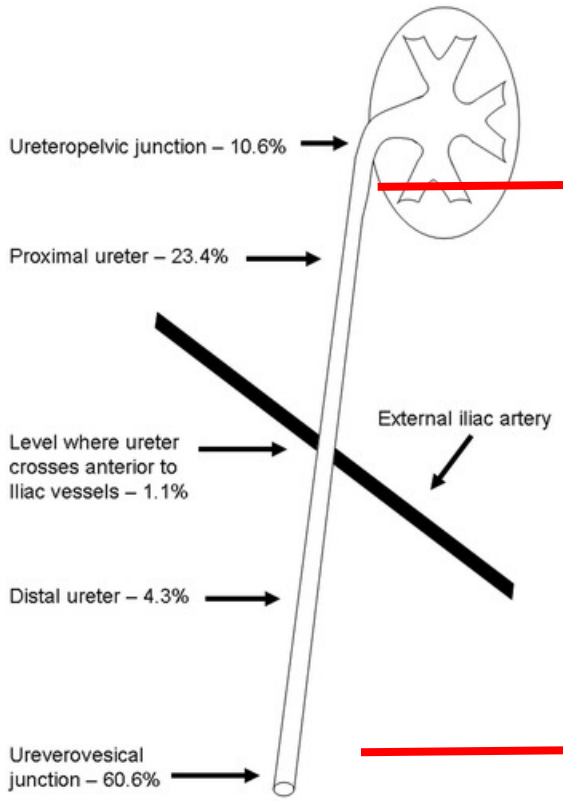
What Dietary intervention should be advised to these children

The diet should be corrected
and appropriate to the child or adolescent's needs and
recommended normal diet for calcium, calories and proteins according to RDA.
The ideal daily intake of sodium varies according to age: 1.2 g for 4-8 years old children, 1.5 g for those aged 9-18 years. The corresponding upper limits are 1.9 g and 2.3 g, above which health risk may be attributable[87]. Potassium is mostly provided
as dairy products, vegetables and fruits. Its optimal recommendations also vary according to age: 3.8 for 4-8
years old children and 4.5 g for those between 9 and 18

Another possible dietary intervention is the reduction of
animal derived protein intake (such as red meat)

Stone formation is also associated with
ingestion of other sugars (sucrose, fructose), vitamins (vitamin C), while magnesium and phytate may impair calculus formation
Fats and sugars need to be avoided, because they
may predispose to obesity,

Indications of surgical intervention in pediatric nephrolithiasis



Intractable pain, obstruction or associated infection.
Proximal ureter include: calculi with a diameter > 5 mm; calculi with diameter < 4 mm associated with complete obstruction, urosepsis, solitary kidney, renal function deterioration, intractable symptoms, and no migration of the calculus for six weeks

Distal Ureter: calculi with diameter > 7 mm; calculi with diameter < 6 mm associated with complete obstruction, urosepsis, solitary kidney, renal function deterioration, intractable symptoms, and no migration for six weeks

Moreira Guimarães Penido MG et al . Pediatric primary urolithiasis. 2015 WJN

Approach to surgical intervention in pediatric nephrolithiasis

Minimally invasive surgeries preferred…

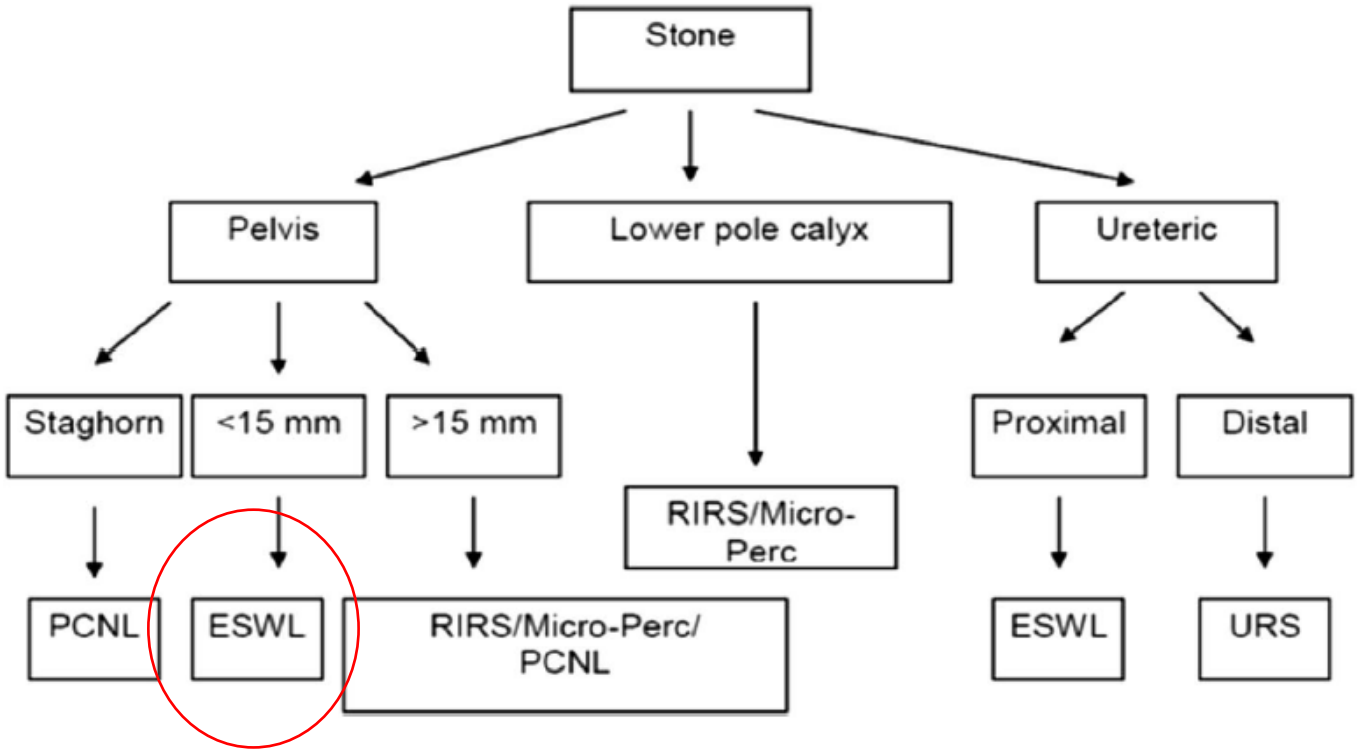
General anaesthesia needed for all procedures

Open surgery needed in

- Associated structural abnormalities (pelvi-ureteric or ureterovesical junction obstruction),
- Large burden of infective and staghorn stones,
- Large bladder calculus particularly in augmented bladder

Approach to surgical intervention in pediatric nephrolithiasis

First Choice: ESWL
? Long term effects of shock wave on developing kidney



Surgical options available for pediatric NL (in terms of treatment of smaller infants)

"**micro-perc**" system: a 4.85 Fr "all-seeing needle" is used for direct access with no need for dilatation.

Stone-free rate - 83 and 90%,

[but the success rate decreases if micro-perc is used for stones > 2 cm and those in an obstructed collecting system]

- Ureteroscopy/retrograde intrarenal surgery - less invasive technique than the percutaneous renal surgery [58 and 100% success rate]

especially for stone sizes < 2 cm or stones located in the lower pole calices, where ESWL is contraindicated

How are they followed up in surgical practice/medical practice

Medical Practice

Ultrasound scan

Urine examinations

Urinary excretion of metabolites eg. Calcium, Proteins..

Urine p H

Surgical practice

Ultrasound scan at 4 weeks

Urinalysis 6 monthy

Take home messages

1. Metabolic evaluation for all children

2. Genetics

3. Adequate fluids, dietary modification, targeted therapies

4. Surgical intervention – where indicated

5. Follow up

CHRONIC KIDNEY DISEASE (CKD) IN CHILDREN

Dr.Amarjeet Mehta
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Joint Director
State Organ and Tissue transplant Organisation (SOTTO)

CKD--A SCARY CHALLANGE

IMPORTANCE

- CKD has higher prevalance than appreciated
- It not only results in renal disease,but increases risk of cardiovascular disease
- Outcomes of CKD may be improved with treatment
- Initial diagnosis can many times be with simple tests during the early stage of the disease

DEFINITIONS AND STAGES

- CKD has been defined as the presence of **kidney damage** or GFR<60ml/min/1.73m2 for 3 months or more irrespective of the diagnosis
- **Kidney damage** is usually identified by the presence of markers of disease that are present in the blood,urine,or imaging studies,rather than a kidney biopsy.
- GFR provides the best measure of overall kidney function

ESRD(End Stage Renal Disease :

(*CKD stage 5*)

ESRD is defined as either :

1) GFR 15 mL/min/1.73 m², or
2) Need for the initiation of kidney replacement therapy (dialysis or transplantation).

AZOTEMIA : Biochemical abnormality
i.e. , increase in BUN & serum creatinine values.

UREMIA : Azotemia associated with constellation of clinical sign & symptoms .

NKF-K/DOQI CLASSIFICATION OF CKD

Stage	GFR ml/min/1.73m2	Description	Action plan
1	>90	Kidney damage with normal or increased GFR	Treat primary and co morbid conditions
2	60-89	Kidney damage with mild reduction of GFR	Estimate rate of progression of CKD
3	30-59	Moderate reduction of GFR	Evaluate and treat complications
4	15-29	Severe reduction of GFR	Prepare for kidney replacement therapy
5	<15(or dialysis)	Kidney failure	Kidney replacement therapy

Classification of CKD Based on GFR and Albuminuria Categories: "Heat Map"

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppls*. 2013;3:1-150.

NORMAL LEVELS OF GFR IN CHILDREN AND ADOLESCENTS

AGE (SEX) (ml/min/1.73m)	Mean GFR+SD
1wk (males and females)	41+15
2-8 wk(males and females)	66+15
>8wk(males and females)	96+22
2-12y(males and females)	133+27
13-21y(males)	140+30
13-21y(females)	126+22

Schwartz formula estimates GFR

Creatinine clearance [ml/ min/ 1.73 m^2]

$$\frac{k \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$$

k = 0.413

Pediatr Nephrol.2009;24:113-119

RENAL FAILURE IN INDIA

- 100,000 patients develop renal failure/year
- 90% never see a nephrologist.

- Of the 10,000 RRT is offered in 90%, 10% are unable to afford it.

- 17 to 23% of these patients undergo a renal transplantation.(2500-3500 transplants every year)

END STAGE RENAL DISEASE IN CHILDREN

- ESRD is defined as decline in renal functions where life threatening biochemical abnormalities persist in spite of optimal medical management.
- Prevalence rates unavailable
- Require RRT as Dialysis or Transplantation.
- **Approx 30,000 children in India**

  Less than 50 transplants annually

ETIOLOGY AND OUTCOME OF CKD IN INDIAN CHILDREN

- "CKD in India carries a poor prognosis due to late referral and the limited availability and high cost of renal replacement therapy"
- In children < 5 yr – congenital anomalies are common.
- In children > 5 yr – acquired diseases (glomerulonephritides) & inherited disorders are common.

Causes - CRODH

- C- Chronic Glomerulonephritis-30%
- R – Reflux Nephropathy-15%
- O- Obstructive Nephropathy -30%
- D- Dysplastic Kidney-5%
- H – Hereditary- ARPKD, ADPKD, ALPORT, JVN, CAKUT -10%

No cause -10%

THE KIDNEY

MAINTAINS

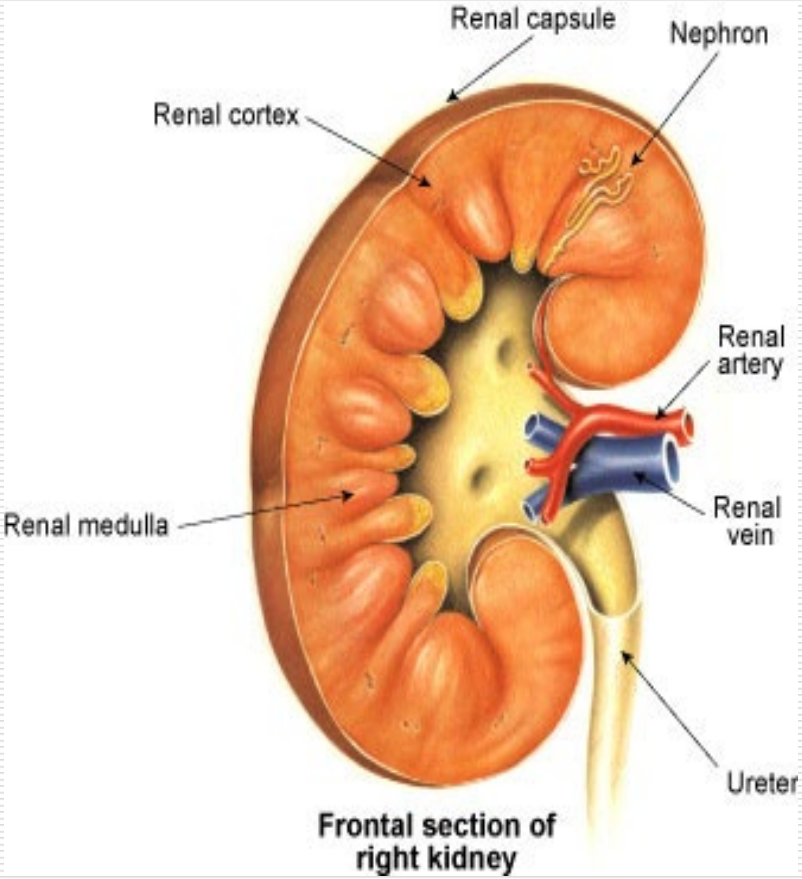
- Fluids balance
- Electrolyte balance
- Acid base balance
- Mineral homeostasis

SECRETES

- Erythropoietin
- Renin-angiotension
- Activated vitamin D

EXCRETES

- Wastes (BUN and creatinine,uremic toxins)
- Drugs



PRESENTATION

- Asymptomatic in its earliest stages (stage I and II).
- Signs and symptoms in advanced CKD :
- Volume overload, CHF
- Metabolic acidosis , Rapid breathing
- Hypertension
- Anemia , malnutrition
- Bone disease (refractory rickets , deformities)
- Cardiovascular disease
- Anorexia, nausea, vomiting
- Short stature , FTT
- Encephalopathy (dec concn., seizures , coma)
- Developmental delay , poor cognitive function
- Delayed puberty
- Bleeding

TEDIOUS WORK TO DO

Evaluation and Treatment

Patients with CKD should be evaluated to determine:

1. Diagnosis (type of kidney disease)
2. Comorbid conditions (such as hyperlipidemia)
3. Severity, assessed by level of kidney function
4. Complications, related to level of kidney function
5. Risk for loss of kidney function
6. Risk for cardiovascular disease.

Evaluation at onset; periodically thereafter

Growth (weight for age, height for age, weight for height)
Blood pressure (stage of hypertension), evidence of end-organ damage.

Laboratory :

CBC ; PBF
Blood urea, creatinine, uric acid; electrolytes; pH, bicarbonate (VBG)
Calcium, phosphorus, alkaline phosphatase; Parathyroid ; 25-hydroxyvitamin D.
Total protein, albumin; transaminases
Iron studies (ferritin, transferrin saturation)
Urinalysis; spot or timed protein to creatinine ratio

Imaging :

Chest radiograph; ECG ; echocardiography
Radiographs for mineral bone disease (rickets, osteomalacia, osteitis fibrosa cystica)(bone age estimation).

Evaluation for cause

History and physical examination
Urinalysis; 24-hr urine protein, creatinine

Suspected structural cause :
USG for kidney, ureters and bladder
MCUG , CT scan with contrast, MR urography
Radionuclide DTPA, MAG-3 scintigraphy

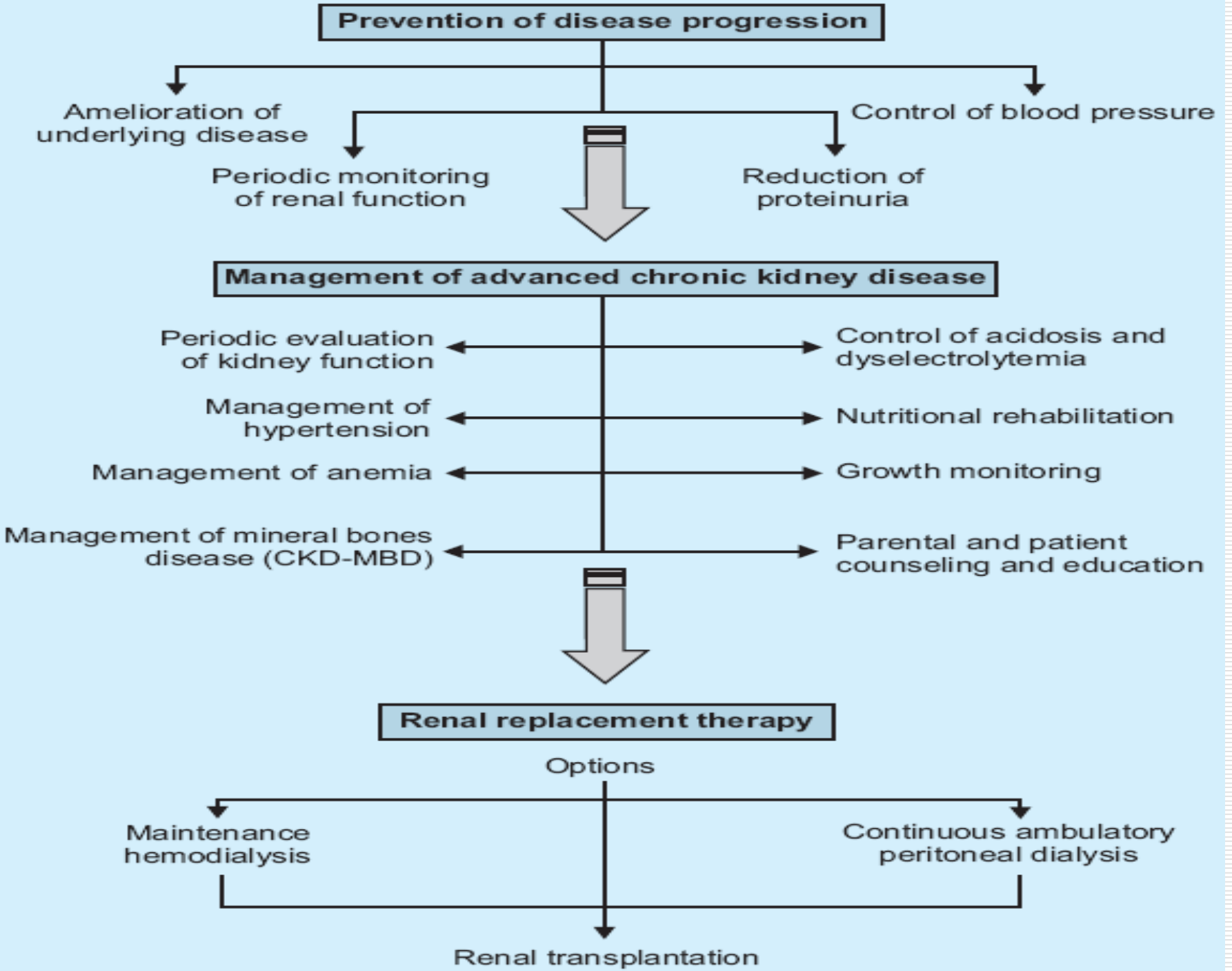
Suspected tubulointerstitial disease :
DMSA renal scan
MR urography
Renal histology (in select cases)

Evaluation for glomerular disease :
Eye; Hearing
C3; ANA , anti dsDNA ab , ANCA
Hepatitis B surface antigen; hepatitis C antibody; HIV antibody
Renal histology

MANAGEMENT OF CKD

ABC of Management of CKD

- **A**- Anaemia,Acidosis
- **B**- Bone Disease
- **C**- Control Proteinuria
- **D**- Drug doses,dyslipidemia
- **E**- Electrolytes
- **F**- Food
- **G**- Growth monitoring
- **H**- Hypertension
- **I**- Immunization


Prevention of disease progression
Amelioration of underlying disease
Periodic monitoring of renal function
Control of blood pressure
Reduction of proteinuria
Management of advanced chronic kidney disease
Periodic evaluation of kidney function
Management of hypertension
Management of anemia
Management of mineral bones disease (CKD-MBD)
Control of acidosis and dyselectrolytemia
Nutritional rehabilitation
Growth monitoring
Parental and patient counseling and education
Renal replacement therapy
Options
Maintenance hemodialysis
Continuous ambulatory peritoneal dialysis
Renal transplantation

A - ANAEMIA IN CKD

- Anaemia should be addressed when hemoglobin falls <80% of the mean level defined for healthy subgroups
- Significant reductions of hemoglobin occur when GFR<30ml/min/1.73m
- KDOQI guidelines recommend a target range of 33-36% for Hct. and 11-12g/dl for hemoglobin for CKD patients

CAUSE OF ANEMIA IN CHRONIC KIDNEY DISEASE

- **DECREASED PRODUCTION**
- IRON DEFICIENCY &VITAMIN B12/FOLLATE DEFICIENCY
- ERYTHROPOIETIN DEFICIENCY
- HYPERPARATHYROIDISM
- NUTRITIONAL DEFICIENCY
- INHIBITORS OF ERYTHROPOIESIS
- ACUTE/CHRONIC INFLAMATION,
- INFECTION AND MEDICATIONS ieACEI

INCREASED LOSS

- INCREASED GI BLOOD LOSS
- IATROGENIC COAGULOPATHY

EFFECTS OF ANEMIA IN CHRONIC KIDNEY DESEASES

Anemia results in

- Decreased physical activity
- Decreased appetite
- Decreased performance on IQ testing
- Impaired cognitive function
- Exercise intolerance
- Growth retardation
- Increase in mortality

Evaluation of Anemia of CKD

- C.B.C.
- Retics
- Peripheral Smear
- Check preexisting conditions i.e.hyperparath.,syst.inflm.cond.
- Assess iron status
- Transferrin Saturation(TSAT)-s.iron x 100 divided by TIBC.Should be kept > 20 %
- S.Ferritin >100 ng /ml.(Total body stores)
- Folate & B-12 levels (Epoitin resistant cases)

Treatment of Anemia

- Correct iron deficiency with oral iron(2-3 mg /kg/day,best given 2-3 hrs. after meals.For patients with decreased iron absorption-Parenteral
- B-12 & folic acid deficiency
- Correct Hyperparathyroidism
- Use Human recombinant Erythropoietin.
- Avoid transfusions if transplant planned.

ERYTHROPOIETIN USE

- Almost universal in children with CKD stage 3 and greater
- May be administered either subcutaneously,IV or intraperitoneally
- Subcutaneously: usually given 2-3 times/week
- Dose 60-600 units/Kg/week
- Advent of erythropoietin has decreased need for transfusions and therefore decrease in incidence of preformed antibodies that influence future renal transplantation.Also decreased incidence of iron overload.
- Long acting ESA available. Once a week

ACID BASE BALANCE

Acidosis in CKD is due to :

1. Diminished reabsorption of filtered bicarbonate,
2. Decreased renal Ammonia production decreased acidification by distal nephron.
3. Persistant acidosis may adversely affect growth

- Treatment is with oral base therapy in a dose of 2-3 mEq/kg, started if serum Bicarbonate level is <15 mEq/l to maintain around 20 mEq/l

B – BONE DISEASE

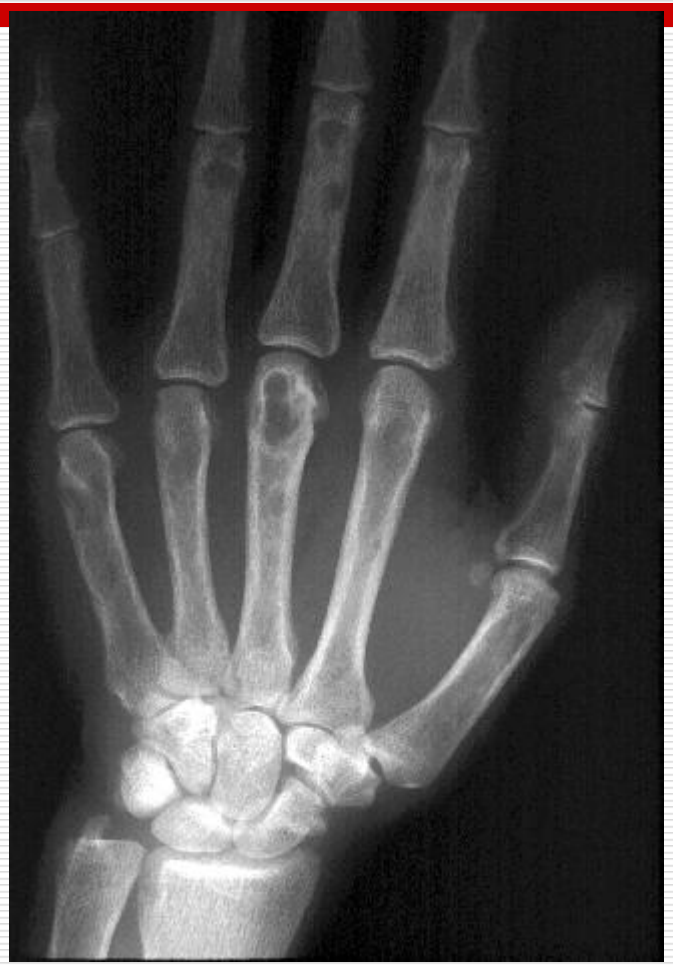
(CKD-MBD)

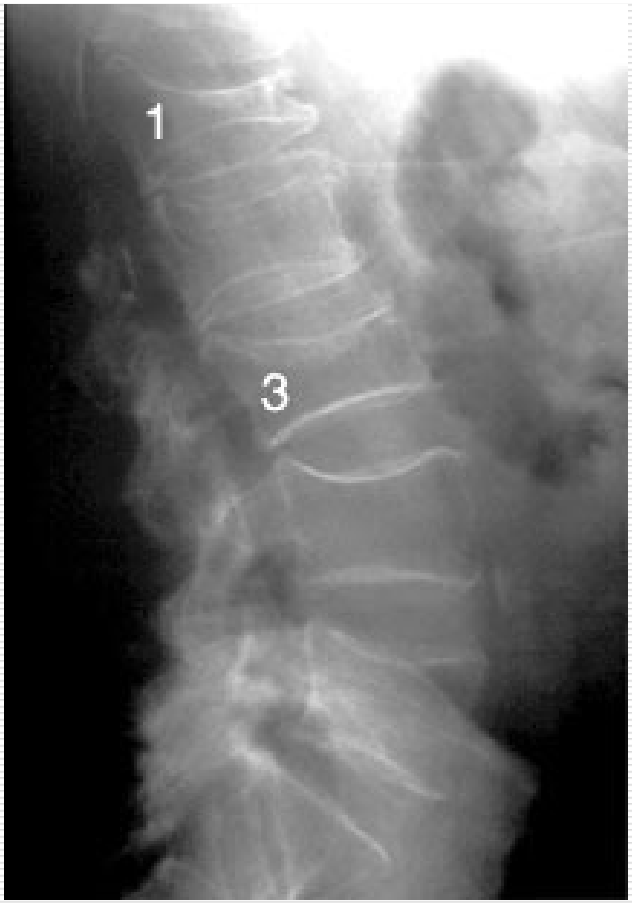
- Secondary Hyperparathyroidism-
  Decreased renal P excretion →hyperphophatemia
- Hypocalcemia
- Impaired production of 1,25-dihydrovit D.

High turnover (PTH 200-300 pg /ml)
Low turnover (PTH <100 pg/ml)

Bone Pain, Fractures, Linear Growth Failure, Delayed Skeletal Maturation, Deformities mimicking VDDR, Slipped epiphyses.

proximal myopathy,Band Keratopathy, Pruritus
Extraskeletal calcification

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B- Bone Disease - Management

- **Reduce Phosphates in diet (800-1000 mg/day) – Ds (Dairy ,Dark soda drinks)**

- **Phosphate Binders – (Serum P –normal age,range & no <2.5 mg/dl)**
  -Aluminum hydroxide – Not recommended (Neurological dysfunction)
  -Calcium Based (Carbonate,Acetate) **Ca X P < 65**
  -Calcium Free (Sevelamer,Lanthanum)

- **1,25 dihydroxyvitamin D3 (Cautiously)**

- **Adequate Ca intake –**
  Limit to 2 x RDA (Diet & Binders), Max 2500mg/day. Usual starting dose 50-60 mg/kg/day of Calcium with MEALS.
- **Monitor PTH levels (Maintain around 150-300 pg/ml**

- **Recognize high Cardiovascular morbidity due to vascular calcification (CIMT)**

C- CONTROL PROTEINURIA

- Progression of CKD centers on impaired glomerular perm selectively to plasma macromolecules such as Protein.
- Protein Reabsorption → Up regulation of pro-inflammatory & vasoactive molecules → Scarring
- ACEI & ARB useful role

D-DIET **(PROTEIN/CALORIES)**

- Excessive protein intake and severe restriction of protein both have a deleterious effect on patients with CKD
- Consensus is to give the recommended dietary allowance of protein (RDA) which is about 1gm/Kg/day & calories100% of RDA.High Density if fluid restricted.
- Vitamins supplemented.Avoid A and C.

Age	Protein Energy©
0-6 months	2.2 g/kg/day 120
6-12 months	1.8 g/kg/day 100
1-10yr	1.2 g/kg/day 80-90
11-14yr	1.0 g/kg/day 60
15-18yr	0.9 g/kg/day 50

D - Dyslipidemias

- Leads to progressive renal injury.Poor Data.
- Diet:->2 yrs. Sat.fatty acids<10% of calories.
- Fat-Not >30% & no <20% of calories.
- Dietary Cholesterol < 300 mg/day.
- Drugs:-Only in >10 yrs.age (after 6-12 mo.diet), LDL Chol.>160mg/dl, h/o IHD,obesity,DM.
- Statins, fibrates on short term. Monitor side effects

D - DRUGS

- Clearance and metabolism of a number of drugs depend on level of kidney function
- Frequency and dosing may have to be adjusted in patients with CKD to prevent toxicity
- Pediatric handbooks and micromedex are helpful resources to adjust dosage and frequency of drugs based on creatinine clearance (not GFR)

- **www.kdp-baptist.louisville.edu/renalbook**

E-ELECTROLYTE BALANCE

Electrolyte balance is fairly well maintained until 75% of the function is lost.

- Sodium balance is maintained in CKD by a progressive increase in the fractional excretion of sodium by remaining nephrons, Fractional excretion cannot increase >20-30% of filtered load and therefore sodium loading can result in hypernatremia
- Conversely children with polyuria may have difficulty conserving sodium and can develop hyponatremia.
- **No edema/Normal BP-usual Na intake is allowed**
- **BP high - 0.8 – 1 gm./day**

ELECTROLYTIC BALANCE

Hyperkalemia results from

- Increased dietary intake, Use of ACEI,
- Use of aldosterone inhibitors ie.spironolactone
- Acute metabolic acidosis
- Pts.with persistant Hyperkalemia should be treated with K-exchange resins.
- Hypokalemia may be seen in patients with RTA or Fanconi's syndrome and with the use of diuretics
- If serum K <3 mEq/l mausami, oranges,almonds,green vegetables given

F-FLUID BALANCE

- In general,children with obstructive uropathies have a concentrating defect and therefore are polyuric - these children get dehydrated easily
- Children with nephrotic syndrome tend to become fluid overloaded secondary to hypoalbuminemia

  It is prudent to restrict fluids to insensibles +losses in children with renal failure

G - GROWTH IN CKD

Causes of growth retardation in CKD

- Metabolic acidosis
- Inadequate nutritional intake
- Anemia
- Renal osteodystrophy
- Pertubations of the growth hormone-insulin like-growth-factor axis

MANAGEMENT OF GROWTH RETARDATION IN CKD

- Correct fluid and electrolyte imbalance
- Correct acidosis
- Optimize nutrition
- Control secondary hyperparathyrodism (to less than 3 times the normal value)
- Use of recombinant human growth hormone (rhGH)

rhGH

- FDA approved for children with CKD(GFR<60ml/min/1.73m) in the presence of growth retardation(SDS more negative than –2.00)
- *No provocative testing for GH levels is required prior to starting therapy*
- Starting dose 0.05mg/Kg/day, 7 days a week subcutaneously
- Because of potential adverse effects : intracranial hypertension,avascular necrosis,slipped capital femoral epiphysis:ophthalmologic consultation and hip radiographs should be obtained prior to starting the therapy

rhGH

- Can be used in children as young as 6 months of age
- Can be used in adolescents at stages III and IV of puberty
- When 50%ile for midparental height is achieved,rhGH may be temporarily discontinued

H – HYPERTENSION

- Uncontrolled hypertension accelerates progress of CKD
- Goal of BP should be <95% ile for age,height percentile and gender

Pathophysiology of HT in CKD

- Sodium retention & Fluid overload .
- Activation of the renin–angiotensin–aldosterone system .
- Sympathetic hyper activation.
- Endothelial dysfunction and chronic hyperparathyroidism.
- Renalase : activity is markedly reduced in patients with ESRD.
- Iatrogenic hypertension : EPO , glucocorticoids and cyclosporine A.
- Endothelial NO synthase : suppressed by hyperparathyroidism

ANTIHYPERTENSION AGENTS

- **A**:angiotensin converting enzyme inhibitors (_____prils) angiotension 1 receptor blockers (____sartans)
- **B**:beta blockers(___ols)
- **C**:calcium channel blockers (___pines)

  centrally acting antihypertensives(clonidine)
- **D**:dilators(vasodilators) ie hydralazine,minoxidil)

  diuretics

I- IMMUNIZATION/INFECTION

- Routine immunization has been shown to be safe and generally effective in CKD patients
- Annual influenza vaccinations during the flu season
- Antibody responses have been variable and may be lower necessitating booster doses .
- UTI and RTI common infections.Symptoms may be mild or absent.Treated Judiciously.

NEUROCOGNITIVE DEVELOPMENT

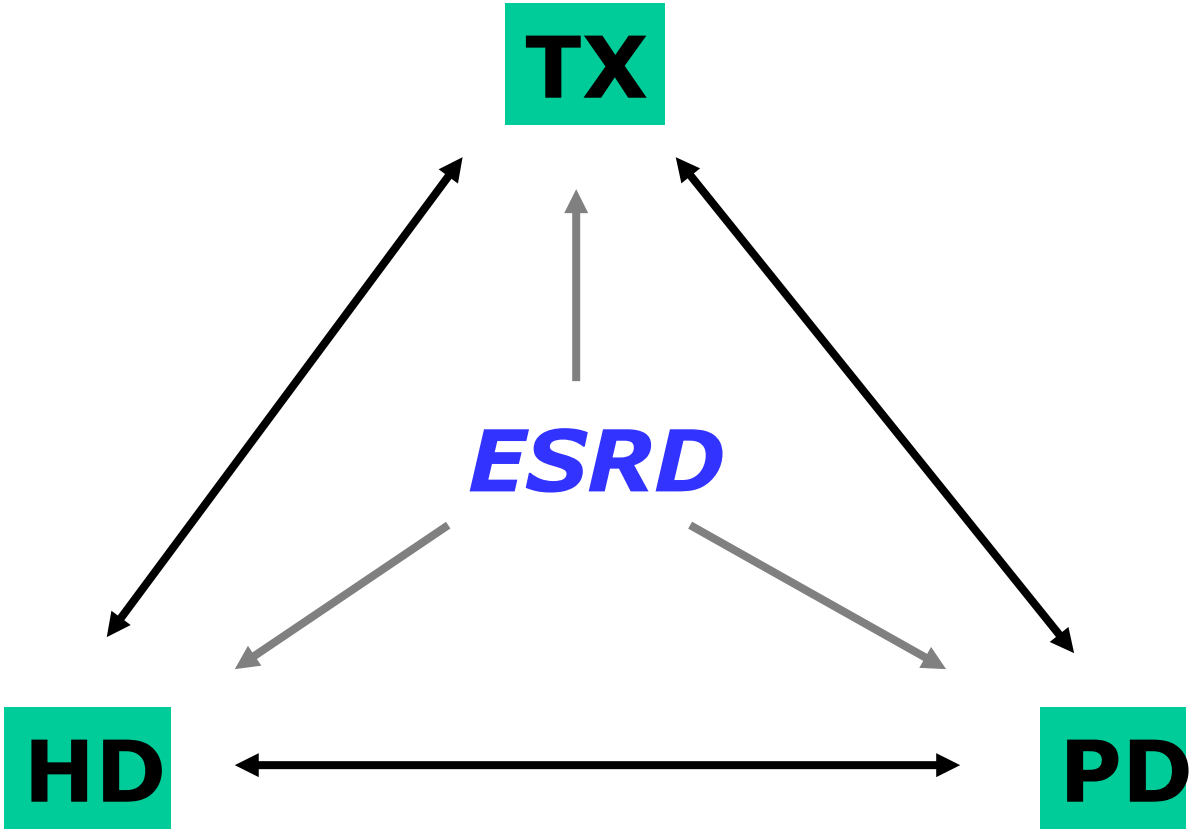
- Decrease in IQ points of about 10-30 % depending on the stage of CKD
- Impairment of cognitive function

- Psychological depression

  Uremic toxins most likely culprit,but aluminium toxicity must ruled out

RENAL REPLACEMENT THERAPY

Choice of Therapy

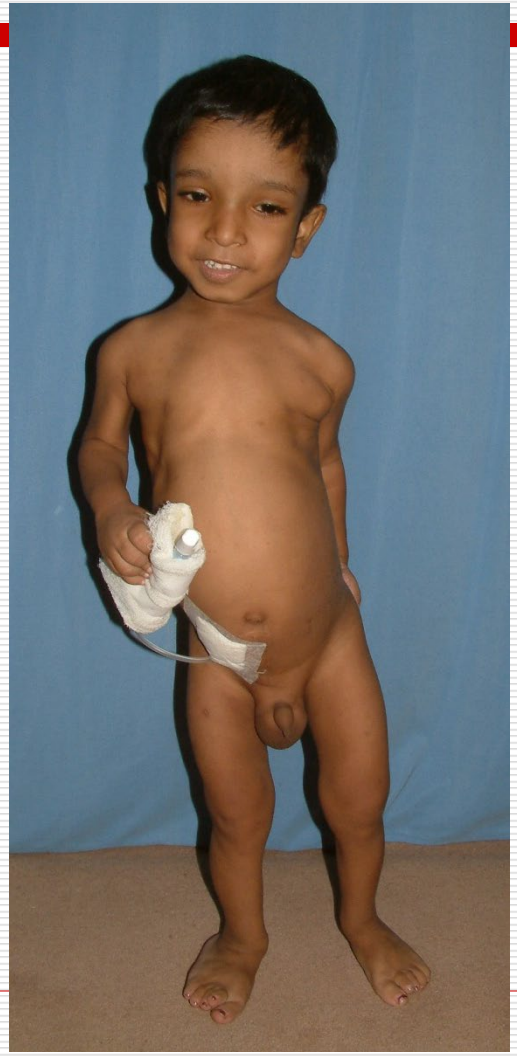


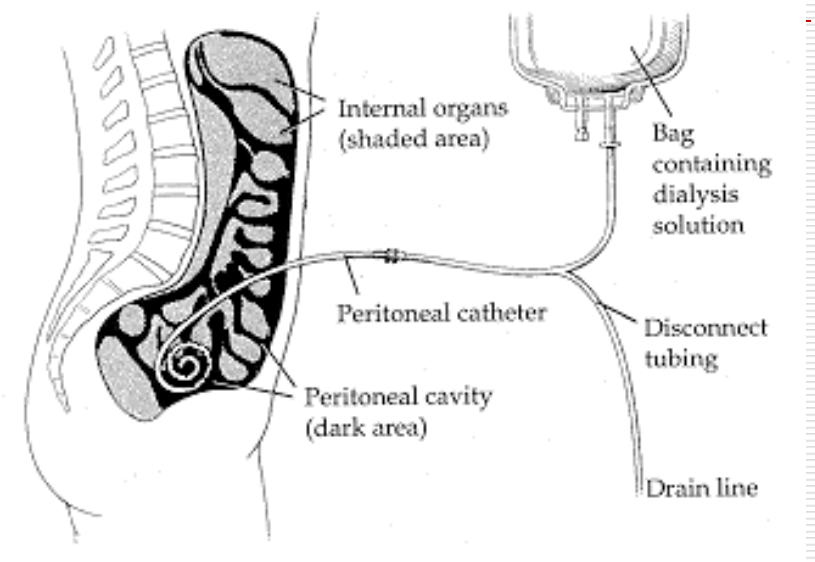
ESRD in Children

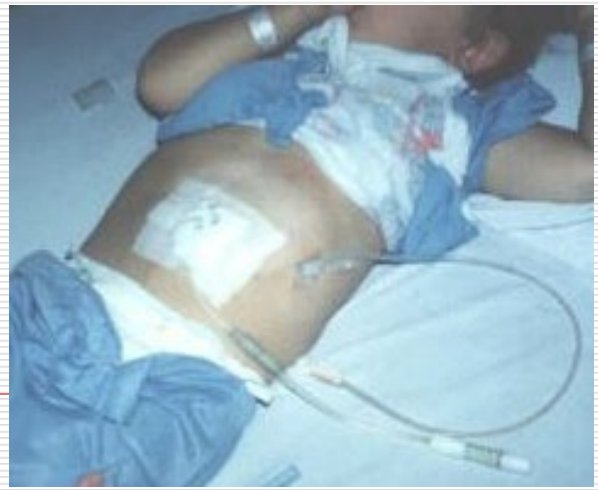
CKD -Prevalance – 17%

1962	Hemodialysis
1971	Pediatric transplantation
1991	Continuous ambulatory peritoneal dialysis

Chronic peritoneal dialysis








90
100

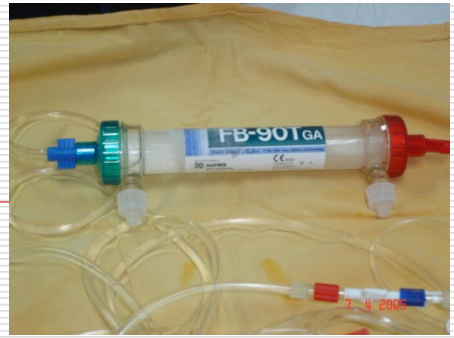
Hemodialysis feasible in >2 yr age

Technical expertise, expense

Central venous access (internal jugular, subclavian, femoral) 90%

Duration 8-10 hr/wk [2-3 sessions]

Dialyzers reused 3-4 times



Indian Pediatr 2002; 39: 375-380

Quality of Life

Because of challenges in access to care, over 50% of patients with advanced CKD are first seen when the eGFR is <15 ml/min per 1.73 m^2

Chronic cycle of dialysis, transplantation

Significant dietetic restrictions

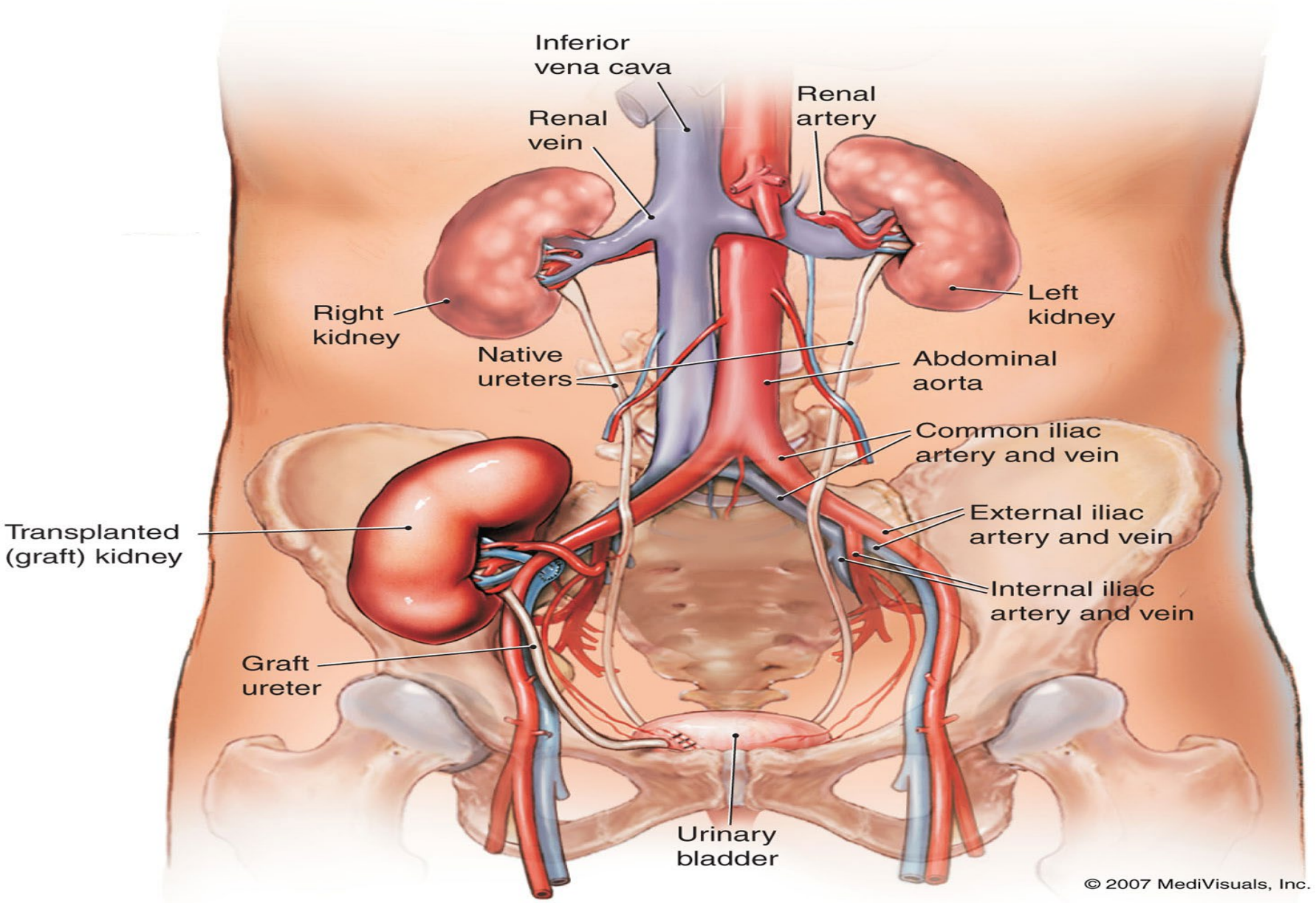
Parents assume responsibility

Medication side effects

Social isolation; dependence; immobility

Dialysis bridge to transplantation

A Grafted (Transplanted) Kidney



TRANSPLANTS (SMS Exp.)

AGE

- 10 years : 1
- 14 years : 3
- 16 years : 1
- All boys
- Donor Mom 5

Explanted -1(Due to thrombosis & Ischemia)

ASSESSMENT OF EFFICASY OF INTERVENTION

- The most commonly used indicators are GFR and proteinuria
- Biopsy is frequently used as a diagnostic tool may sometimes allow us to guage long term responses to therapy
- In the future,morphometry, to access glomurular size of degree of tubulointerstitial injury;in situ hybridization,or PCR of specific areas to examine specific abnormal gene expression and its alteration by therapy,may prove useful.

INDIAN SCENERIO -CKD

- 1.3 billion people are served by 1850 nephrologists , unequally distributed but mostly concentrated in urban centers.
- Nephrology training positions are inadequate to grow the workforce, and the situation is worsened by "brain drain" to developed countries.
- 2017-There are over 130,000 patients receiving dialysis, and the number is increasing by about 232 per million population, a reflection of increasing longevity in general.
- Patients referred late are often anemic, have lower likelihood of hepatitis B immunization, start dialysis without an arteriovenous fistula, and have poorer prognosis and higher mortality at dialysis initiation.
- Protein energy wasting is present in 68%–93% of patients on dialysis from middle and lower socioeconomic strata .
- HD is the most common modality followed by transplantation, and PD is a distant third.
- India is estimated to have about 120,000 patients on HD & 8500 patients on PD
- Transplantation practices are dependent on state welfare funding, brain death declaration practice, personal religious beliefs.

The THOA has led to organ sharing partnerships between private and government hospitals in some states, and this has revolutionized deceased donor transplantation.SOTTO Rajasthan has done 51

CJASN -13(5):p 802-804, May 2018. | *DOI:* 10.2215/CJN.091808172018

Indications –RRT (a,e,i,o,u)

Indications for starting renal replacement therapy

Indication	Comments
Anuria or oliguria	Urine volumes < 200 ml/12 hours
Hyperkalaemia	Serum potassium persistently > 6.5 mmol/litre
Severe acidaemia	pH < 7.1
Serum urea > 30 mmol/litre or creatinine > 300 µmol/litre	Values are not absolute, only a guide
Refractory fluid overload	Especially if compromising lung function
Uraemic complications	Encephalopathy, pericarditis, neuropathy or myopathy
Temperature control	Hyper- or hypothermia
Drug overdose	See Figure 7
Sepsis	

A –acidosis,Anuria

E – Electrolyte (K,Na)

I – Intoxiation

O- Overload

U – Uremic complications

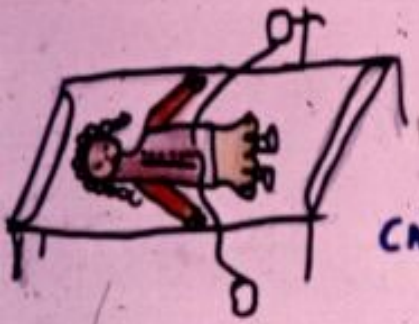
(encephalopathy,Pericarditis)

CONCLUSION

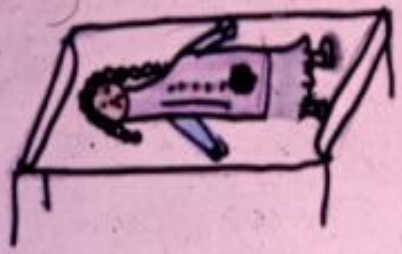
- CKD is on the rise in all the patient groups
- Treatment of ESRD with dialysis and transplantation are costly and need enormous technical expertise
- Therefore early detection and management of CKD in an attempt to prevent progression or retard progression to ESRD would be highly beneficial

I AM 5 YEAR OLD JASMINE SUFFERING FROM CHRONIC RENAL FAILURE I HAVE BEEN THROUGH

PERITONIAL DIALYSIS

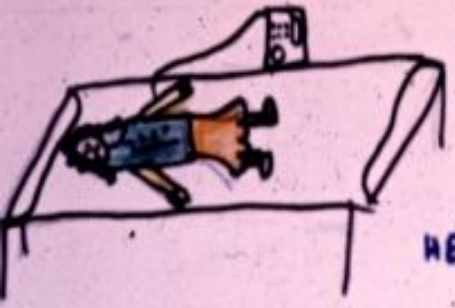


CAPD



LAPAROTOMY

MY DONOR (MUMMY)



HEMODIALYSIS

AND FINALLY TRANSPLANT

JASMINE AFTER TRANSPLANT

Thanks

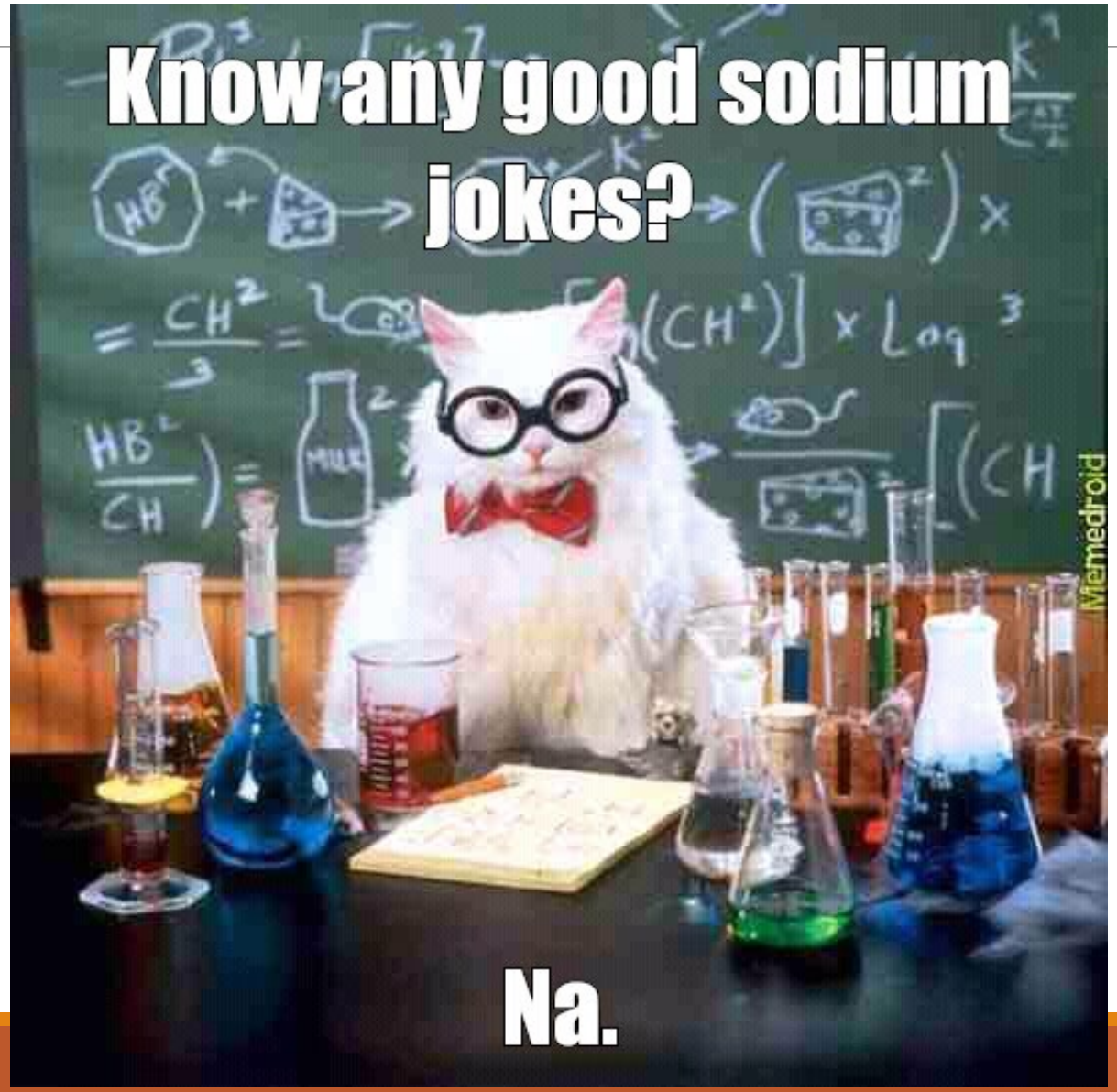
be kind to KIDNEYS

Approach to dysnatremias

RW THERGAONKAR

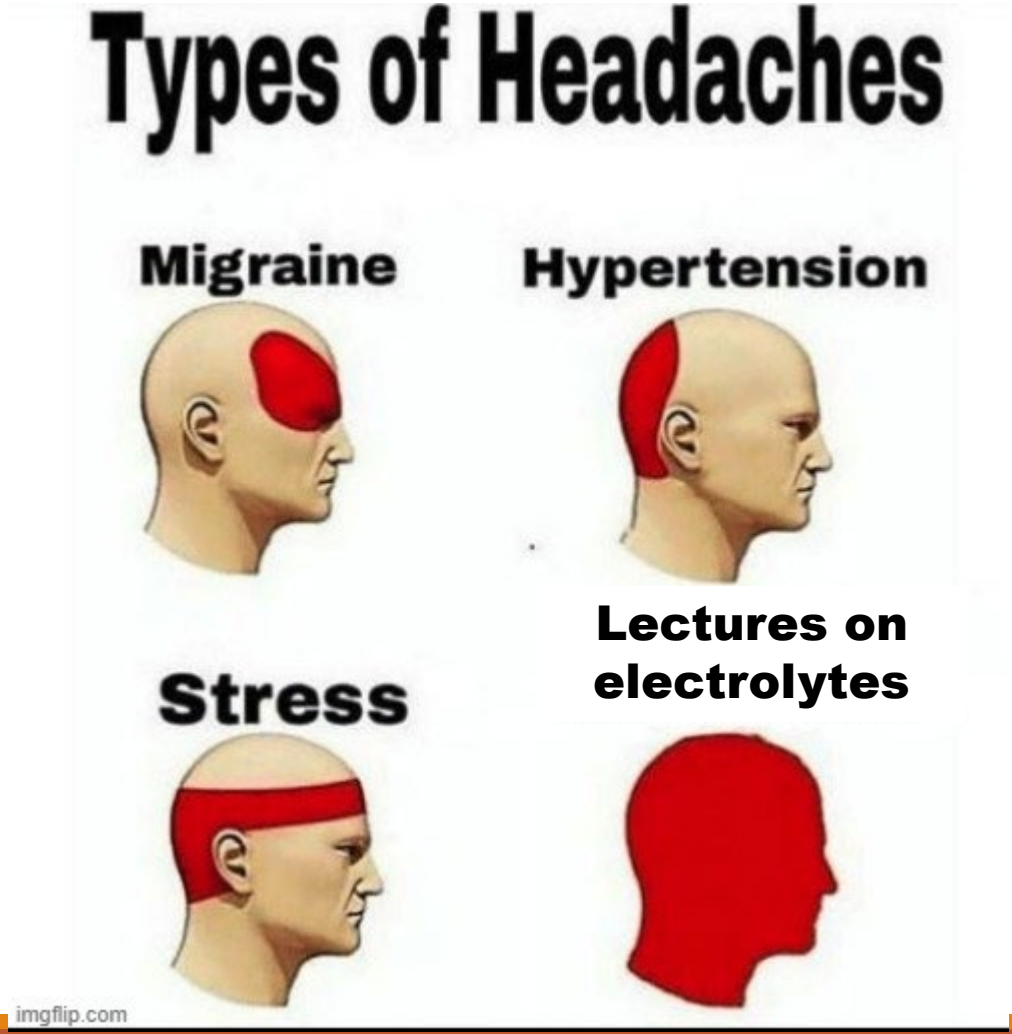
The sodium memefest

“Na”tu- “Na”tu



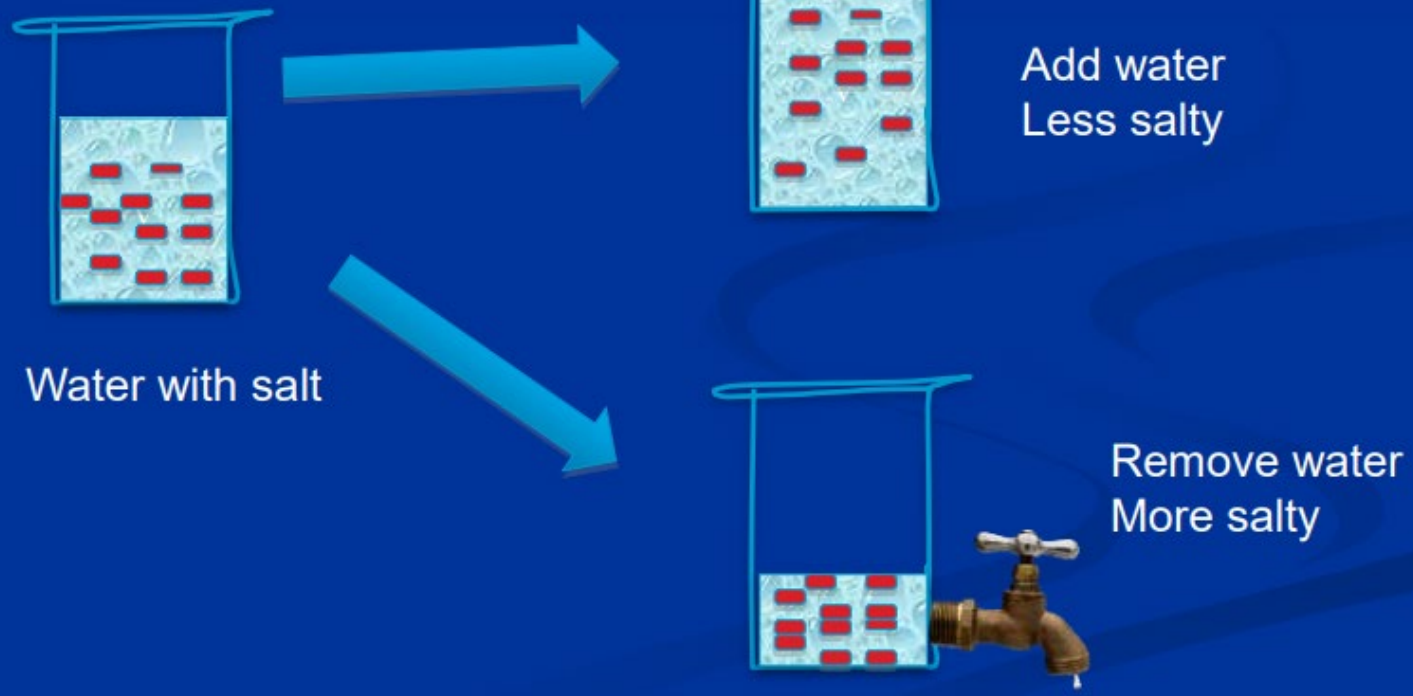
How are you going to be tortured by this talk?

- Overview of water and sodium homeostasis
- Hyponatremia
  - Definition & clinical features
  - Causes – focus on SIAD, CSW, hospital acquired hyponatremia
  - Diagnostic approach
  - ODS
  - Treatment
- Hypernatremia
  - Definition
  - Causes & approach
  - Treatment



Na & Water

Sodium is unique among electrolytes… because water balance, not sodium balance, usually determines its concentration.



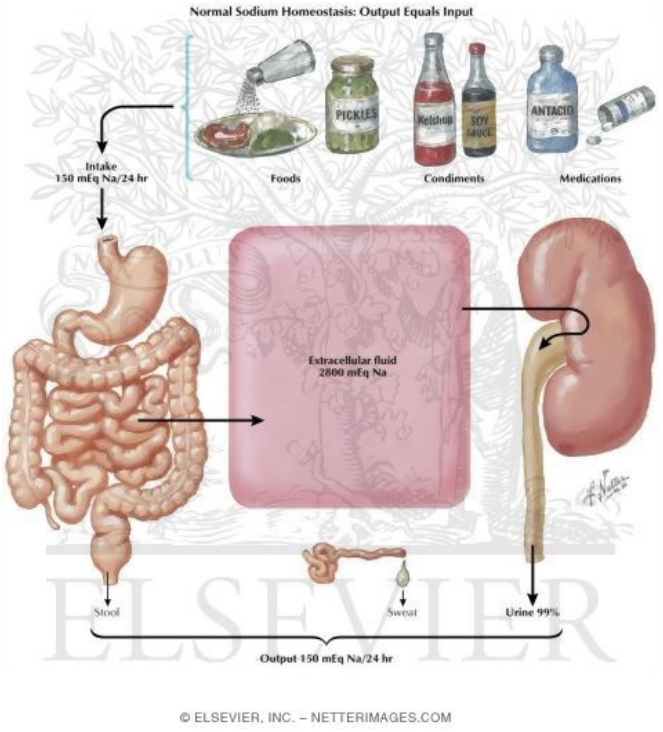
Osmo.reg. Vs Vol.reg

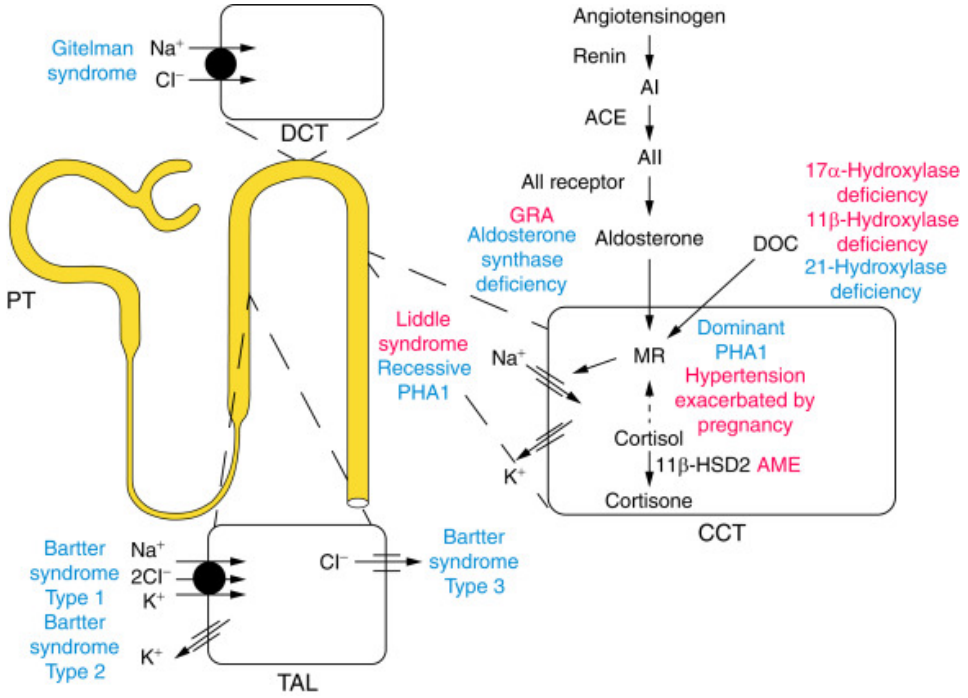
- What is sensed?
- Plasma OSMOLALITY
- Sensor?
- Osmo Receptor
- Effector?
- ADH and Thirst
- Final say
- Water excretion / retention

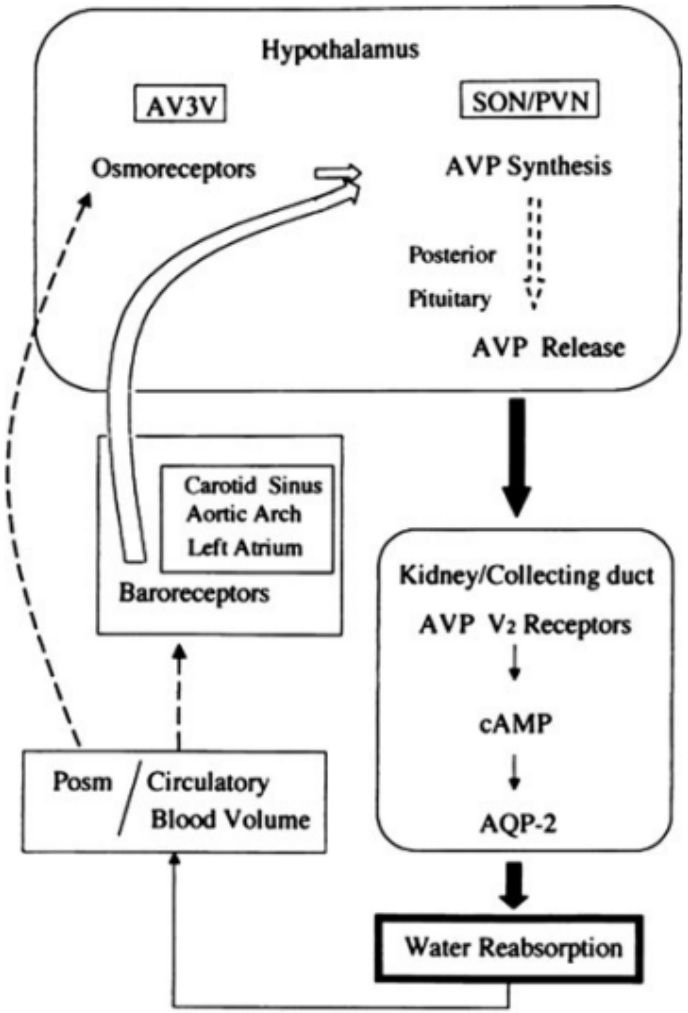
The body protects volume
At the expense of osmolality.

- What is sensed?
- Eff.Circ.Blood Volume
- Sensor?
- Baroreceptors
- Catotid sinus / Aortic /Renal Afferent Arterioles
- Effector?
- RAAS, ANP, Sympathetic System
- Final say
- Urine Na excretion/Retention

Sodium and water homeostasis recap







Moritz M. Sodium and water disorders: evaluation and management. In: Pediatric Nephrology 8th edition

Hyponatremia

- Def: Serum Sodium < 135 mEq/L
- **Disorder of water homeostasis**
- Psuedohyponatremia
  - Sodium estimation can be factitiously low in patients with hyperlipidemia and hyperproteinemia if measured by flame photometry (indirect method)
  - Measurement b… method) is more…
- Non hypotonic h…
  - Hyperglycemia … 1.5 mEq/L fall w…
  - Other causes: m…

Estimated to occur in

- 2% gen population
- 15% hospitalized children
- 30% hospitalized children on IV fluids

Why does it occur?

- Free water ingestion – unlikely cause – adults …

Table 3. Symptoms and findings in hyponatremia [Adrogué, 2005].

Mild to moderate
Headache, lethargy, slowness, poor concentration, depressed mood, lack of attention, impaired memory, nausea, restlessness, instability of gait and falls, muscle cramps, tremor
Advanced
Confusion, disorientation, somnolence, vomiting, hallucinations, acute psychosis, limb weakness, dysarthria
Grave
Seizures, hemiplegia, severe somnolence, respiratory insufficiency, coma, death

Causes of hyponatremia

Hypovolemic

- Extrarenal
  - GI losses: diarrhea, vomiting, fistulae
  - Skin losses: excess sweating, cystic fibrosis, burns
  - Third spacing: pancreatitis, peritonitis, abdominal surgery
- Renal
  - Diuretics
  - Pseudo hypoaldosteronism
  - Renal tubular acidosis
  - Cerebral salt wasting

Euvolemic

- SIAD
- Water intoxication
- Post-surgical
- Hypothyroidism
- Glucocorticoid deficiency

Hypervolemic

- Edema forming states
  - Nephrotic syndrome
  - Liver cirrhosis
  - CCF
- Renal insufficiency
  - AKI
  - CKD

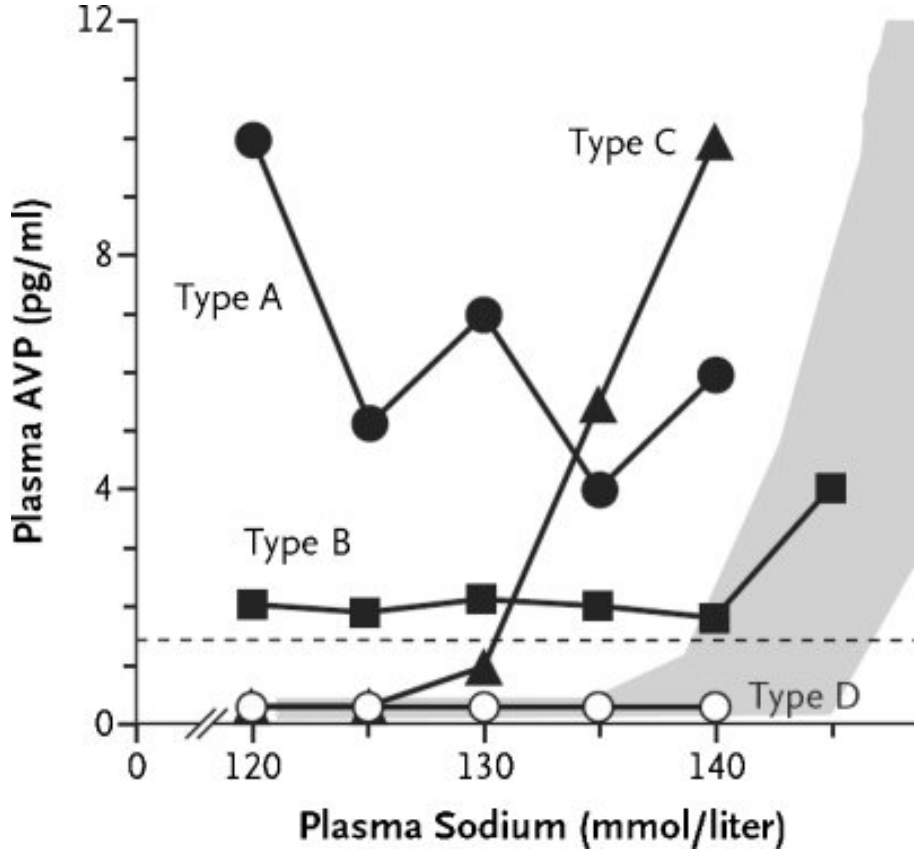
A Syndrome of Renal Sodium Loss and Hyponatremia Probably Resulting from Inappropriate Secretion of Antidiuretic Hormone*

WILLIAM B. SCHWARTZ, M.D.,† WARREN BENNETT, M.D.,‡ SIDNEY CURELOP, M.D.§
Boston, Massachusetts

and FREDERIC C. BARTTER, M.D.
Bethesda, Maryland

SIADH: a condition characterized by hypotonic and euvolemic hyponatremia along with urinary hyperosmolarity, resulting from antidiuretic hormone (ADH) release in the absence of adequate stimuli.

Term replaced by SIAD



NDT Plus (2009) 2 [Suppl 3]: iii5–iii11

Table 3. Causes of SIADH

Malignancy	Lung disease	CNS disease	Drugs	Miscellaneous
Lung cancer (small cell, mesothelioma)	Infections (bacterial, viral, tuberculosis, abscess)	Infections (meningitis, encephalitis, AIDS, abscess)	Antiepileptics	Idiopathic
Oropharynx	Cystic fibrosis	Stroke (CVA, subarachnoid, subdural)	Antidepressants (mainly SSRI's)	Transient (nausea, pain, stress)
GI-tract (stomach, duodenum, pancreas)	Status asthmaticus	Hydrocephalus	Antipsychotics	Hereditary
Genitourinary tract		Brain tumour	Anaesthetics	Exercise associated
Endocrine thymoma		Head trauma	Chemotherapy (ifosfamide, cylcofosfamide, vincristine)	
Lymphomas		Multiple sclerosis	AVP analogues	
Sarcomas (Ewing)		Guillain–Barré syndrome	MDMA ('Ecstasy')	
		Shy–Drager syndrome		
		Lewy body dementia		

NDT Plus (2009) 2 [Suppl 3]: iii5–iii11

"any patient admitted to hospital should be considered to be at risk of SIADH"

Cerebral salt wasting

- May also be called “syndrome of inappropriate natriuresis”
- Inappropriate and excessive secretion of natriuretic peptides leads to hydrosodic renal losses and hypovolemia
- Response: RAAS activation and ADH secretion
- Seen most commonly in the setting of neurosurgery/subarachnoid haemorrhage
- Important but difficult to differentiate from SIAD
- Signs of volume depletion are often not seen
- Similar laboratory findings (reduced serum osmolality, urine osmolality >100 mOsm/kg, urine sodium concentration >30 mmol/l)
- Treatment: solute replenishment, sometimes fluodrocortisone

Moritz M. Sodium and water disorders: evaluation and management. In: Pediatric Nephrology 8th edition

Hospital acquired hyponatremia

- Area of concern because of the traditional approach of using hypotonic maintenance fluids: N/5 saline, N/4 saline, etc
- No evidence for this approach
- Hospitalized children are at risk of SIAD: pulmonary disorders, mechanical ventilation, intracranial injury, infection
- Hyponatremia – dangerous if underlying CNS injury
- Hypotonic fluids: high risk of hospital acquired hyponatremia
- AAP CPG: “most important measure to prevent hyponatremia is to avoid using hypotonic fluids in patients with clear risks for nonosmotic AVP secretion”
- Exceptions: situations of excess free water loss, neurosurgical disorders, heart disease/hepatic/renal impairment, children on chemotherapy, infants < 28 days may need different IV fluid composition

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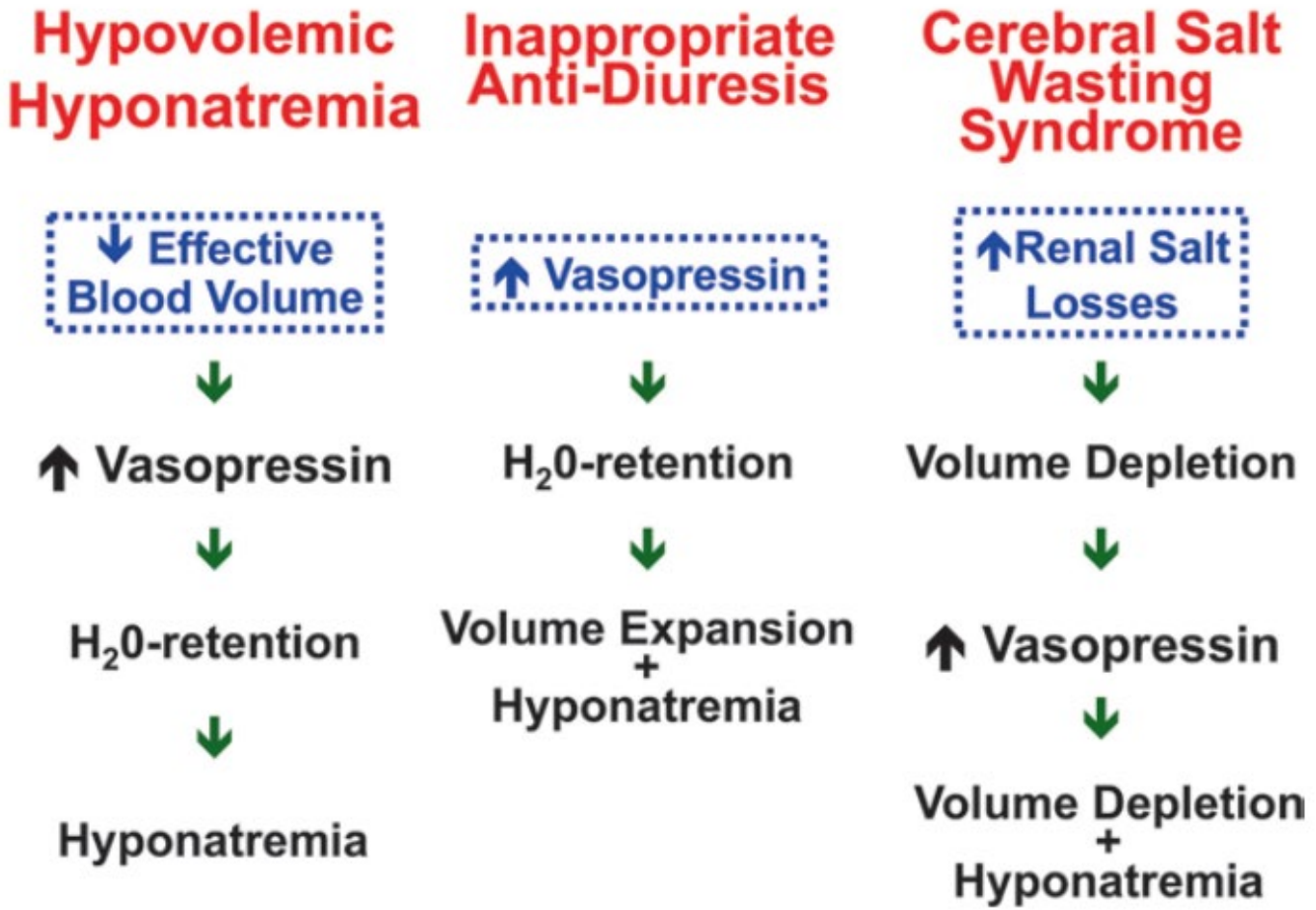
In summation



Osmotic demyelination syndrome

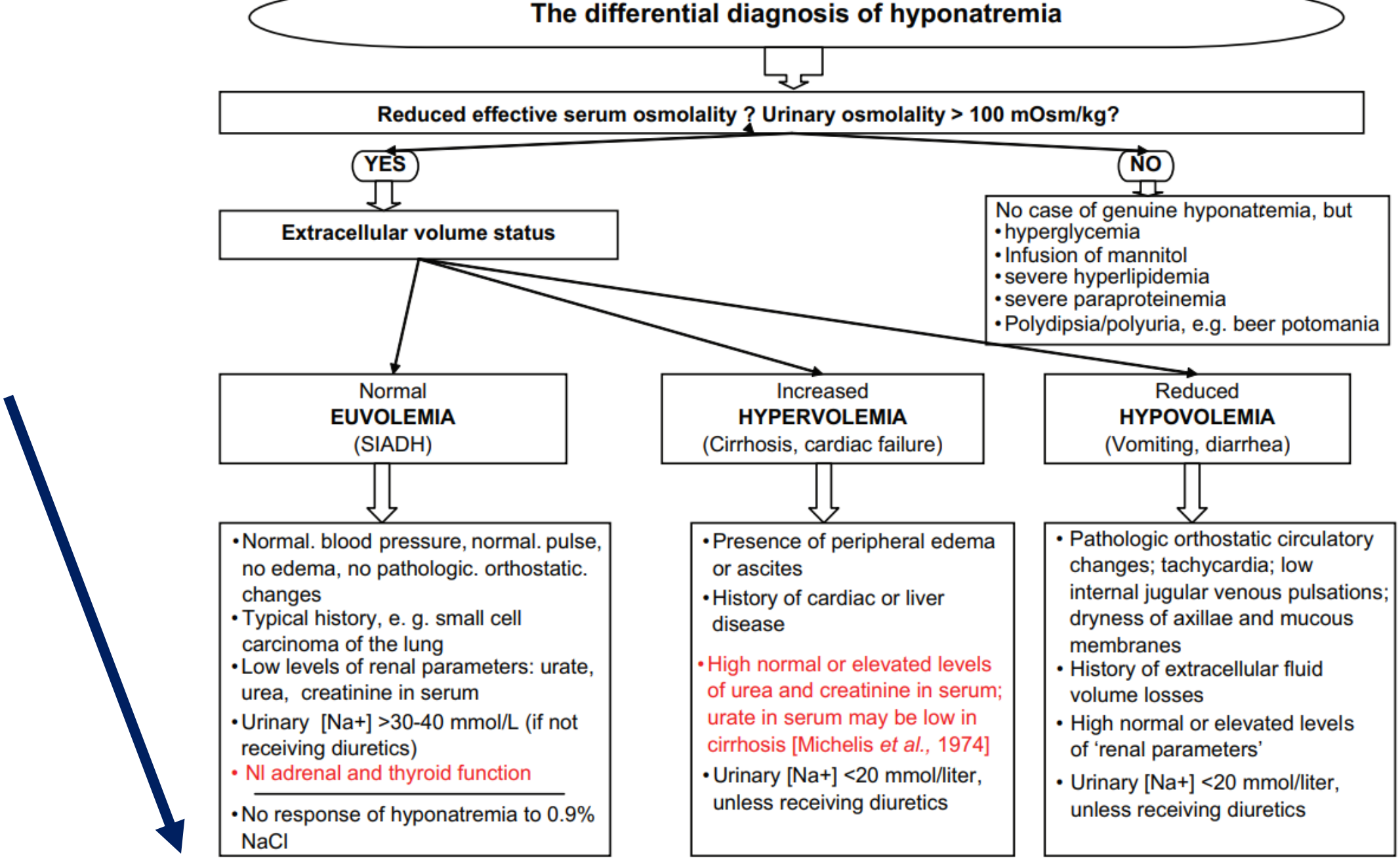
- Correction of hyponatremia by greater than 20–25 mEq/L over 24 hrs can result in cerebral demyelination
- Usually seen in chronically hyponatremic patients of greater than 48-h duration with serum sodium <115 mEq/L
- Other risk factors: hypokalemia, thiazide diuretic use, severe liver disease, malnutrition, hypophosphatemia and hypoxia
- Clinical course: biphasic: initial improvement followed by deterioration over 2-7 days
- Clinical features: mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, a pseudocoma with a “locked-in stare” and ataxia
- Best diagnosed by MRI approximately 14 days following hyponatremia correction

Moritz M. Sodium and water disorders: evaluation and management. In: Pediatric Nephrology 8th edition

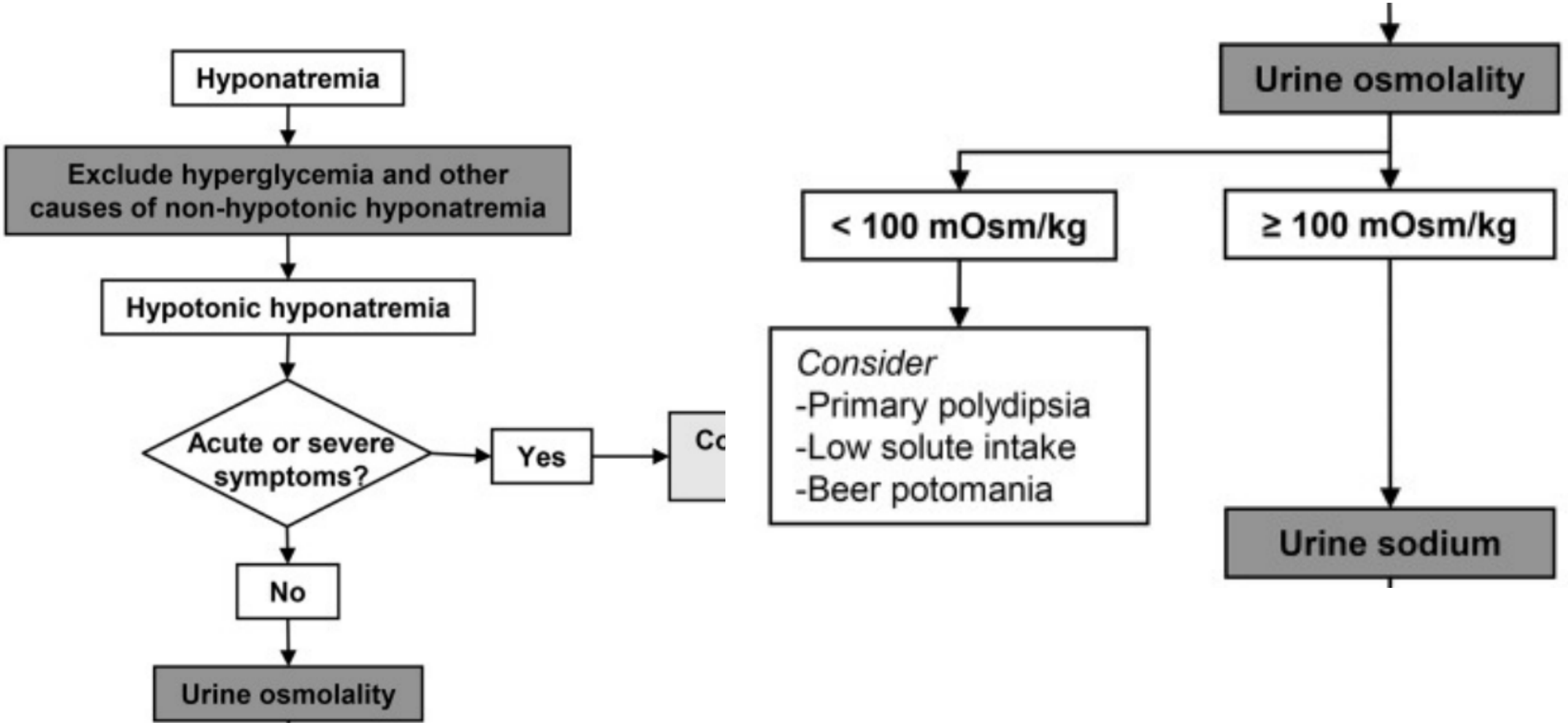
Classifications of hyponatremia

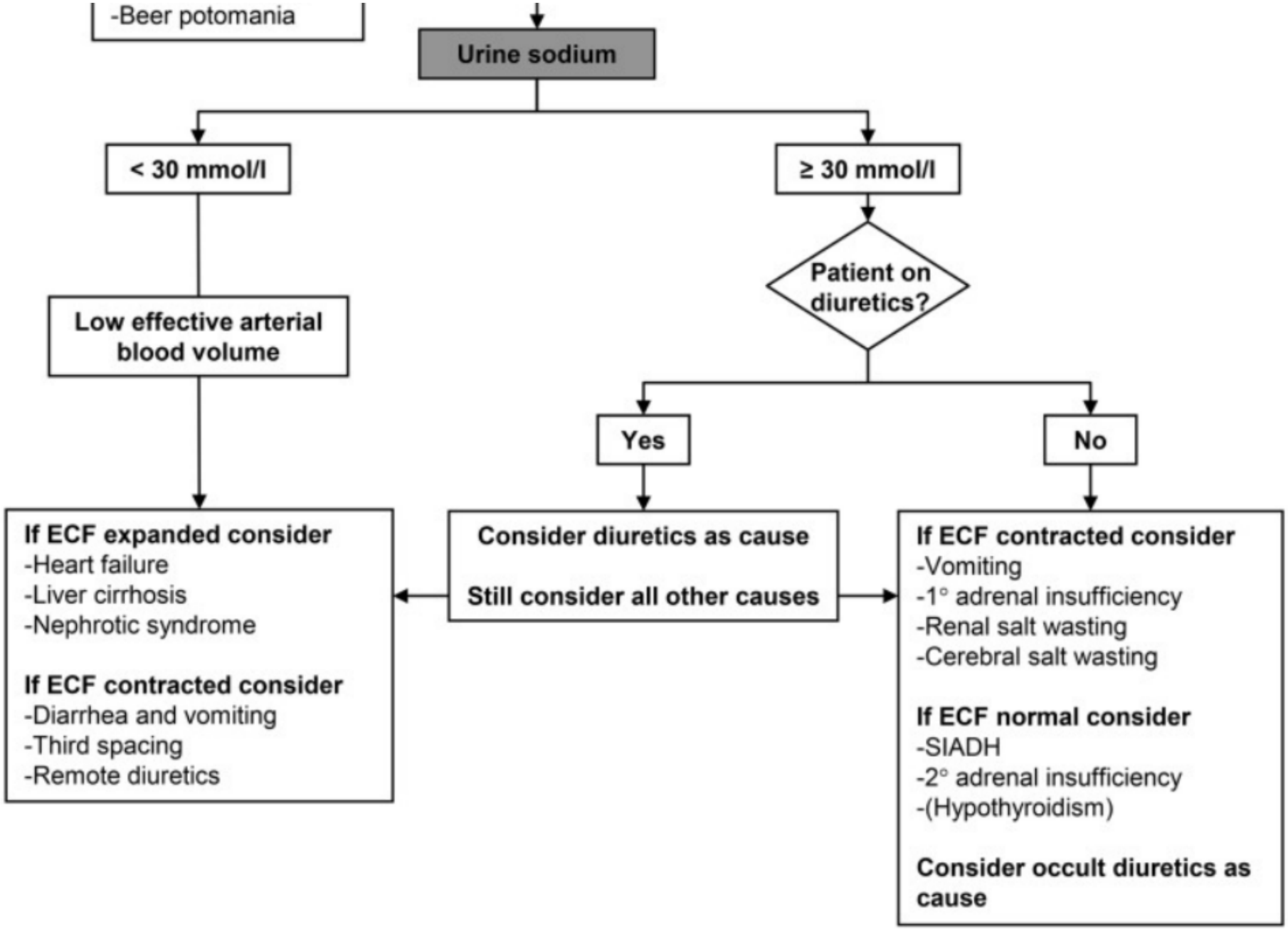
Classification	Criteria	Limitations of Clinical Utility
Moderate (125–129 mmol/L) versus severe/profound[a] (<125 mmol/L)	Absolute S_{Na} concentration	Symptoms do not always correlate with degree of hyponatremia
Acute versus chronic	Time of development (cutoff 48 h)	Time of development not always known
Symptomatic versus asymptomatic	Presence of symptoms	Many symptoms aspecific; chronic hyponatremia may be symptomatic
Hypotonic, isotonic, or hypertonic	Measured serum osmolality	Ineffective osmoles (*e.g.*, urea, ethanol) are also measured
Hypovolemic, euvolemic, hypervolemic	Clinical assessment of volume status	Clinical assessment of volume status has low sensitivity and specificity

[a]S_{Na}<125 mmol/L is defined as "severe hyponatremia" by the United States guideline, and as "profound hyponatremia" by the European guideline.[7,9]



Ther Adv Endocrinol Metab (2012) 3(2) 61–73


Hyponatremia
Exclude hyperglycemia and other causes of non-hypotonic hyponatremia
Hypotonic hyponatremia
Acute or severe symptoms?
Yes
No
Urine osmolality
Urine osmolality
< 100 mOsm/kg
≥ 100 mOsm/kg
Consider
-Primary polydipsia
-Low solute intake
-Beer potomania
Urine sodium


-Beer potomania
Urine sodium
< 30 mmol/l
≥ 30 mmol/l
Low effective arterial blood volume
Patient on diuretics?
Yes
No
If ECF expanded consider
-Heart failure
-Liver cirrhosis
-Nephrotic syndrome
If ECF contracted consider
-Diarrhea and vomiting
-Third spacing
-Remote diuretics
Consider diuretics as cause
Still consider all other causes
If ECF contracted consider
-Vomiting
-1° adrenal insufficiency
-Renal salt wasting
-Cerebral salt wasting
If ECF normal consider
-SIADH
-2° adrenal insufficiency
-(Hypothyroidism)
Consider occult diuretics as cause

Treatment of hyponatremia

Acute/symptomatic

Hypertonic (3% saline)

- By formulae: Adrogué–Madias or Barsoum–Levine
- Fixed bolus regimen
- Rationale for fixed bolus
  - Partial correction is adequate
  - No need for calculations so lesser chances of error
  - Limits risk of overcorection
  - Proven in a retrospective study

Chronic hyponatremia

- Fluid restriction
  - 1st line of treatment
  - Effective in approximately 70% patients
  - U_{Na} ≥130 mmol/L and U_{Osm} ≥500 mOsm/kg predict nonresponse
- Vaptans
  - Trials reported improvement in Na levels but survival benefit not established
  - Low risk of PDS
  - Adverse effects: overcorrections, hepatotoxicity, cytochrome P450 inhibition
- Urea
  - Produces osmotic aquaresis
  - Limited studies show similar effect as vaptans
  - USA: commercially available lemon-flavored urea powder drink (Ure-Na)

Comparison of the United States and European guidelines

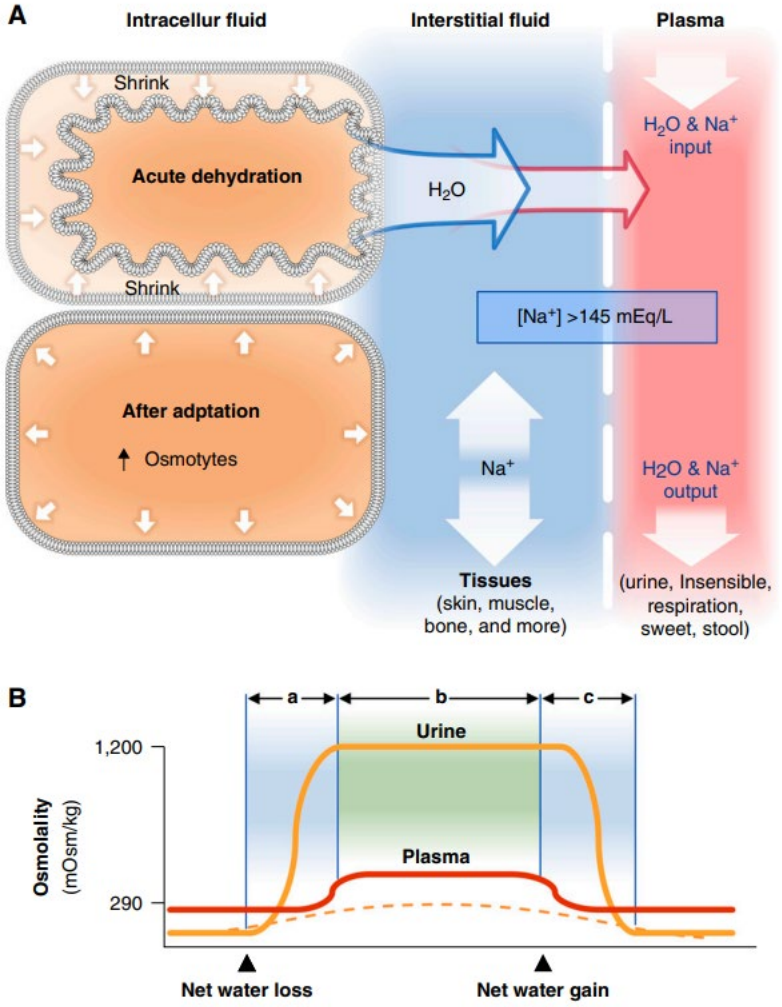
Pediatrics

- Bolus 3% NaCl 2 ml/kg over 10 min (X 3 as needed)
- Check S Na after 2nd bolus
- Stop if improvement on symptoms, rise of S Na > 10 mEq/L within 5 hrs

Chronic hyponatremia		
SIAD	Fluid restriction (first line)	Fluid restriction (first line)
	Demeclocycline, urea, or vaptan (second line)	Urea or loop diuretics + oral NaCl (second line)
		Do not recommend or recommend against vaptan[a]
		Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction	Fluid restriction
	Vaptans[b]	Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS)	No minimum
	Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	Limit: 10 mmol/L per d

Hypernatremia

- Def: Serum Sodium > 145 mEq/L
- Causes
  - Free water loss
    - Diabetes insipidus
  - Hypotonic fluid loss
    - Osmotic diarrhea
  - Hypertonic fluid gain
    - Intentional salt poisoning!



Clinical manifestations

- Seen more often if sudden rise in serum sodium
- Chronic hypernatremia (> 48 hrs): brain adjusts by generating idiogenic osmoles – amino acids, unmeasured organic substances
- Cerebral dehydration
  - Functional manifestations – hypertonia, nuchal rigidity, brisk reflexes, myoclonus, asterixis, chorea, seizures
  - Rupture of delicate bridging veins – intracranial hemorrhage
- Venous sinus thrombosis
- Cerebral demyelination
- Rhabdomyolysis

Clinical approach

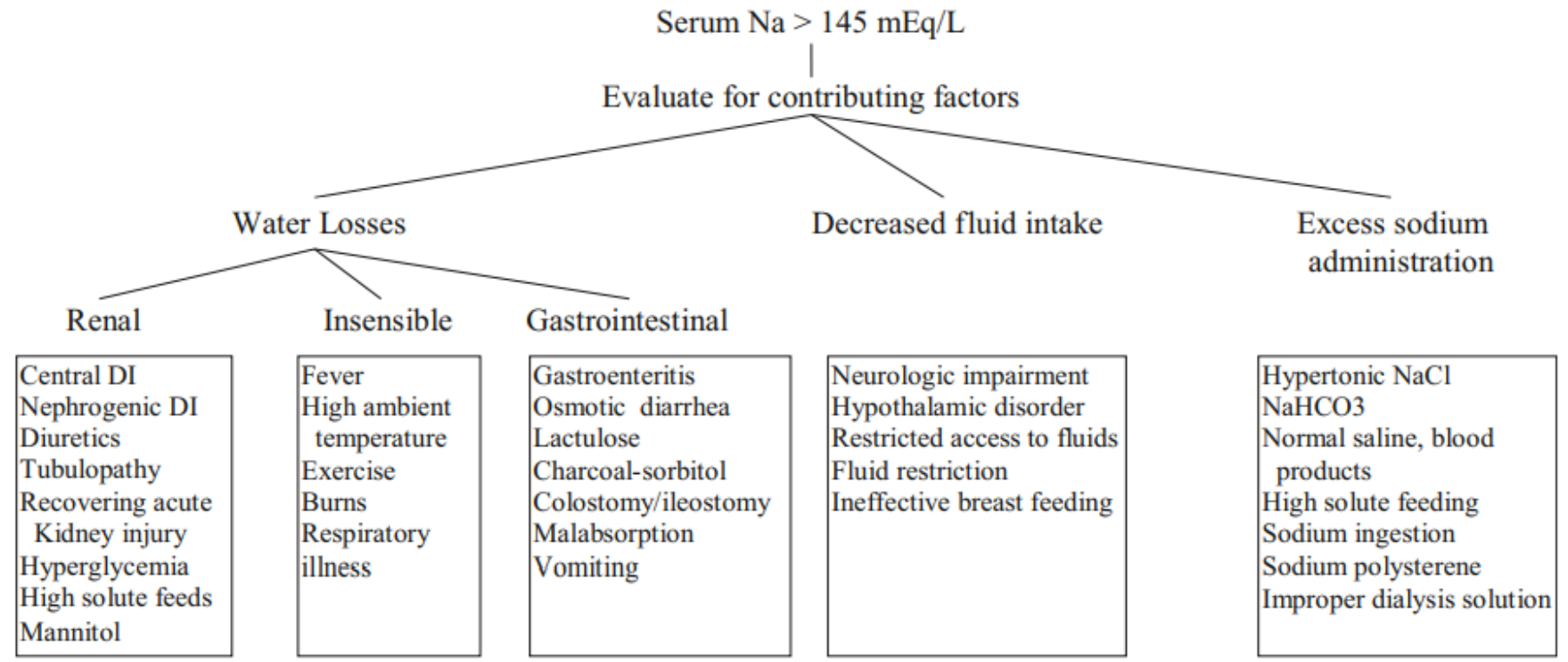


Fig. 4 Diagnostic approach to hypernatremia

Treatment

Formulae for free water deficit

TBW X [140/plasma Na -1)
(TBW = 0.6 X BW)

4 ml X BW X Desired Change in Na (mEq/L)

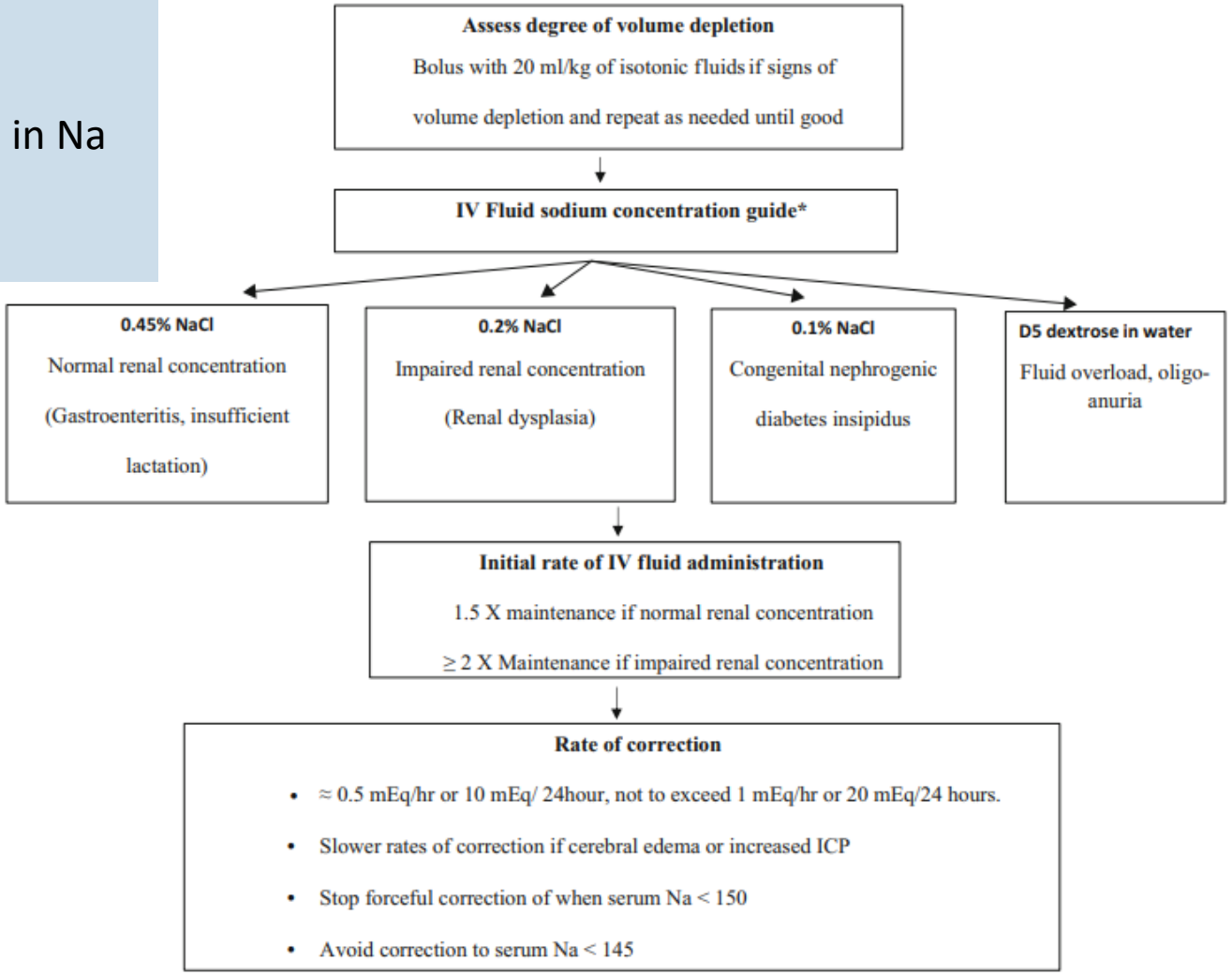


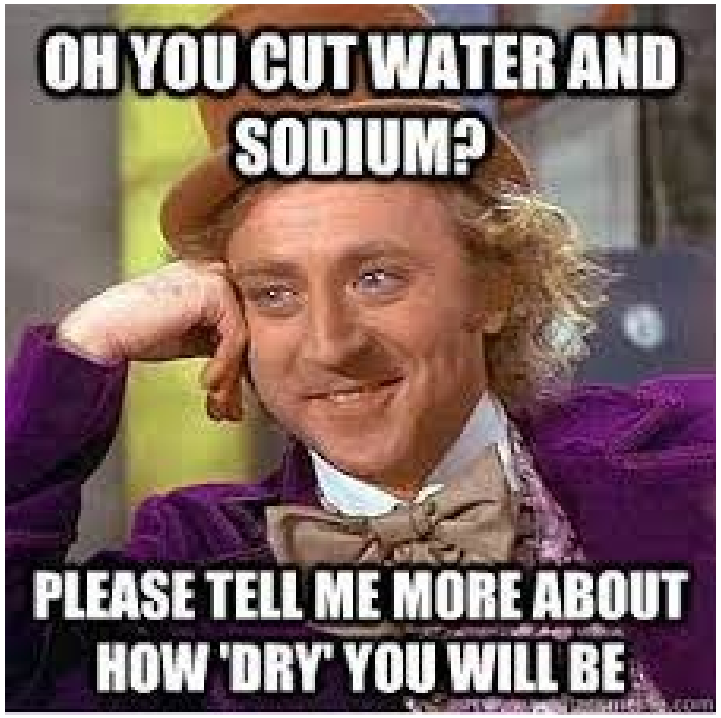
Fig. 6 Management of hypernatremia

To sum up

- Physiological basis of dysnatremia: crosstalk between osmosensing and barosensing
- Caveats in measurement of sodium
- Hypo vs hyper osmolar dysnatremia
- Hypovolemic, isovolemic or hypervolemic state?
- Aggression in correction: acute vs chronic, severity of symptoms, avoid overzealous therapy

Thank you


Chhayasfood.com
HUSBAND: I THINK THE SALT IS MORE
WIFE: 👆😂🙏
Meme Thursday


OH YOU CUT WATER AND SODIUM?
PLEASE TELL ME MORE ABOUT HOW 'DRY' YOU WILL BE


God : *creates ocean*
Humans : Great ! We won't be thirsty ever again !
God :

Approach to Dyskalemia

MD, FACEE (PEM), MNAMS
FISPN,FIPNA (AIIMS)
FISPD (Heidelberg),FRCPCH (GOSH, London)
Professor
Division of Pediatric Nephrology
Department of Pediatrics,
LHMC, New Delhi

Learning Objectives

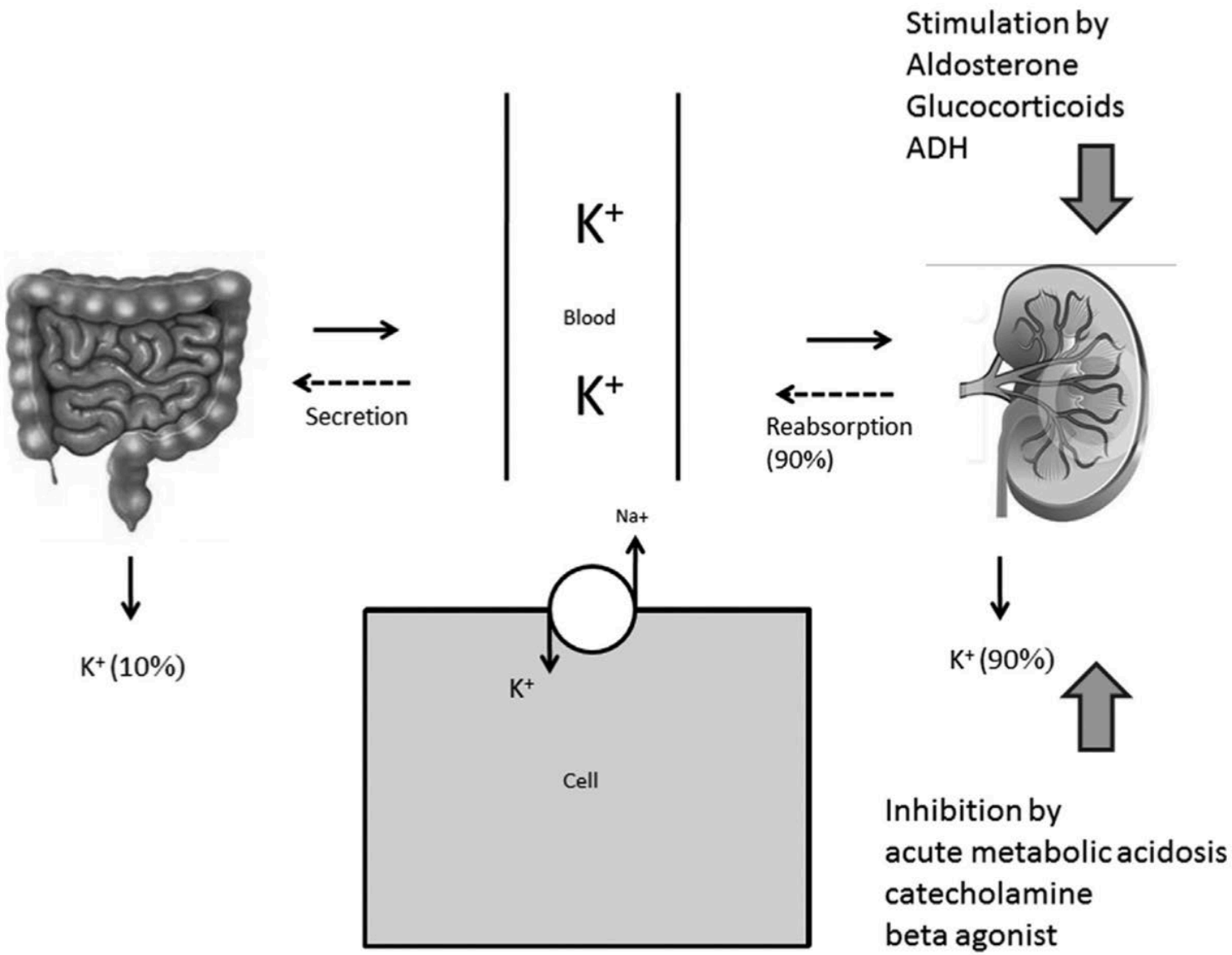
- Definitions
- Pathophysiology
- Etiology
- Clinical Approach
- Management

Dyskalemia in Children

- Hyperkalemia: >5.5 m Eq/L
- Hypokalemia: <3.5 m Eq/L
- Psedohypokalemia / Pseudohyperkalemia
- Mild to life threatening clinical manifestation
- Hypokalemia (38 %) is the commonest electrolyte disorder in ED, followed by Hyponatremia (31%) and Hyperkalemia (22.4%)

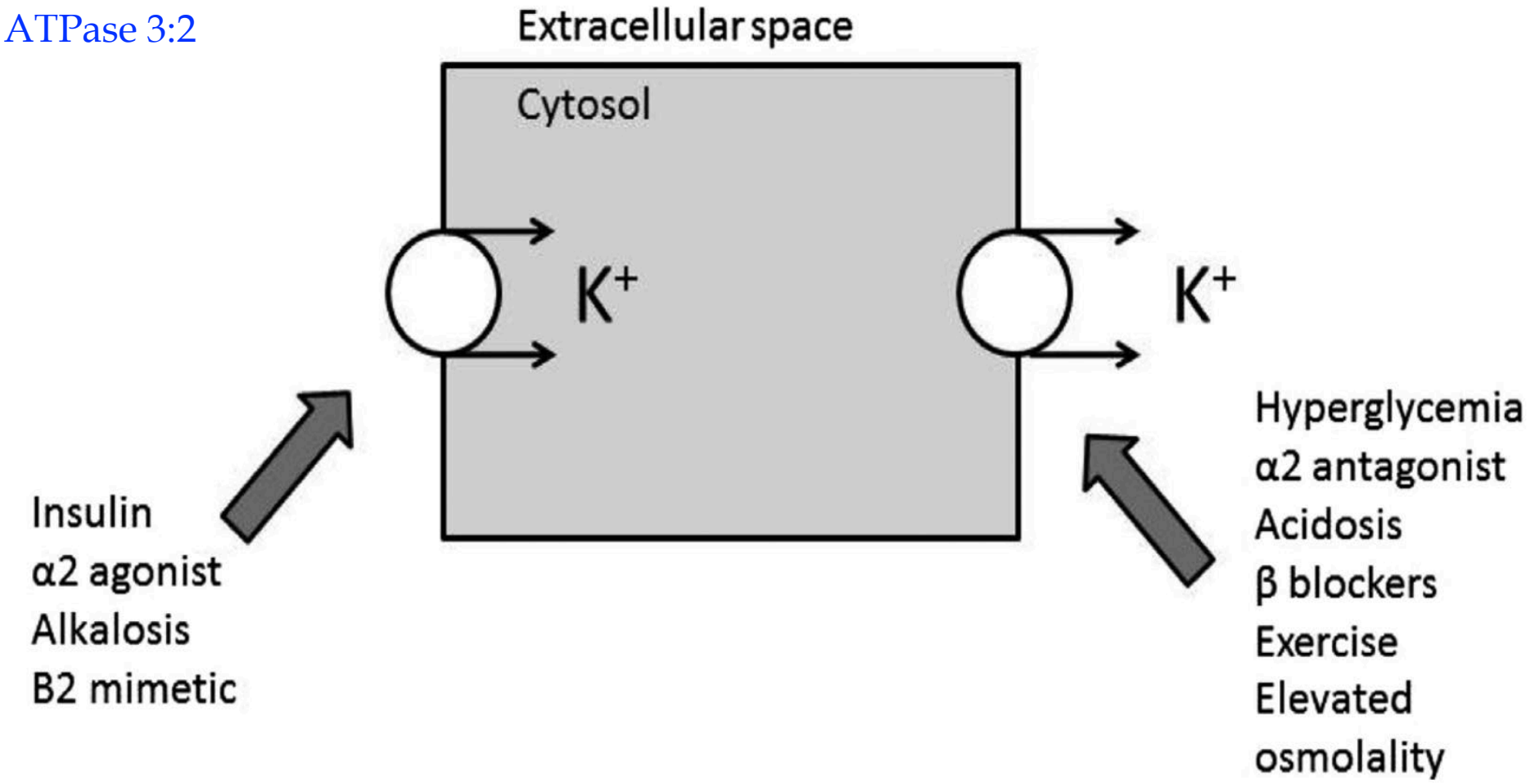
Pediatr Neonatol. 2022;63(6):575-581.

External Balance of Potassium

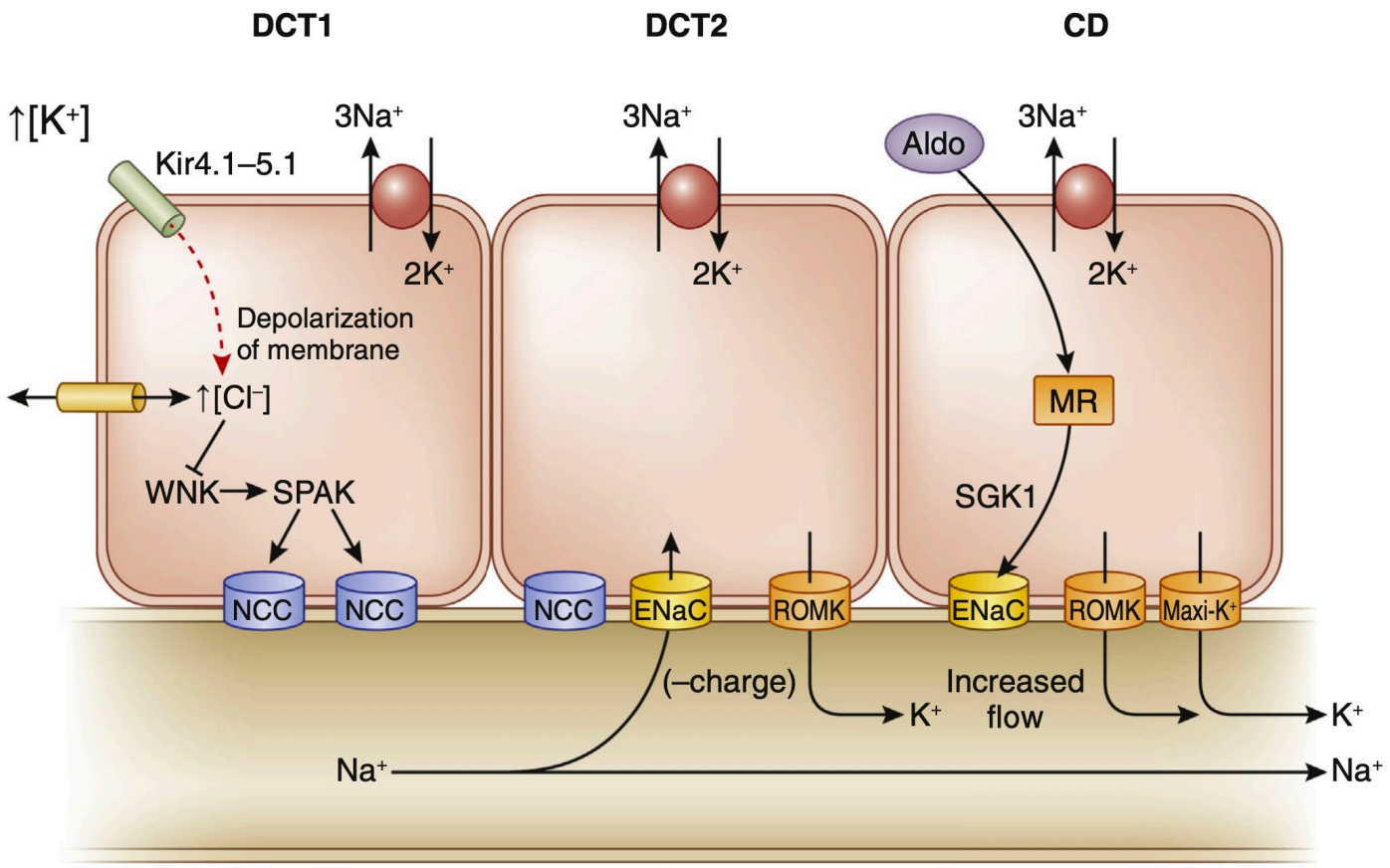


Internal Potassium Balance

Na K ATPase 3:2



Potassium Handling in the Kidney

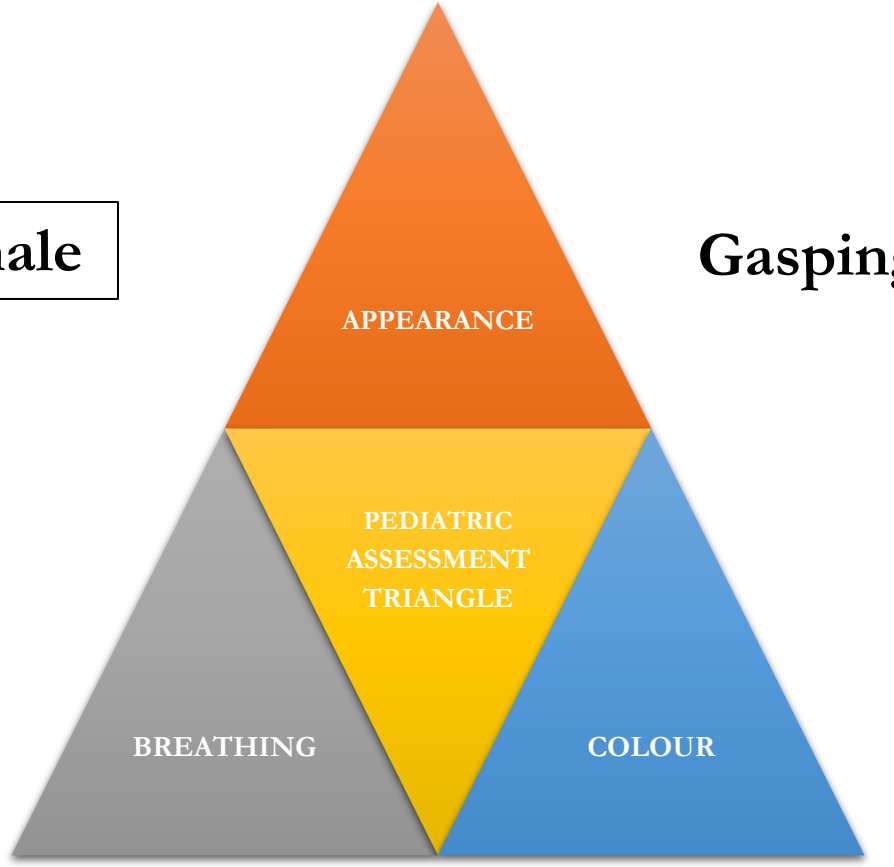


Case 1

Initial Impression; Pediatric Assessment Triangle

13 months, female

Gasping, Lethargic



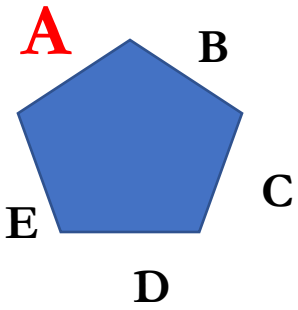
Shallow breathing

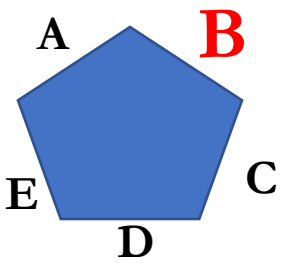
Dusky

Intervention- Attached to monitor; Humidified oxygen

Primary Survey

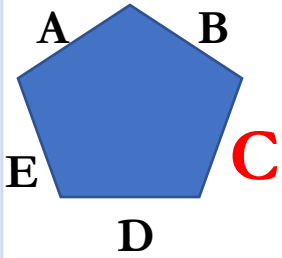
A **AIRWAY**	• Open and maintainable
B **BREATHING**	• Gasping • Shallow • B/L breath sounds vesicular • B/L conducted sounds • SpO2 82% at room air





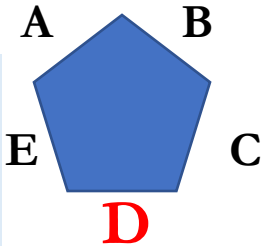
C
CIRCULATION

- HR - 118/minute, regular
- Feeble pulses
- BP-70/50
- Temp- 97 ^{0}F
- CRT > 3 secs



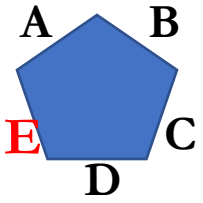
D
DISABILITY

- Paucity of movements
- GCS – E3V3M3, Dextrose- 33 mg/dL



E
EXPOSURE

- Sparce hair



ER Evaluation and Intervention

Evaluation and Identification	Intervention
Respiratory failure	Intubated with 4 mm ID tube, attached to ventilator
	IV access secured; blood samples taken Catheterised to monitor urine output
Shock, Respiratory Failure	
Hypoglycaemia	Bolus 5ml/kg 10% dextrose Ringer's lactate : 75 ml over 60 min

Focused History

Sign and symptoms:

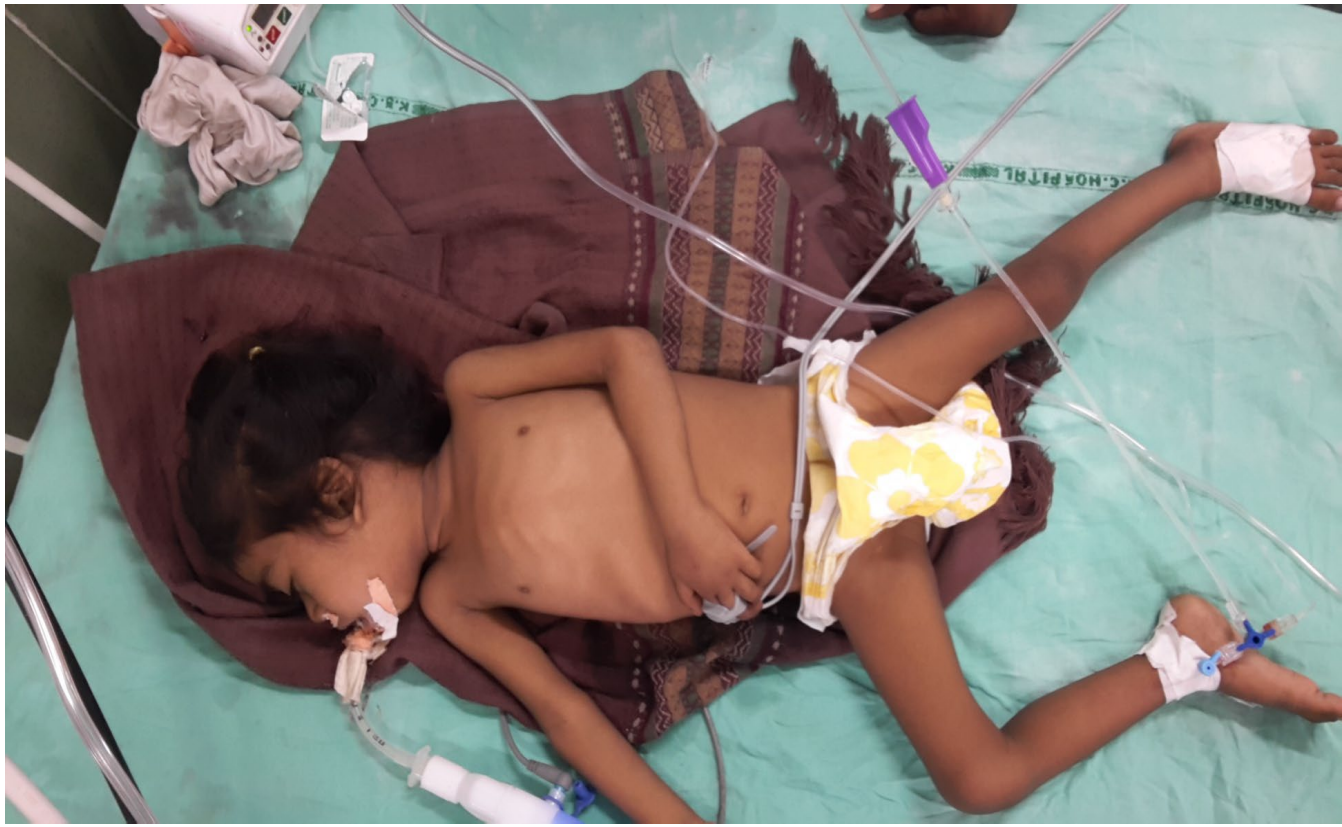
- Loose stools 5 days
- Vomiting 3 days
- Bottle feeding, partially immunized
- PR 150 per minute, feeble, Intubated, Blood pressure 70/50 mm Hg
- Dehydrated
- Weight: 5.0 Kg
- Length: 65 cm
- Wt for Lt: <-3SD (78%)
- MAC: 110 mm

Further Course

- Bolus 5ml/kg 10% dextrose
- Ringer's lactate : 75 ml over 60 min
- Tachycardia persisting: HR 130/min
- Cefotaxime
- Serum Na 135 meq/L
- Serum K 2.6 meq/L
- pH 7.32
- HCO_3^- 18 mEq/L
- pCO_2 50

SAM/Respiratory failure/Shock

Hypokalaemia/ Hypoglycaemia



Severe Hypokalaemia

- Neuromuscular dysfunction: Ascending pattern
- Lower extremity, trunk, upper extremity
- Respiratory failure
- Smooth muscle dysfunction: nausea, vomiting, voiding dysfunction
- Management: IV Potassium chloride

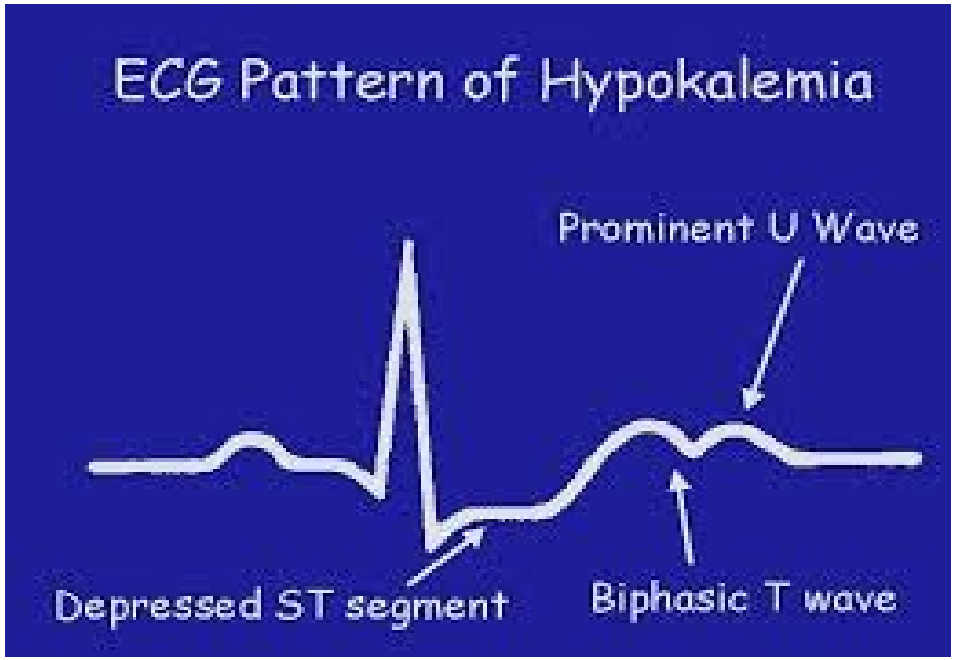
  0.3 mEq/kg/hour for 3 hours

  followed by maintenance by 40 mEq/L
- Repeat K^+: 3.5 mEq/L

Aetiology of Hypokalemia

Decreased K intake	Increased renal excretion	Increased GI losses	Increased cellular uptake
	Diuretics	Diarrhea	Acute alkalosis
	Metabolic alkalosis (chloride deficient)	Laxatives	Insulin therapy
	DKA	Ostomy loses	Elevated beta-adrenergic activity
	Increased mineralocorticoid effect		Increase in bone marrow cell production
	RTA (type1 and type 2)		Hypokalemic periodic paralysis
	Bartter's syndrome		
	Gitelman's syndrome		

- ECG Changes:
  - T-wave amplitude declines
  - U waves develop
  - ST segment depression may result
  - Wide QRS, PR prolongation



Management

- If the child is clinically well, oral therapy is preferable and can be provided two to four times per day as potassium chloride

- Dosing may start at 2 to 5 mEq per kg per day and be adjusted on the basis of serial laboratory assessment.

- If the child is not symptomatic, potassium can be added to the maintenance fluids

- If the child is unable to take oral medications or is symptomatic, intravenous potassium is provided

- In order to avoid insulin secretion, which promotes transcellular shift of potassium into the intracellular space, potassium should be provided in a dextrose-free solution

- Infusion: 0.25 mEq per kg per hour, though emergent conditions may warrant the maximal rate of 0.5 to 1 mEq per kg per hour

Insight into potassium's role in childhood mortality due to severe acute malnutrition

S J P. 2019; 19:44-51

Table 4. Effects of potassium level on mortality (n = 215).

Potassium level	Total	Deaths
Normal potassium	64	2 (3.1%)
Hypokalaemia	151	21 (13.9%)
Classification of Hypokalaemia		
Mild Hypokalaemia	47	1 (2.1%)
Moderate Hypokalaemia	38	4 (10.5%)
Severe Hypokalaemia	66	16 (24.2%)
Extent of hypokalaemia severity		
Severe hypokalaemia (group1: 2.4–2 mEq/l)	27	2 (7.4%)
Severe hypokalaemia (group2: <2 mEq/l)	39	14 (35.9%)

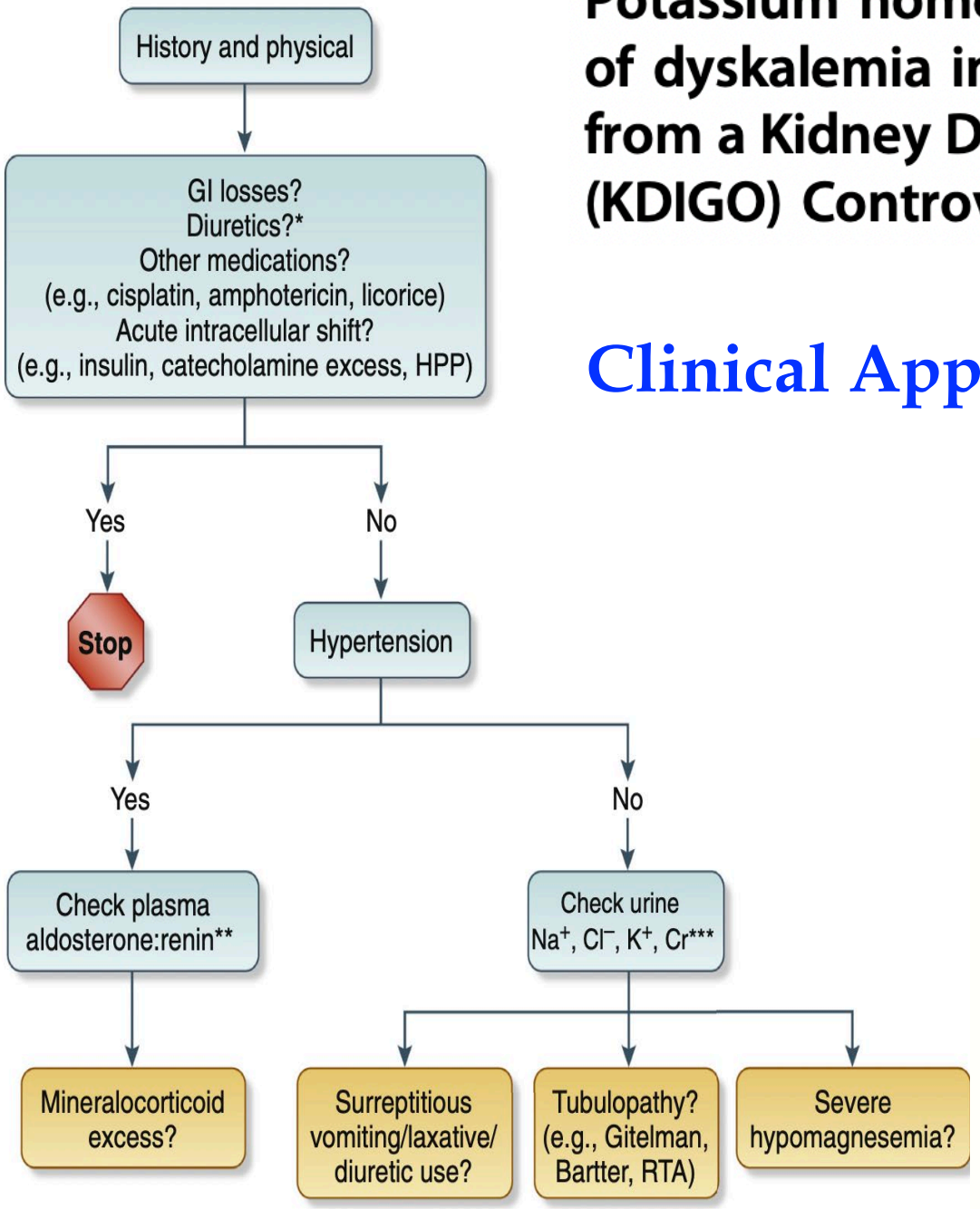
Check for updates

OPEN

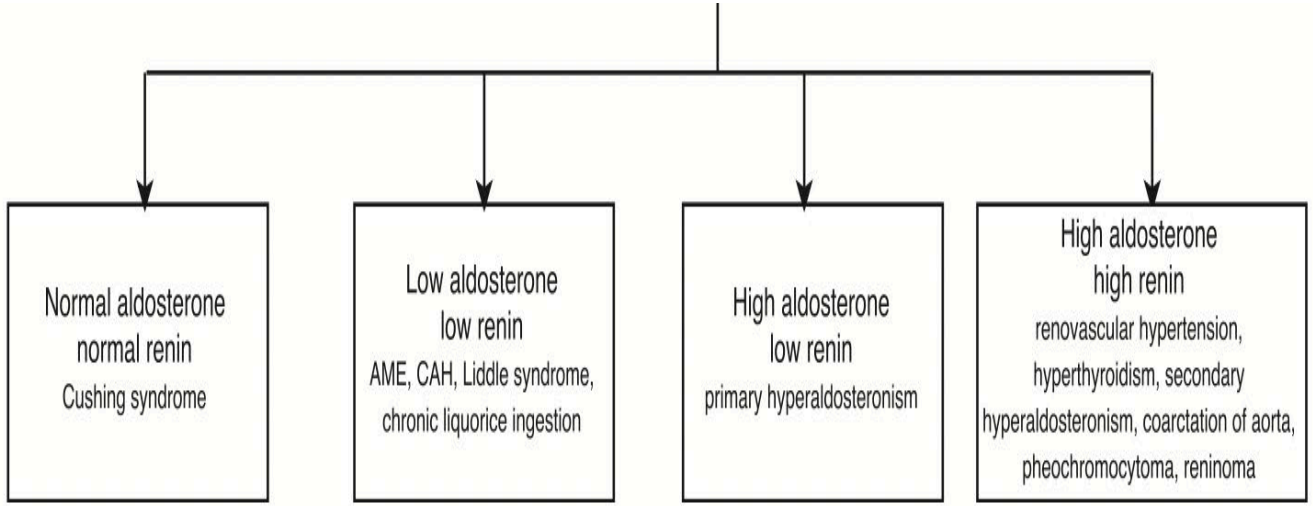
Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Kidney International (2020) **97,** 42–61;

Clinical Approach to Hypokalemia



Renin /Aldosterone Level



Clinical Approach to Tubulopathies

Clinical Features

- Polyuria
- Polydipsia
- Irritability
- Growth failure
- Nephrocalcinosis
- Blood Pressure Abnormality

Initial Investigations

Bloods	Urine	Imaging
Venous blood gas	Urinary dipstick for glucose	Kidney ultrasound
Biochemical profile	Urine microscopy	
+/–	Urine protein:creatinine ratio	
Osmolality	Urine calcium:creatinine ratio	
Renin/aldosterone	+/–	
	Urine B2 microglobulin	
	Urine osmolality	
	Urine metabolic screen	

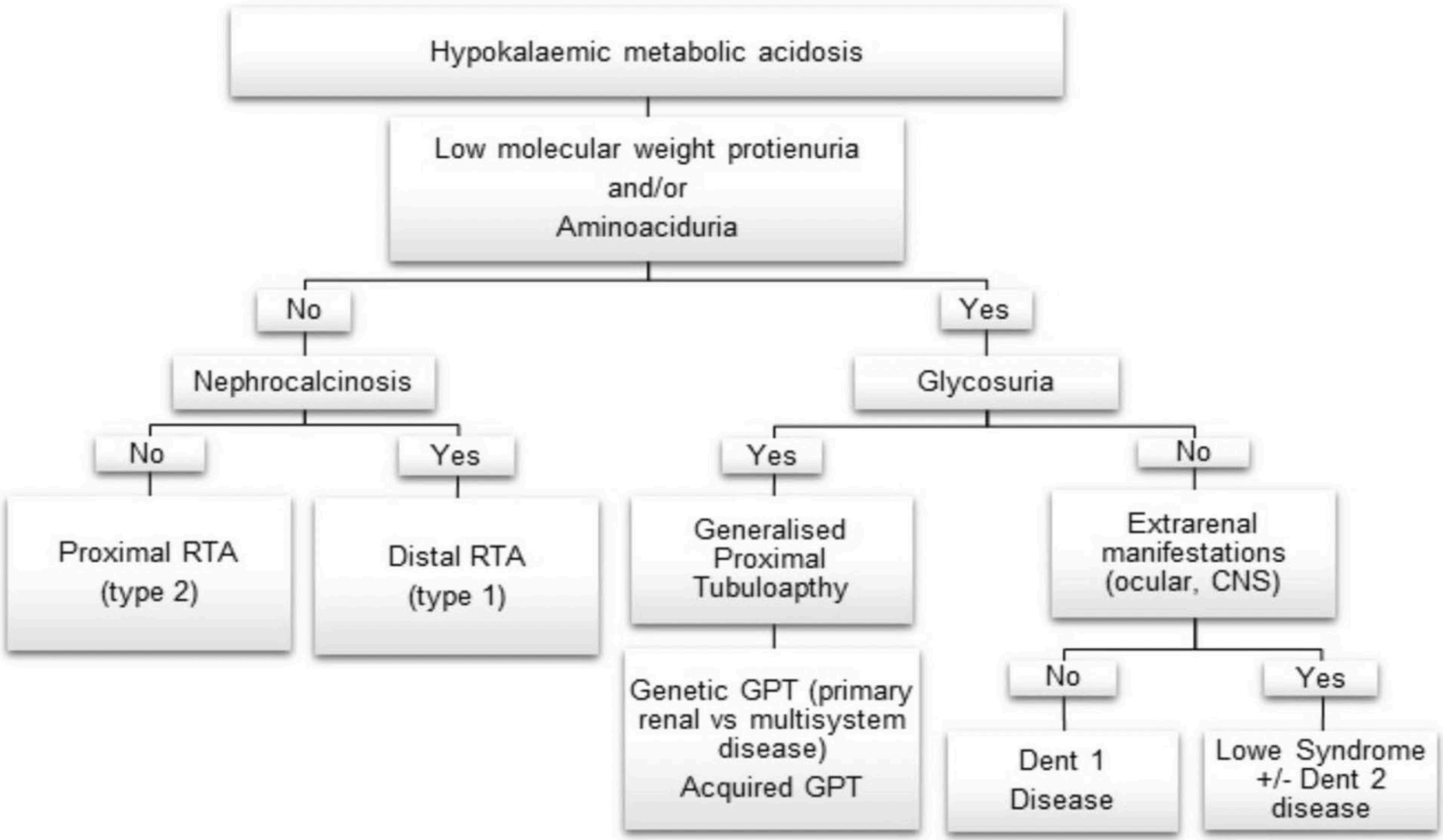
Pediatr Nephrol. 2023;38(3):651-662.

Tubular Handling of Salts

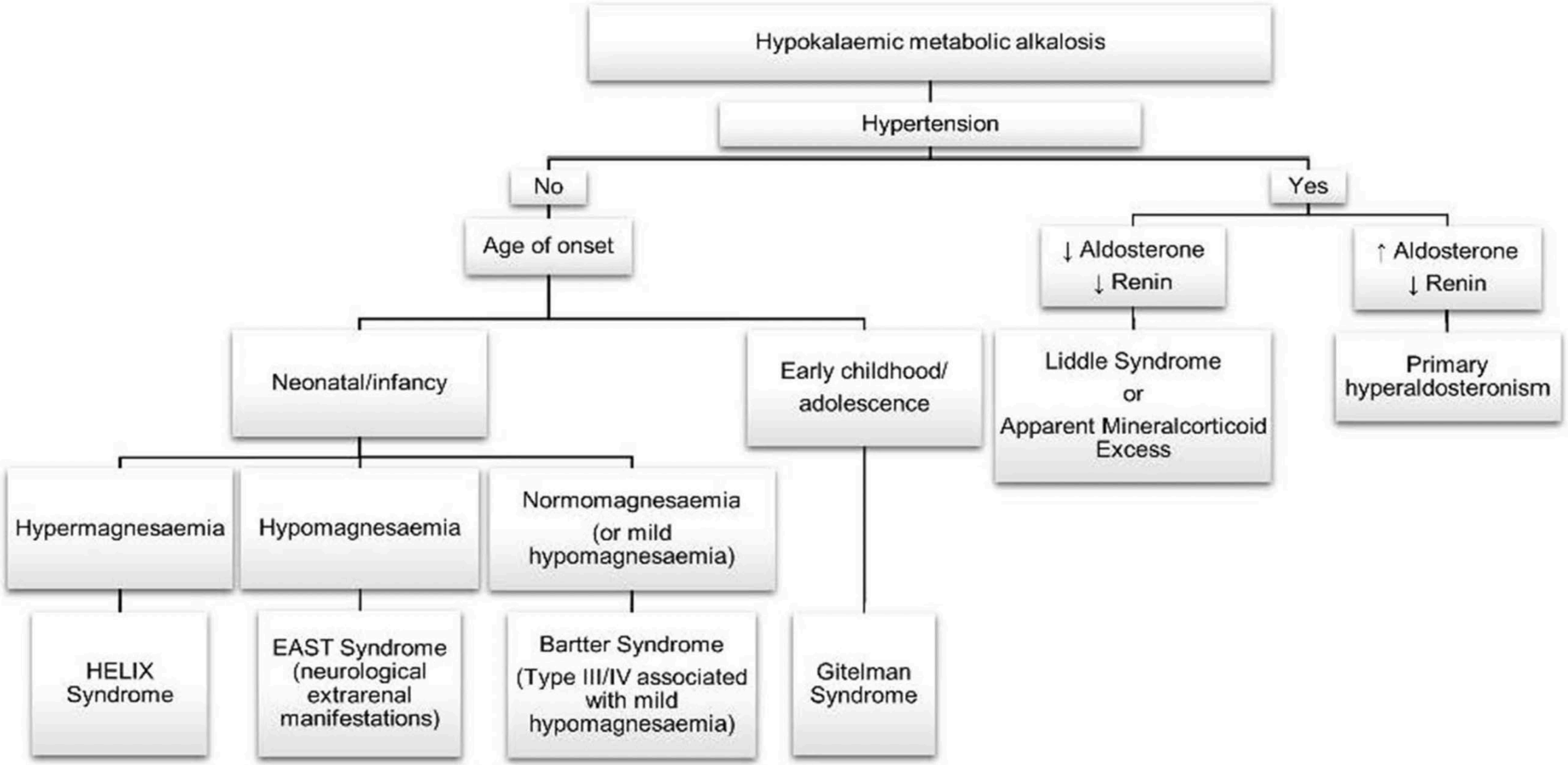
Fractional excretions

	Formula	Normal value	Interpretation
FeNa	$= \frac{Na\ (urine) x\ Creatinine\ (serum)}{Na\ (serum) x\ creatinine\ (urine)} x100$	FeNa <1% *(with normal salt load and normal GFR)*	If >1% suggests: – Kidney salt wasting – Appropriate naturesis in the context of salt load
FeMg	$= \frac{Mg\ (urine) x\ Creatinine\ (serum)}{Mg\ (serum) x\ creatinine\ (urine) x\ 0.7} x100$	FeMg < 4%	> 4% suggests – Kidney wasting magnesium in setting of hypogmagnesaemia
TTKG	$= \frac{K\ (urine) x\ Osmlality\ (serum)}{K\ (serum) x\ Osmolality\ (urine)} x100$	TTKG 4–6% *(Interpretation dependent on kalaemic state)*	In hypokalaemic states – <2% suggests appropriate kidney handling – >4% suggests kidney losses
TmP/GFR	$= PO4\ (serum) \left[\text{PO4 (urine)} x\ \text{Creatinine} \frac{\text{serum}}{\text{urine}} \right]$	Varies with age	< lower limit of range – Kidney phosphate wasting Ranges: Birth: 1.43–3.43 mmol/L 3 mths: 1.48–3.30 mmol/L 6 mths: 1.15–2.60 mmol/L 2–15 years 1.15–2.44 mmol/L

Hypokalemic Metabolic Acidosis



Hypokalemic Metabolic Alkalosis

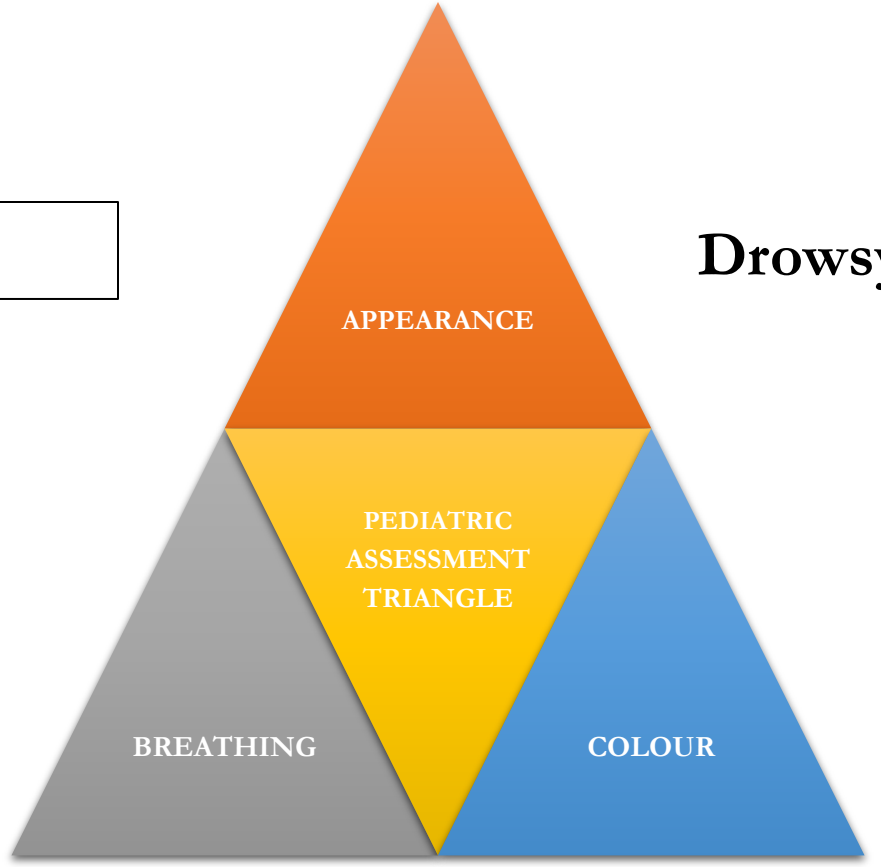


Case 2

Initial Impression; Pediatric Assessment Triangle

8 years, female

Drowsy, GTCS



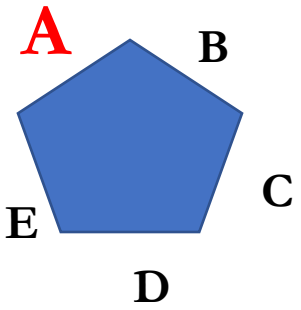
Normal

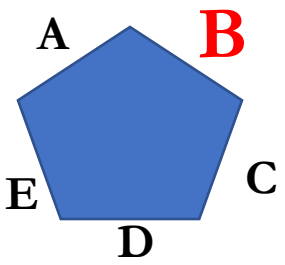
Pale

Intervention- Attached to monitor; Humidified oxygen

Primary Survey

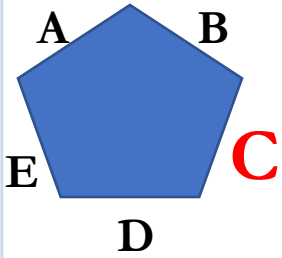
A **AIRWAY**	• Open and maintainable
B **BREATHING**	• Normal • B/L breath sounds vesicular • B/L conducted sounds • SpO2 95% at room air





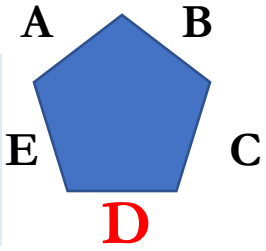
C
CIRCULATION

- HR - 118/minute, regular
- Well palpable
- BP 150/120 mm Hg (>99th centile)
- Temp- 99.4 ^{0}F
- CRT <3 secs



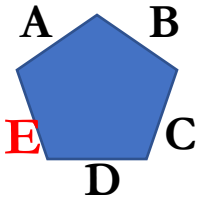
D
DISABILITY

- Abnormal movements
- GCS – E3V3M6, Dextrose- 33 mg/dL



E
EXPOSURE

- Pale



ER Evaluation and Intervention

Evaluation and Identification	Intervention
Seizures	Midazolam Dextrose (5 ml/kg, 10% dextrose) Phenytoin
	IV access secured; blood samples taken Catheterised to monitor urine output
AKI/AKI on CKD	
Hypertensive Emergency	Inj. Frusemide Inj. Nitroprusside

Focused History

Sign and symptoms:

- Fever, vomiting x 2 days
- GTCS 6 hours back for 10 minutes followed by drowsiness
- History of blood transfusion due to pallor
- Pallor +, no icterus, rash, short stature+
- Fundus-vessels constricted, haemorrhages+
- Abdominal tenderness +
- Chest / CVS –WNL
- No renal bruit

ABL90 SERIE

ABL90 ABL90HEIDELBERGIM1 I393-090R023C 10:02 12.04.2016
PATIENTENBERICHT Kapillare KfH - K 65uL Probe Nr. 9515

Identifikation

Personal ID	926850005940
Patienten ID	noora
Nachname (Pat.)	
Vorname (Pat.)	
Probentyp	Keine Angabe
T	37,0 °C
$FO_2(I)$	21,0 %

Blutgas Ergebnis

pH	7,206	
pCO_2	27,7	mmHg
pO_2	41,4	mmHg

Oxymetrie Ergebnis

$ctHb$	12,0	g/dL
Hct_c	36,7	%
sO_2	65,4	%

Elektrolyt Ergebnis

cK^+	7,2	mmol/L
cNa^+	129	mmol/L
cCa^{2+}	1,10	mmol/L
cCl^-	98	mmol/L

Metabolit Ergebnis

$cGlu$	30	mg/dL

Säure Basen Status

$cHCO_3^-$ (P,st)$_c$	12,3	mmol/L
ABE_c	-15,6	mmol/L

Meldungen

c Kalkulierte(r) Wert(e)
0207: Fälligkeit(en) im Kalibrierpack vorhanden

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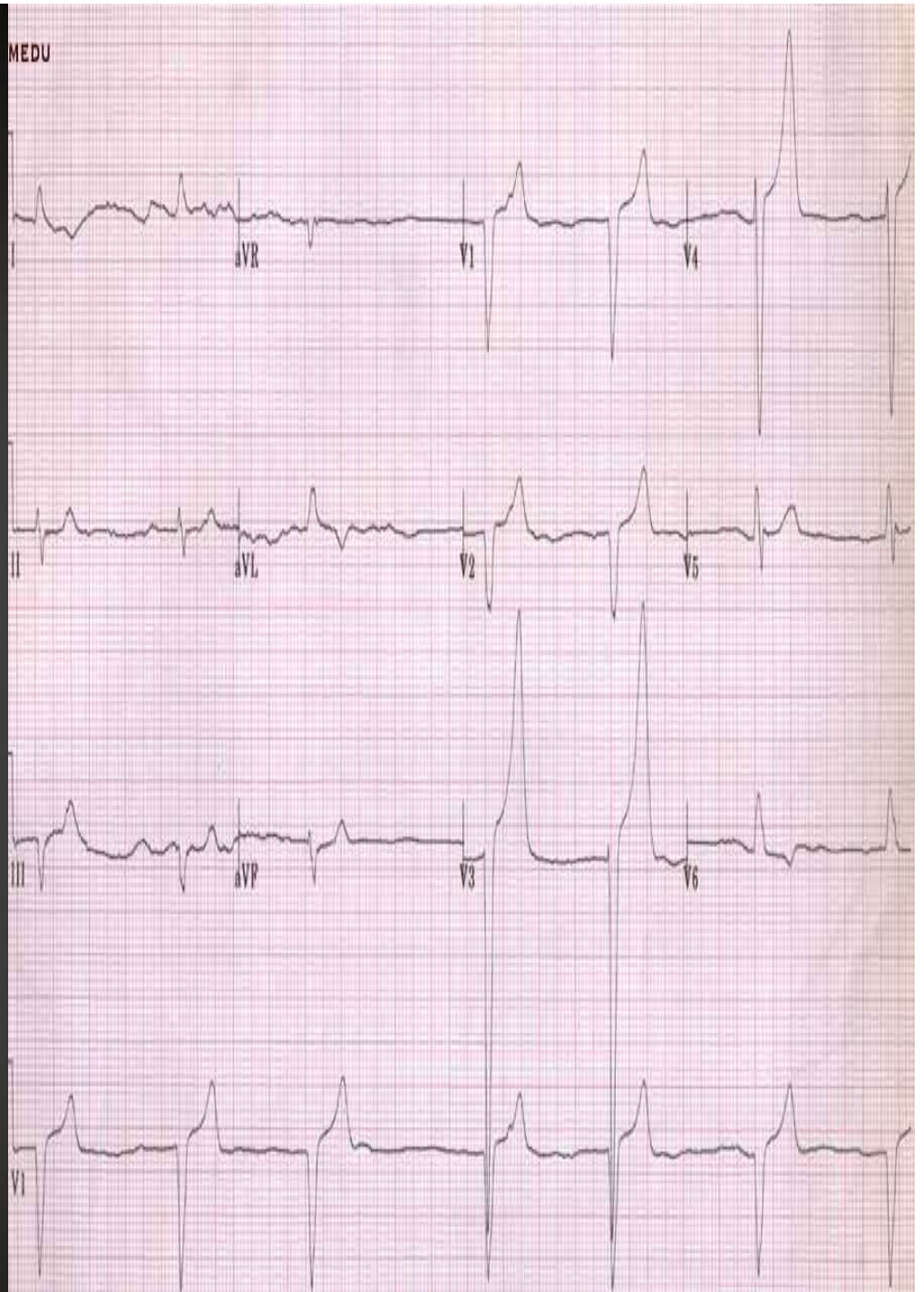
Gedruckt: 10:02:50 12.04.2016

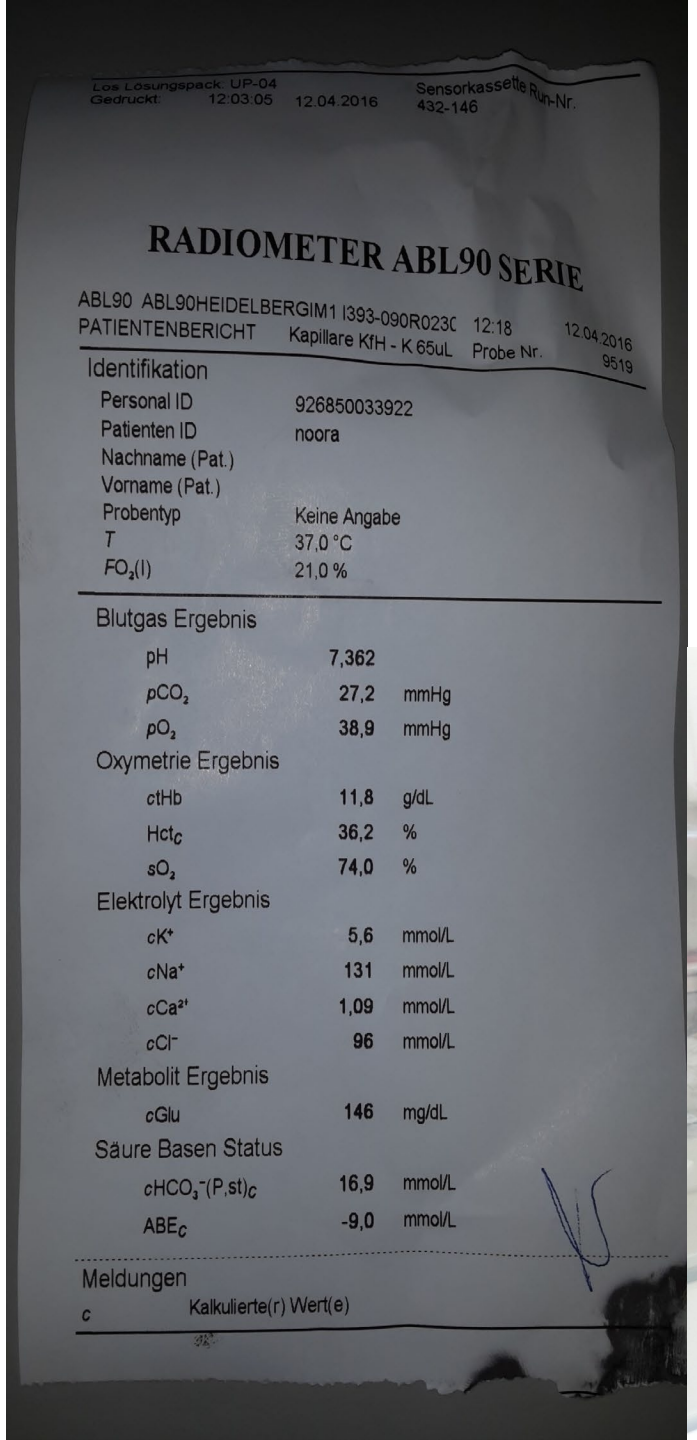
Sensorkassette Run-Nr.
432-146



Treatment

- IV Glucose: 2ml/ kg bolus; 10 % dextrose
- IV Calcium/antibiotics
- $NaHCO_3$: 1 mEq/kg diluted 1:1 with 5% Dextrose
- Nebulized salbutamol
- Nitroprusside infusion: 0.5 microgram/kg/min & titrated
- After 12 hours of infusion amlodipine added in doses of 0.5 mg/kg/d (Ped Nephrology ICU)

Repeat BG after 4 hours



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RADIOMETER ABL90 SERIE

ABL90 ABL90HEIDELBERGIM1 I393-090R023C 12:18 12.04.2016
PATIENTENBERICHT Kapillare KfH - K 65uL Probe Nr. 9519

Identifikation

Personal ID	926850033922
Patienten ID	noora
Nachname (Pat.)	
Vorname (Pat.)	
Probentyp	Keine Angabe
T	37,0 °C
$FO_2(I)$	21,0 %

Blutgas Ergebnis

pH	7,362	
pCO_2	27,2	mmHg
pO_2	38,9	mmHg

Oxymetrie Ergebnis

ctHb	11,8	g/dL
Hct_c	36,2	%
sO_2	74,0	%

Elektrolyt Ergebnis

cK^+	5,6	mmol/L
cNa^+	131	mmol/L
cCa^{2+}	1,09	mmol/L
cCl^-	96	mmol/L

Metabolit Ergebnis

cGlu	146	mg/dL

Säure Basen Status

$cHCO_3^-(P,st)_c$	16,9	mmol/L
ABE_c	-9,0	mmol/L

Meldungen

c Kalkulierte(r) Wert(e)

Investigations

- TLC 15500/cu mm, P70
- Urea 120 mg/dL, Cr 2.8 mg/dL, P 7.0 mg%, SAP 2200 IU/L
- LFT: Normal, Urinalysis-no proteinuria, no active sediment
- Peritoneal Fluid: 200 cells
- USG abdomen: RK 6.5X3.0 cm, LK 4.4X 2.5 cm; Small diffusely echogenic kidneys (L>R)

Diagnosis: CKD/Hypoglycaemia/Hyperkalaemia/Hypertensive Emergency/ Peritonitis

Causes of Hyperkalemia

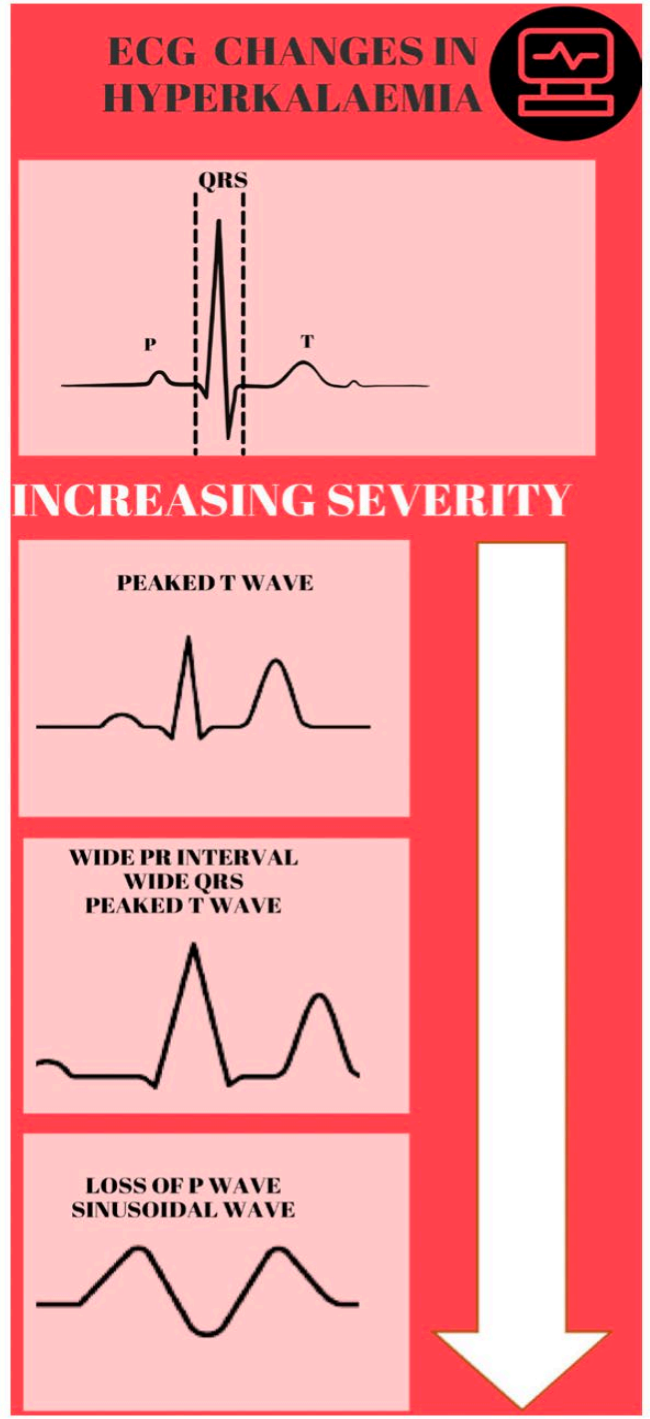
Increased intake		Decreased renal excretion	Extracellular shifts
EXOGENOUS Sources	ENDOGENOUS Sources		
Large volume packed red blood cell transfusion	Burns, Trauma, Rhabdomyolysis, Hemolysis, Tumor lysis syndrome	Acute Kidney Injury or chronic kidney disease	Metabolic acidosis
Potassium salt infusions		Hypovolemia	Insulin deficiency
NSAIDs ACE inhibitors Amiloride Spironolactone Eplerenone Tacrolimus Cyclosporine		Mineralocorticoid deficiency	Beta-adrenergic receptor antagonists

Clinical Features

- Cardiac dysrhythmias: most serious consequence
- Toxicity is exacerbated by a rapid rise in K conc., acidosis, hyponatremia, and hypocalcemia
- Neuromuscular effects are rarely evident at potassium concentrations <8 mEq/L
- Include paresthesias, skeletal muscle weakness, and ascending flaccid paralysis
- Respiratory muscles are typically spared

EKG changes

1. Narrow peak T waves
2. Shortened QT interval
3. Progressive lengthening of the PR interval
4. Widening of the QRS complex
5. Loss of P-wave amplitude and eventual “sine wave” pattern when the QRS merges with the T wave.



Risk Based Classification

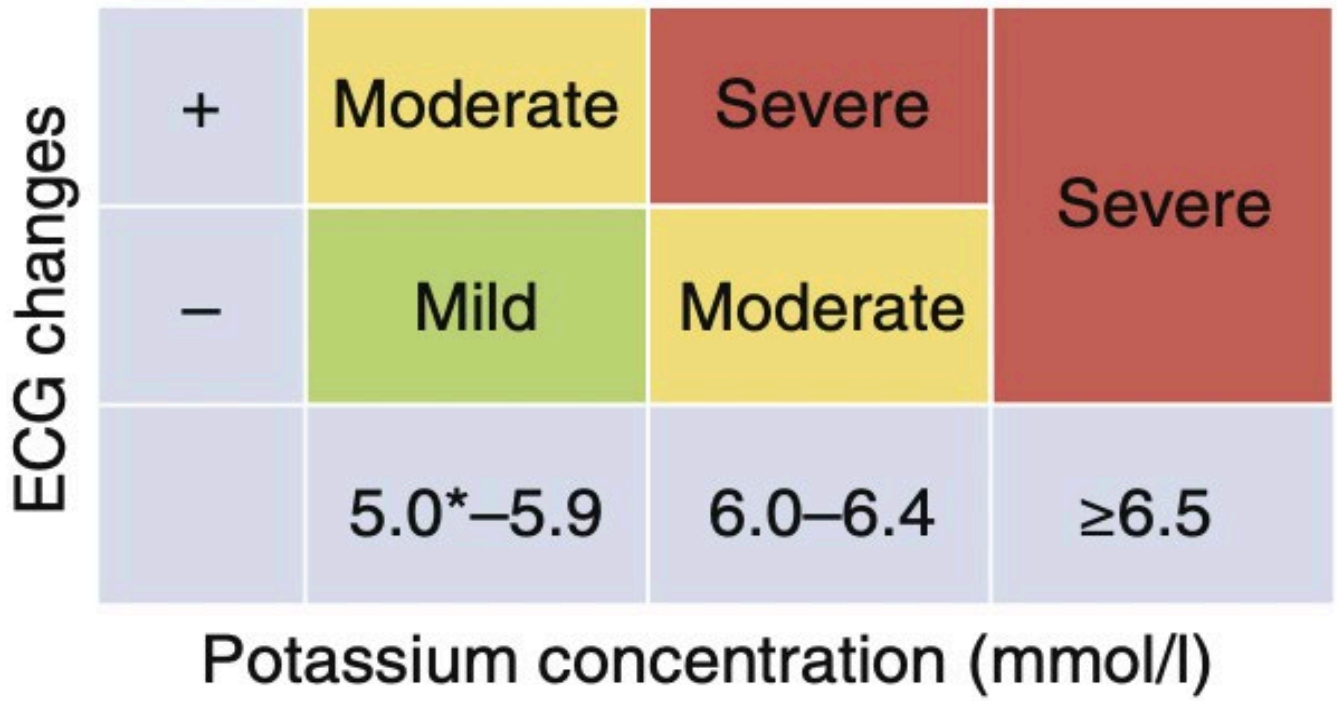
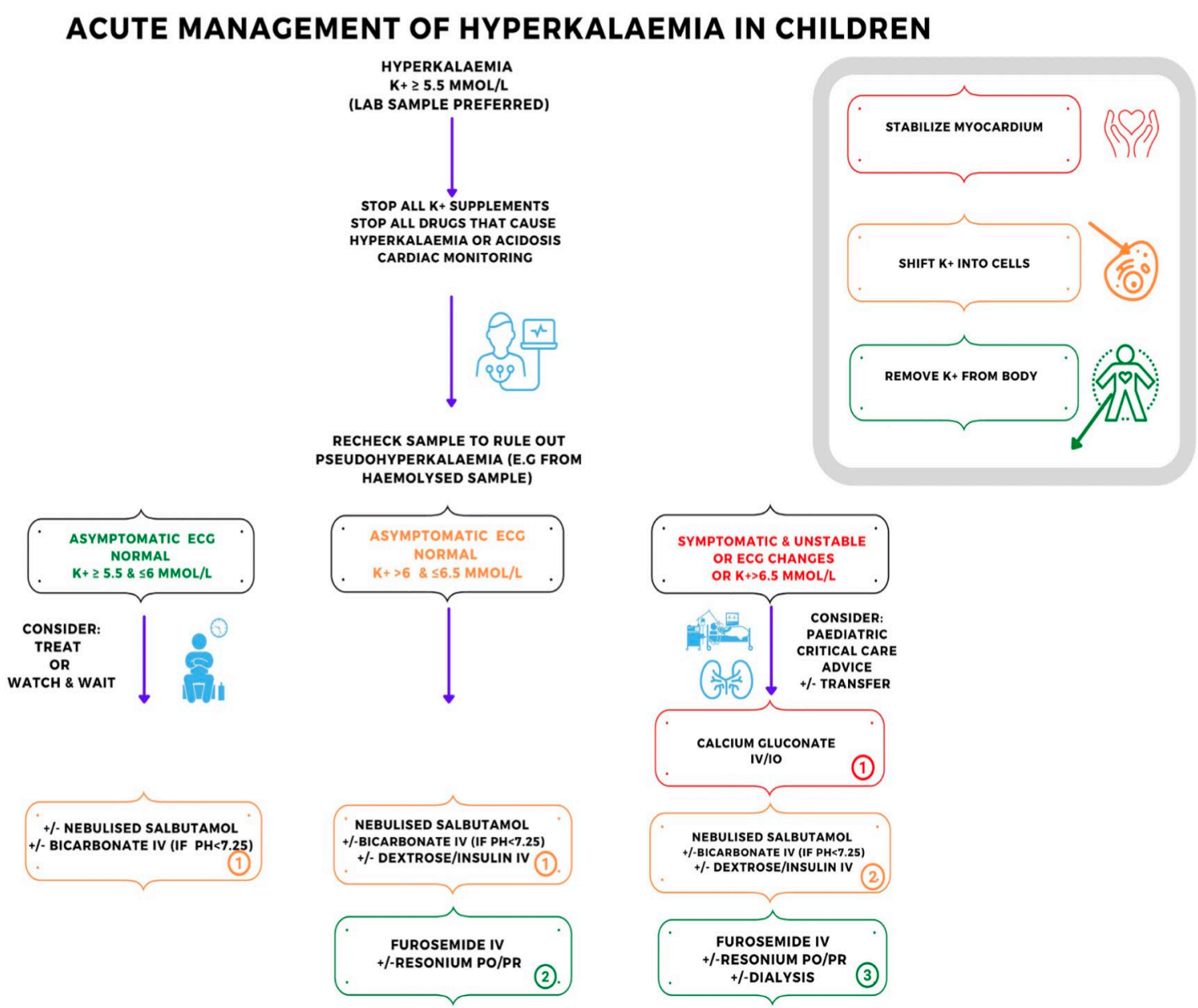


Figure 4| Severity of acute hyperkalemia: expert opinion-based risk classification. *5.0 or upper limit of normal range. ECG, electrocardiogram.



Box 2 Acute management of hyperkalaemia

Membrane stabilisation

Calcium gluconate

- 0.11 mmol/kg (0.5 mL/kg of calcium gluconate 10%), given over 5–10 min.
- Dose repeated after 5 min if ECG changes persist.
- Effect lasts 30–60 min.

Shifting potassium into cells

Salbutamol

- Nebulized salbutamol, 2.5–5 mg repeated as required.
- Beware of tachycardia in patient prone to arrhythmias; consider membrane stabilisation first.

Sodium bicarbonate

- 1 mmol/kg or 'half correction' (dose in mmol=0.15×weight×base deficit).
- Most effective when patient has concurrent metabolic acidosis.
- Check ionised calcium; correction of acidosis can exacerbate hypocalcaemia.

Insulin infusion

- 0.1–0.6 units/kg/hour (neonates).
- 0.05–0.2 units/kg/hour (>1 month).
- Run with glucose infusion: 0.5–1 g/kg/hour (5–10 mL/kg/hour 10% dextrose).

Reducing total body potassium

Potassium diuresis

- Loop diuretics, for example, furosemide.
- Larger doses required in renal failure: discuss with paediatric nephrologist.

Polystyrene sulfonates, for example, calcium resonium

- 0.5–1 g/kg PO or PR.
- Contraindicated in neonates with reduced gut motility and obstructive bowel disease.
- HD or CVVH more effective than PD.

CVVH, continuous venovenous haemofiltration; HD, haemodialysis; PD, peritoneal dialysis; PO, per os / by mouth; PR, per rectum / rectally.

Summary Slide

Early identification, algorithmic approach and appropriate interventions for dyskalemia can prevent adverse outcomes in critically ill children.


DIVISION OF PEDIATRIC NEPHROLOGY
DEPARTMENT OF PEDIATRICS
KALAWATI SARAN CHILDREN'S HOSPITAL, NEW DELHI


4
3
2
1

Thanks!

Approach to Nocturnal Enuresis

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Department of Pediatric Nephrology

SAT Hospital,Govt. Medical College, Thiruvananthapuram

Kerala

Outline

- Background
- Definitions
- Pathophysiology
- Approach
- Managment
- Conclusion

Case Scenario

8 year old boy has never been dry at night .He wants to go for an for an overnight camp as part of the scout program. Child is desperate to stop his bedwetting before his trip. Parents supportive, keen to help him overcome this problem.

Back ground

- Nocturnal Enuresis -A common problem in children
- It causes lot of psychological trauma to the child ,concerns parents and will become an internal issue in the family
- Worry will be is this problem a benign self limiting one or are there underlying serious illness ?

So we will be discussing in depth how to help these children & Families----

Also how to suspect and rule out underlying serious diseases ------

Nocturnal enuresis or intermittent nocturnal incontinence

- A common problem in children
- Isolated nocturnal enuresis also called mono symptomatic nocturnal enuresis.

Twice as common among boys as girls.

No need to worry too much as it resolves spontaneously

At 5 years 15 percent children are incompletely continent of urine.

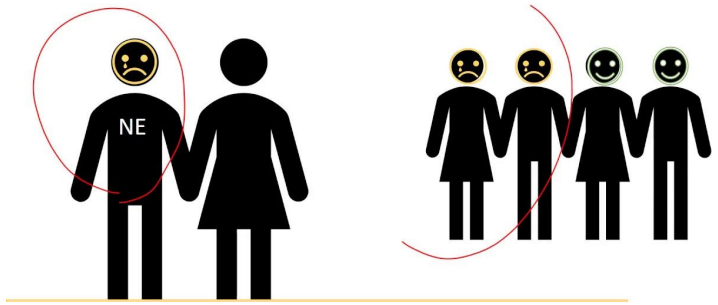
Spontaneous Resolution rate 15% per year

5 years	–15 percent
6 years	– 13 percent
7 years	– 10 percent
8 years	– 7 percent
10 years	– 5 percent
12 to 14 years	– 2 to 3 percent
≥ 15 years	– 1 to 2 percent

The longer the enuresis persists, the lower the probability that it will spontaneously resolve…….

Epidemiology

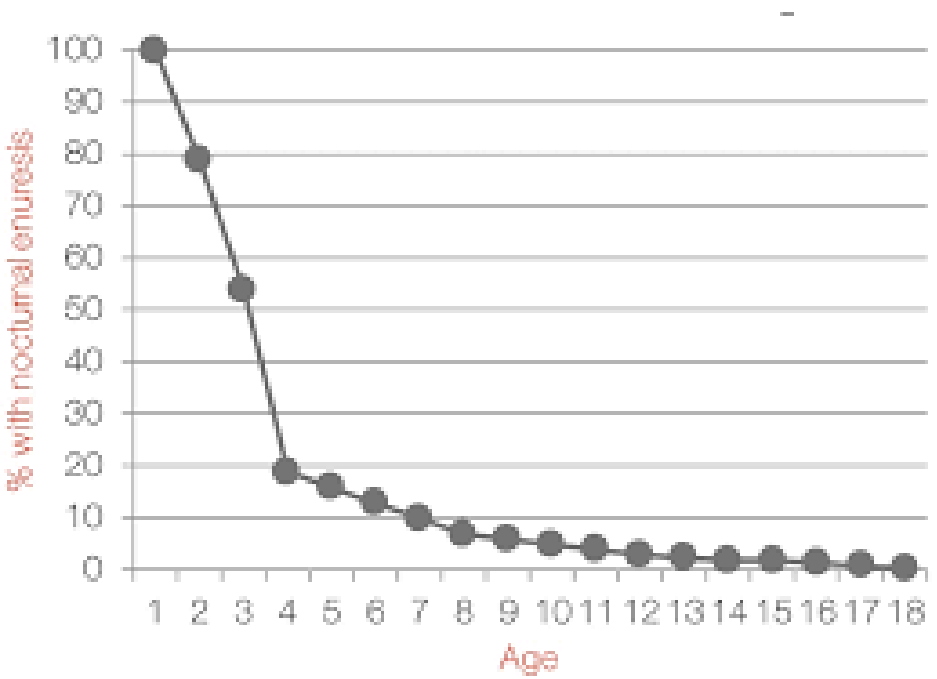
- Children with nocturnal enuresis - 60% boys.
- 50% positive family history
  - If one parent enuretic, each child has 44% risk
  - If both parents enuretic - 77% risk.
- Polygenetic
  - Usually transmitted in an autosomal dominant fashion
  - Candidate genes localized to chromosomes 12 &13



PNE affects 20% at the age of 5 year

Spontaneous resolution -15% every year thereafter.

Frequency in adults less than 1%.



Definitions ----Standardised Terminologies---

International Children's Continence Society

Enuresis

Synonymous with intermittent nocturnal incontinence- discrete episodes of urinary incontinence during sleep in children ≥5 years

- Mono symptomatic Enuresis
- Non mono symptomatic Enuresis

Mono symptomatic Enuresis

- Primary
- Secondary

Austin PF, Bauer SB, Bower W, Chase J, The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. AU Neurourol Urodyn. 2016;35(4):471.

Definitions ----Standardized Terminologies---

Nocturnal enuresis (bedwetting)-Involuntary discharge of urine during sleep by a child old enough to be expected to have full bladder control.

- Child is labelled as having enuresis if
  - Wetting is **regular**
  - Occurring **at least three times per week**
  - Persists **beyond 5 years** for girls & **6 years for boys.**

Nocturnal Polyuria

Night time urine 20-33% of total voided volume & is More than 130% of EBC

DSM V criteria more precise: repeated voiding into bed at least **twice a week** for **three consecutive months a year**, or causing significant distress in a child aged five years or older.

Mono symptomatic enuresis

- Enuresis in children without any other lower urinary tract symptoms and without a history of bladder dysfunction

Non Monosymptomatic Enuresis

Enuresis in children with other lower urinary tract symptoms, including :

- Increased (≥8 times/day) or decreased (≤3 times/day) voiding frequency
  - Daytime incontinence
  - Urgency ,Hesitancy (difficulty initiating voiding)
  - Straining (application of abdominal pressure to initiate and maintain voiding)
  - A weak stream, Intermittency (micturition occurs in several discrete spurts)
  - Holding maneuvers (strategies used to postpone voiding)
  - A feeling of incomplete emptying, Post micturition dribble
  - Genital or lower urinary tract pain

Mono symptomatic enuresis

Primary enuresis

- Children who have never achieved a satisfactory period of nighttime dryness
- 80 percent of children with nocturnal enuresis

Secondary enuresis

Children who develop enuresis after a dry period of at least six months

Stressful event (eg, caregiver divorce, birth of a sibling)

Stool retention and suboptimal daytime voiding habits

Exact cause of secondary enuresis remain unknown.

Pathophysiology

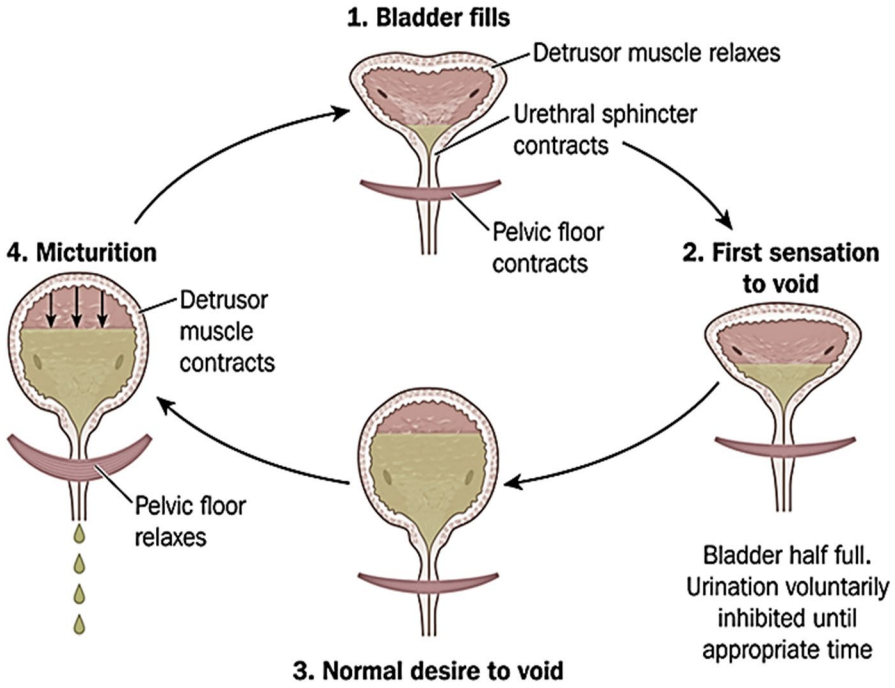
Bladder Control

- Infancy- coordinated, reflex voiding as often as 15 to 20 times per day
- After 2 years - Average bladder capacity (Ounces)-(Koff Formula)

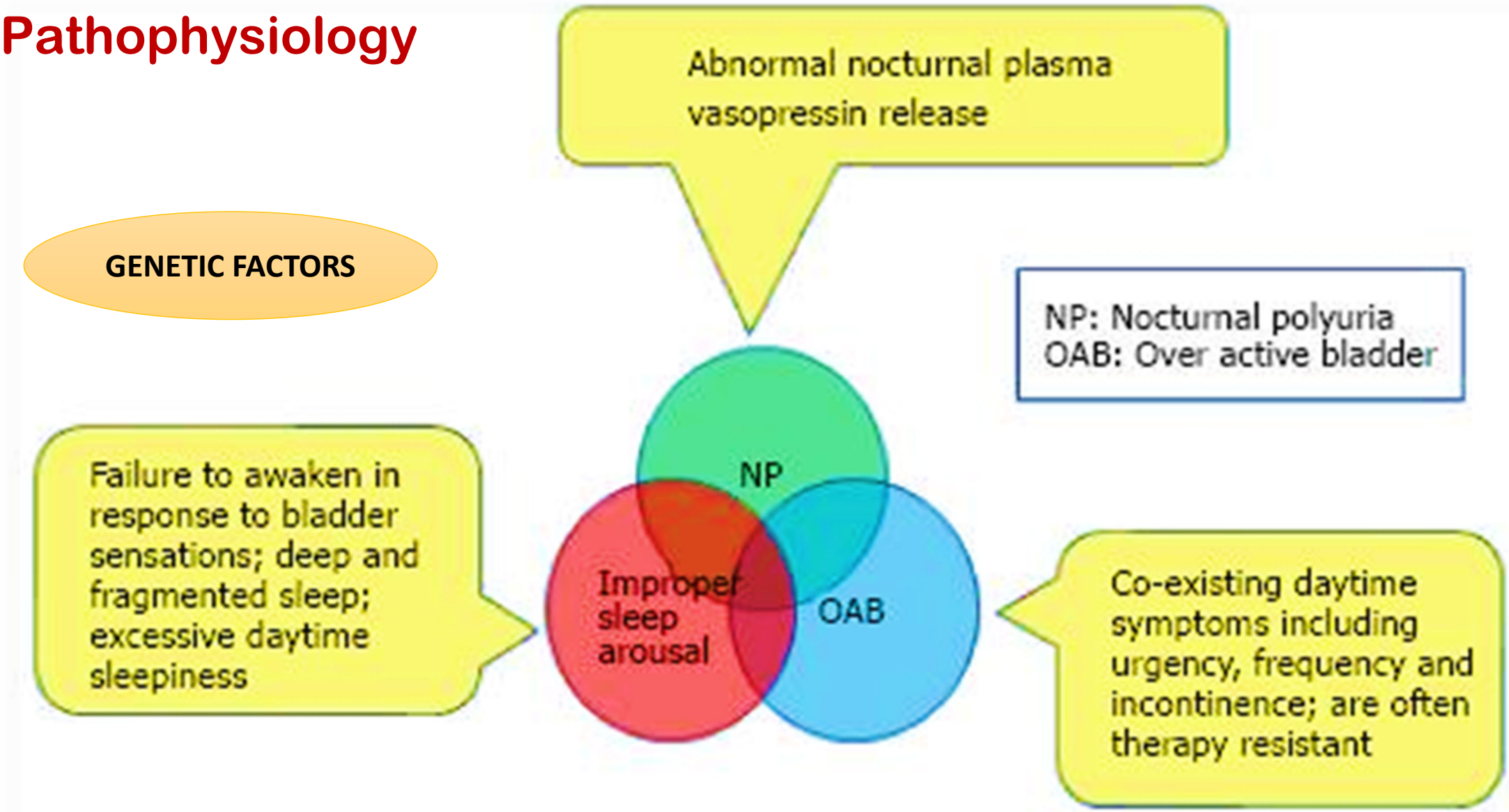
  = Age (year)+ 1 (Up to the age of 12-14 year)
- At 2-4 year, toilet training started
- Transitional phase refers to the period when children are acquiring bladder control.
- Everyone is a born bed-wetter.
- As one grows older, the brain continually develops
- By the age 5-6 years, full control of the bladder is attained in the majority.

Bladder and Bowel Control

- Follows a sequential pattern
- A child first achieves
  - Night time bowel continence
  - Daytime bowel control
  - Daytime bladder control
  - Night time bladder control
- Girls typically acquire bladder control before boys
- Bowel control is typically achieved before urinary control.
- By 5 year of age
  - 90-95% nearly completely continent during the day
  - 80-85% are continent at night



Pathophysiology



Aetiology

Unknown;Unclear---Theories? Maturational Delay? Developmental Delay?

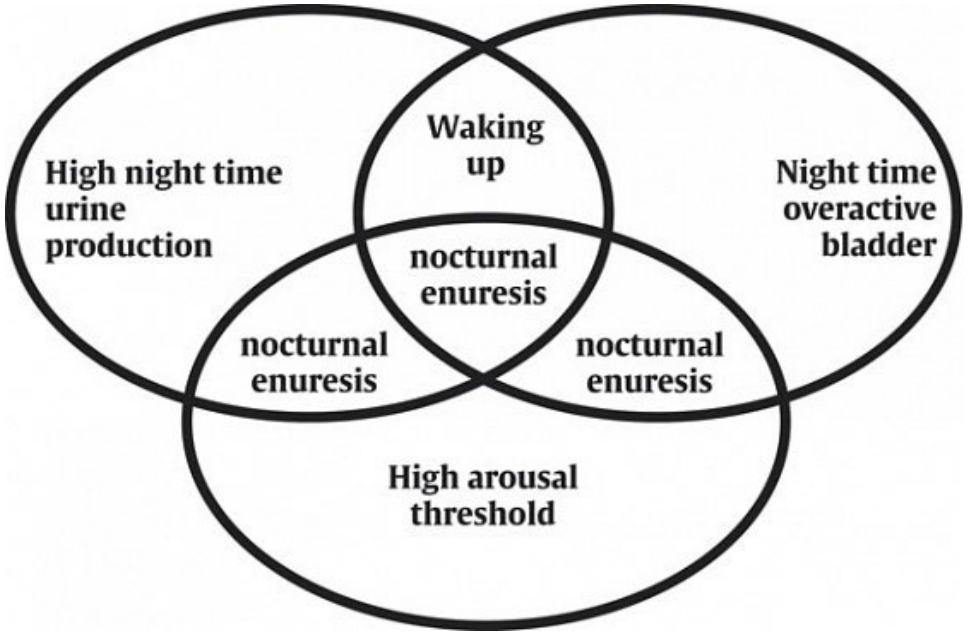
Not fully understood

Combination of factors

- Sleep arousal difficulties
- Production of large volumes of urine
- Bladder dysfunction

Bladder dysfunction

- Diminished functional bladder capacity
- Slow development of bladder control



Emotional & Behavioural issues not causative--- but may influence the treatment outcome

Adapted from Wolfish NM. *J*; 166(6): 2444-7 [1]

CPS-management of primary nocturnal enuresis (revised Aug 2007)[2]

Comorbid Conditions?

Constipation

- Less than 2 defecations/week
- More than 1 encopresis/week
- Retentive Posturing
- Large fecal mass
- Painful /hard bowel movements

Obesity

Unexplained

Snoring/OSA

- Insufficient arousal response
- Insufficient ADH Release in sleep

Behavioral

- ADHD
- Social Problems
- Parental discord

IMPACT------

8 year old boy never been able to achieve complete night time dryness since being potty trained .They have tried fluid restriction before bed, and mother tries to wake him during the night, but he is a deep sleeper.

25-30% of parents punish(physically abuse) children

Feel that the child is deliberately wetting the bed

Difficulty in coping with bedwetting

Express anger, negativity, or blame.

IMPACT------

Psychological ramifications

Impaired personal, social and emotional behaviour

Only parental fighting and divorce perceived as worse than bedwetting

Bed wetting benign and self-limiting
Why Bother--- Just Dismiss & Ignore!

A source of embarrassment and social stigma.

Intolerance
Resentment
&
Rejection from Parents & siblings

Negative Psychosocial development
Low self Esteem
Poor adjustment in society

Always Address the Problem of nocturnal enuresis

Nocturnal Enuresis can Affect Anyone

Approach to Nocturnal Enuresis

A 5 step approach

Step 1

Establish the correct diagnosis.

Step 2

Exclude other treatable diseases like urinary tract infection.

Step 3

Assess need for active treatment.

Step 4

Reassure and support parent and the child at all times.

Step 5

Offer various treatment options if deemed necessary.

STEP I- Establish correct diagnosis

Is it Incontinence ?
Is it Enuresis?
Is there Encopresis?

Incontinence is neurogenic or anatomic

Enuresis is almost always functional

Rule out an anatomical or a neurologic anomaly

Differentiate mono symptomatic from non mono symptomatic enuresis

- Sleep arousal difficulties
- Production of large volumes of urine
- Bladder dysfunction

Case 1

8 year old boy has never been dry at night . Child is desperate to stop his bedwetting before his trip. Parents supportive, keen to help him.

Enuresis is monosymptomatic and primary ---- But few Clarifications needed

- Can we get some idea about the volumes voided? –Polyuria ? Polydypsia ? DI ; DM , CKD, salt wasting tubulopathy
- Does he have other LUT symptoms like urgency, frequency, daytime incontinence?
- Bowel habits---- constipation (seen in 33-74%)
- Ask for the drink and voiding diary
- Snoring? OSA (10-54%)
- Behavioral issues? ADHD ;Autism ?
- Motor developmental delay ? Learning problems ?
- Red flag signs of CKD ? Weight loss ,bony deformities,spine /lower limb abnormalities

Primary Monosymptomatic Enuresis

- No daytime Symptoms
- No UTI
- Good stream
- No constipation

No Further evaluation

<5%have organic basis

Non mono symptomatic NE

- Generally secondary
- Daytime symptoms
  - Frequency/Urgency
  - Holding maneuvers
  - Accidents
- Recurrent UTI
- Poor stream/straining
- Constipation
- Polyuria
  - Diabetes mellitus,Diabetes insipidus
  - Chronic renal failure, Renal dysplasia
  - Renal tubular acidosis
  - Bartters syndrome

Diagnosis

Rule out other possible conditions

- Structural or neurological problems-learning Disabilities
- Storage or voiding dysfunctions
- Daytime wetting
- Urinary tract infection
- Polyuria
    - Diabetes mellitus
    - Diabetes insipidus
    - Chronic renal failure
    - Renal tubular acidosis
    - Renal dysplasia
    - Bartters syndrome

Hjalmas et al. *J Urol* 2004;171:2545-61

Assess the Pattern of Bedwetting & Fluid Intake

- How many nights a week does bedwetting occur?
- How many times a night does bedwetting occur?
- Does there seem to be a large amount of urine?
- At what time of night does the bedwetting occur?
- Does the child wake up after bedwetting?

Assess child's fluid intake throughout the day

Ask whether fluid is restricted

Keep a Voiding Diary for 2 weeks-

Fluid intake, bedwetting, and toileting patterns for 2 weeks

- Sleep arousal difficulties
- Production of large volumes of urine
- Bladder dysfunction

Case 1. Drink and Voiding diary --was similar for the week

Time	Drinks	Voided volumes	Comments
6 am		200 ml	
8 am	50 ml		Not moved bowels
8:15 am		90 ml	(moves every 2-3 days
1 pm	100 ml		Passes hard stools
3 pm		250 ml	
3.30 pm	200 ml		
6.00 pm	250 ml	200 ml	
8.00 pm	250 ml		
9.00 pm	200	200 ml	
Total	1050 ml		Wet at night

Number of voids and bladder capacity are normal

Expected bladder capacity: (Age+1) x 30 = 270 ml

(range 65-150%)

What is the diagnosis ? Appropriate initial management ?

Assessment

- Complete Physical Examination
- Assess after voiding to assess the possibility of a chronically distended bladder or loaded bowel.
- Complete neurologic Examination
- Look for Spinal abnormalities.
- Adenoid hypertrophy & Sleep disorders

Ultrasonography
Uro- flowmetry
Only in voiding dysfunction

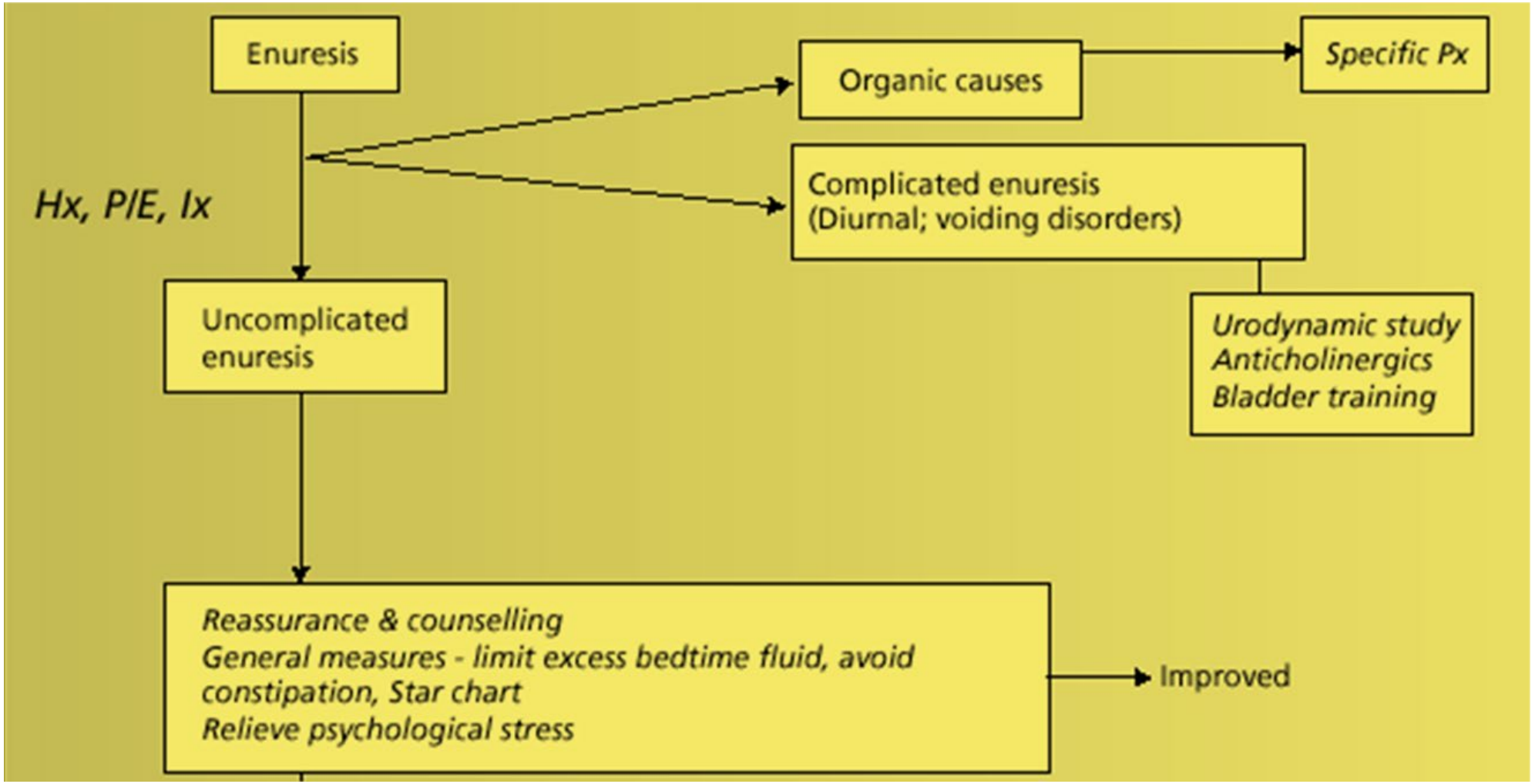
Investigation

Do not perform urinalysis routinely

Urinalysis if the child has:

- Recently started bedwetting (few days or weeks)
- Daytime symptoms
- Any signs of ill health
- History, symptoms or signs suggestive of UTI
- History, symptoms or signs of diabetes mellitus.

APPROACH TO ENURESIS



Treat Enuresis!

Factors

- Age
- Severity of wetting
- Psychosocial impact on the patient & family.

Active intervention

- Above 7 years of age
- Wets 3 or more nights per week.

Treat younger child with less frequent episodes of bedwetting- if it burdens the sufferer or the family to a significant extent.

Goals of treatment

- To remain dry and prevent accidents
- To reduce the number of wet nights
- To reduce the impact of enuresis on the child and family
- To avoid recurrence

Steps of Management

Interventions either alone or in combination.

1. Education and reassurance (spontaneous resolution)
2. Motivational therapy (e.g. star chart)
3. Active Interventions
    a. Enuresis alarms
    b. Desmopressin

Initial management

Urotherapy i.e. Nonsurgical, nonpharmacological management

- Educate child & parents about condition
- Let the child take control
- Inform the child that enuresis is a common condition, it likely affects other members of her peer group
- Help eliminate guilt & shame
- Ask the child to drink more during the day Fluid intake: 50 ml/kg/d (max 2L): ***to be consumed throughout the day -*** and less during the evening.
- No caffeine intake before bedtime
- Advise about good bladder bowel habits
- Address the constipation: good bowel hygiene

Case 1 contd.

- Follow-up at 2-weeks: re-inforced adequate drinking during day, voiding at bedtime, bowel hygiene
- 8 weeks later: drinking better during the day, has some dry nights but continues to wet the bed most nights
- What next ?

Treatment

Best approach

Expectations

Counselling

Reassurance

Not a Physical Abnormality

Blaming Parent needs support

Supportive Family

Motivation

Successful Outcome

Active Participation

Goal Oriented Approach

Consistent Follow up

Months for successful results

Motivational therapy

Good first-line therapy

- younger children (between five and seven years of age)
- Do not wet the bed every night

  - Motivate the child to accept some responsibility for the treatment program.
  - He can keep a record of progress.
  - Initial rewards should be given for agreed-upon behaviour (e.g. going to the toilet before bedtime) rather than dryness.
  - Successively larger rewards, agreed upon in advance for
  - Longer compliance with agreed-upon behaviour
  - Longer periods of dryness (e.g. sticker calendar for each dry night,book for 7 consecutive dry nights)
  - Penalties (i.e. removal of previously gained rewards) are counterproductive.

Common Management Strategies

- Child to empty the bladder at bedtime
- Daily fluid intake should be concentrated in the morning and early afternoon.
  - Fluid and solute intake minimized during the evening-
  - 40 % of total daily fluid in the morning (7 AM to 12 PM)
  - 40% in the afternoon (12 PM to 5 PM)
  - only 20 % in the evening (after 5 PM).
- Limit fluid consumption & eliminate caffeine late afternoon and onwards
- Clarify the goal of getting up / using the toilet
- Take the child out of diapers
- Consider pull-ups or training pants
- Include child in morning clean up in a non-punitive manner

Adapted from Canadian Pediatric Society. Management of primary nocturnal enuresis. *Paediatrics & Child Health* 2005;10(10): 611-4 (REVISED AUG 2007)

Strategies---

- ✓ The impact of bedwetting can be reduced
  - By using bed protection
  - Washable/ disposable products
  - Using room deodorizers
  - Thoroughly washing the child before dressing
  - Using emollients to prevent chafing.

Response

- Successful - 14 consecutive dry nights
- Significant improvement- Decrease in enuresis events by ≥80 percent
- Relapse- More than two wet nights in two weeks

No improvement occurs after three to six months
Failure of Motivational therapy

Active Intervention

Conditioning Therapy

Pharmacologic Therapy

Conditioning Therapy
Enuresis Alarms

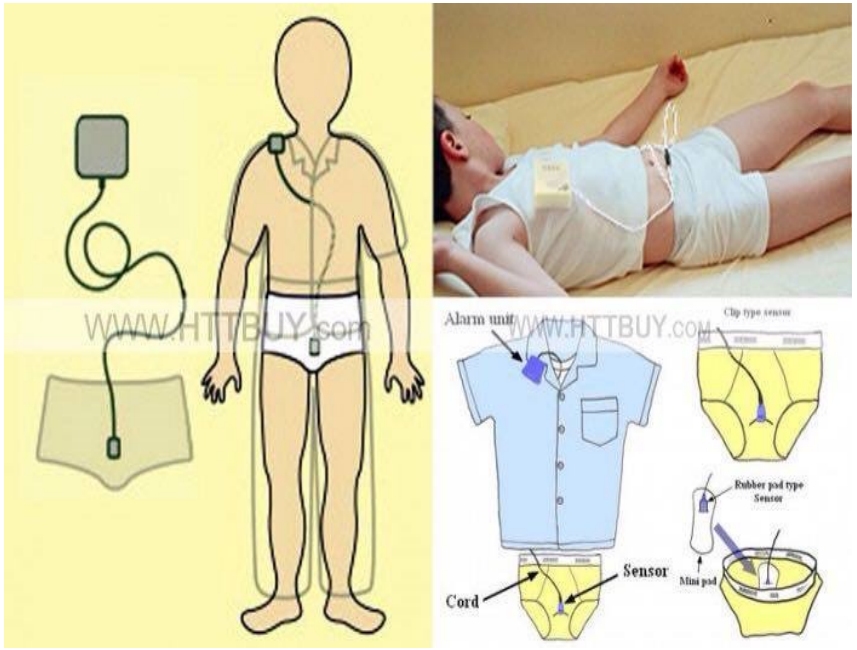
Older Child
Well motivated Family
Supportive parents

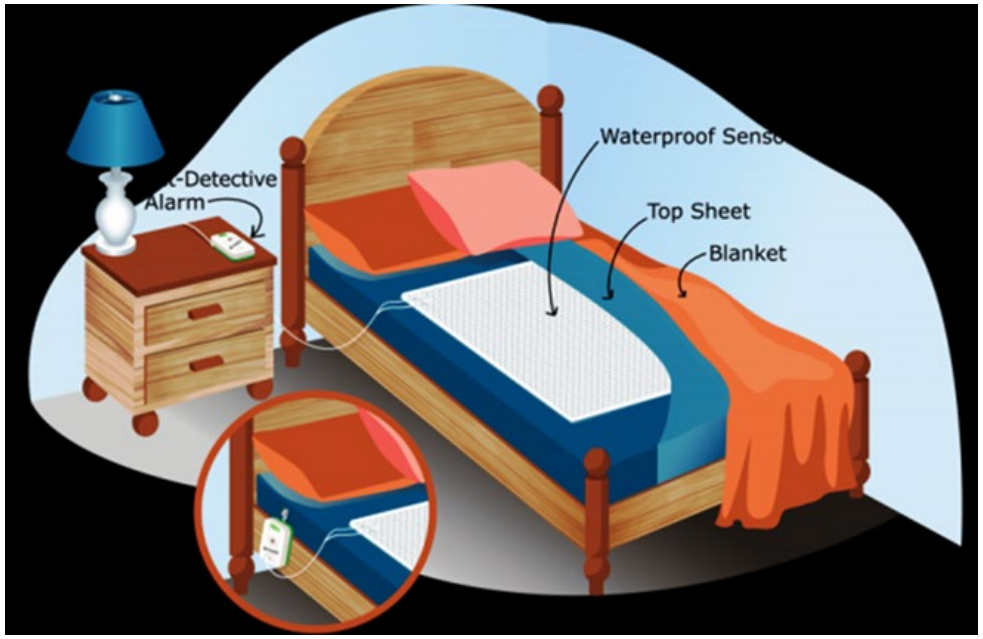
Success of 60%.

Persistence for several months

Long-term result

Bed Wetting Alarms





The family should be instructed that the child is in charge of the alarm.

Each night before going to sleep, the child should test the alarm. With the sound (or vibration) in mind, the child should imagine in detail, for one to two minutes, the sequence of events that occur when the alarm sounds (or vibrates) during sleep.

A diary should be kept of wet and dry nights. Positive reinforcement should be provided for dry nights as well as successful completion of the above sequence of events. Penalties (e.g., the removal of a reward) for wetting episodes appear to be counterproductive.

Burn out------

No improvement occurs after three months
Failure of Alarm Therapy

Pharmacologic Therapy

Desmopressin Acetate-

Synthetic analog of antidiuretic hormone, Reduces urine production overnight

- First-line treatment in children older than five years if failure of
  - Educational
  - Motivational &
  - Alarm therapy.
- Best for children with nocturnal polyuria and normal functional bladder capacity.
- More effective than an enuresis alarm in the short-term
- Relapse rate is high
- More expensive .

Desmopressin

Available as tablet Dose- 0.2-0.6 mg HS

Given orally 30 to 60 minutes before bedtime to reduce urine production during sleep.

Initial dose is 0.2 mg,After 10 to 14 days, increased the dose by 0.2 mg to a maximum dose of 0.4 mg.

Pearls:

- Reduce evening fluid intake
- Avoid if systemic illness with vomiting or diarrhea.
- Limit fluid intake for 8 hours to prevent hyponatremia.

Secondary enuresis -Management

- Identify and correct the stressors
- Then treat as for primary enuresis.
- Reassurance, education and motivational therapies for three to six months.
- Active intervention in the form of alarms and ke desmopressin in older children as the social pressures increase and self-esteem affected.
- Enuresis alarms-most effective long-term therapy
- Desmopressin effective in the short-term.

Indications for referral

- Recurrent or Refractory enuresis
  - Developmental-behavioural Paediatrician
  - Urologist if structural or anatomic abnormalities
- Non mono-symptomatic enuresis
- Developmental, attentional, or learning difficulties
- Behavioural or emotional problems
- Known or suspected physical or neurologic problems
- Parents who have emotional difficulty coping with bedwetting or are expressing anger, negativity, or blame.

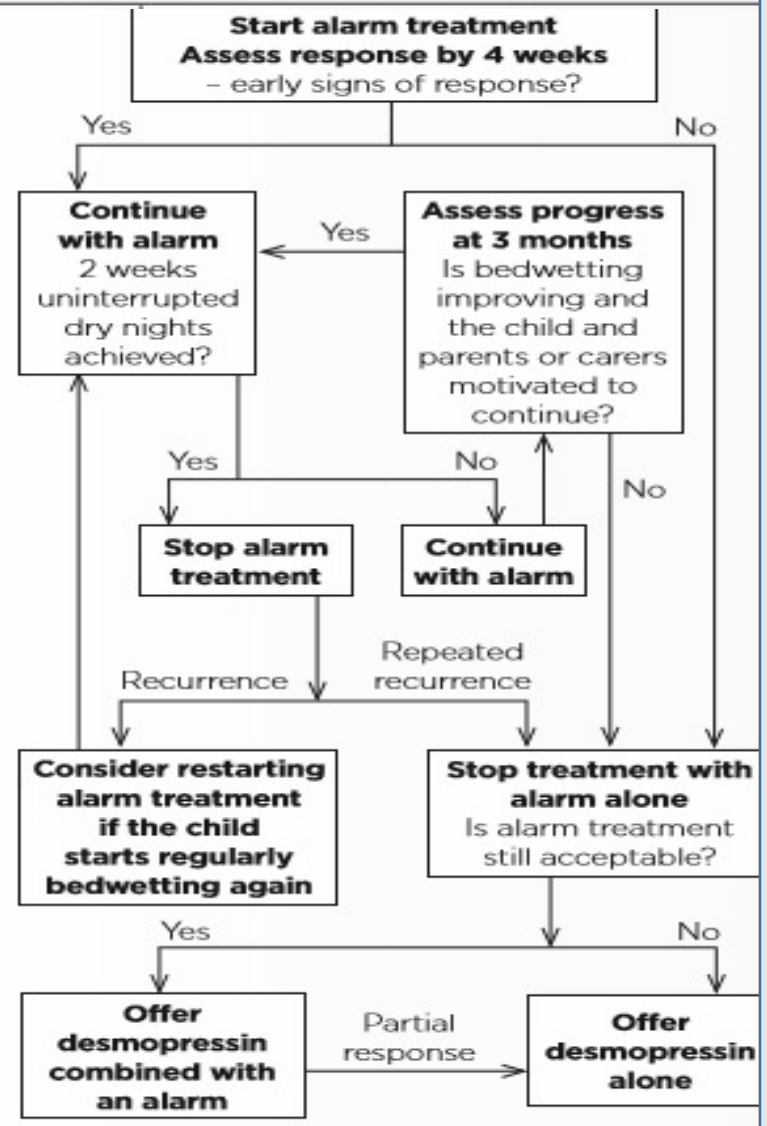
Mono-symptomatic enuresis-Third line treatment

- Tricyclic antidepressants (TCAs)-Imipramine
  - Decreases the amount of time spent in REM sleep
  - Stimulate vasopressin secretion
  - Relax the detrusor muscle.
- Dose- 10 to 25 mg HS and may be increased by 25 mg if there is no response after one week.
- The dose should not exceed 50 mg in children between 6 and 12 years and 75 mg ≥12 years
- Response assessed after one month.
- No improvement after 3 months, discontinue gradually.
- Success - 30-60%.
- Side effects : anxiety, insomnia, and dry mouth.
- One of the most common causes of poisoning by prescription medication in younger siblings.

Other interventions

- Waking the child to urinate
- Bladder training exercises
- Anticholinergic drugs
- Electrical stimulation therapy
- Complementary and alternative therapies.
    - Biofeedback
    - Reboxetine
    - Mirabegron-beta 3 receptor agonist relaxing bladder
    - Botox

. ALGORITHM FOR TREATMENT OF NOCTURNAL ENURESIS (NICE 2010)



Pearls in management

MNE TYPE	Treatment
Normal Urine output & EBC	DDAVP
Maximal voided Volume more than 70% EBC	Alarm
Reduced Nocturnal Bladder capacity	Alarm
Maximal voided Volume less than 65% EBC	DDAVP Resistant
Nocturnal polyuria	DDAVP
Nocturnal polyuria& Reduced bladder capacity	DDAVP& Anticholinergics

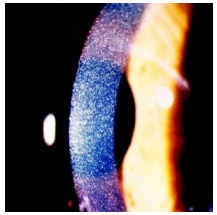
Conclusion

- Nocturnal enuresis is a common problem in children.
- Requires careful assessment and management as it affects the self-esteem of the child and also causes parental anxiety and burn out.
- Education ,motivation and support crucial for behavioural modification.
- Active intervention and medications required in only few children as majority spontaneously resolve over time.
- Keep the pressure off the child by explaining to the parents that this is a long term process and that the child has no control over it.
- A bedwetting alarm for 3 months can be introduced before drugs
- After the 3 months adding desmopressin together with the alarm can be useful.
- Referring the child should be considered if the symptoms persist, or if co-morbidities

WORLD BEDWETTING DAY

TIME TO TAKE ACTION - 30TH MAY 2017

Thank You



Infantile Nephropathic Cystinosis

Case based scenarios

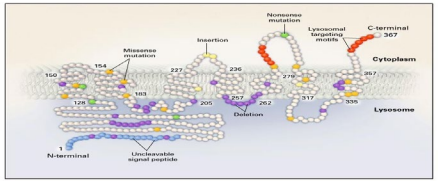
Dr. Sumantra Kumar Raut

MD, DM (Pediatric Nephrology, AIIMS)

Consultant Pediatric Nephrologist

Asst Professor and In-Charge, Nephrology

NBMC, West Bengal

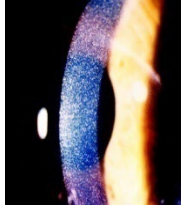


2nd Annual Pediatric Kidney Meet

AIIMS, Jodhpur

28.01.2023

Introduction



- Autosomal **recessive, most common** lysosomal storage disease
  Generalised accumulation of cystine in lysosomes

Prevalence:
1-9/100,000

- Swiss biochemist: Emil (1903)

William A. Gahl,
Senior Investigator, NIH

Incidence 1:167,000 live birth (France)

Pakistani ethnic of West Midlands, UK (1: 3,600)

Orphanet Journal of Rare Diseases, 2016

Limited data from our country

Types

- Nephropathic **infantile** form (most frequent and **severe**): 95%
- Nephropathic juvenile form (intermediate/adolescent): 5%
- Non-nephropathic adult form/ ocular non-nephropathic cystinosis

Case: 1

2y old boy Ismail Khan admitted for FTT
polydipsia - since last 9m; bony changes

No H/O vomiting, dehydration, LUTS, A/N polyhyd
In due course: salt craving

Lab: UO 7.2ml/kg/hr
Ur/Cr: 12/0.3 mg/dl

Up: trace, spot PCR: 1.1,
Ur B2 MG: 21500 ng/ml
UAAG: generalized
Ur Ca: Cr: 1.3 (cystinosis, Lowe, Dents, tyrosinemia)
TMP/GFR: 1.9

USG KUB: B/L sizes OK,
no NC/cyst

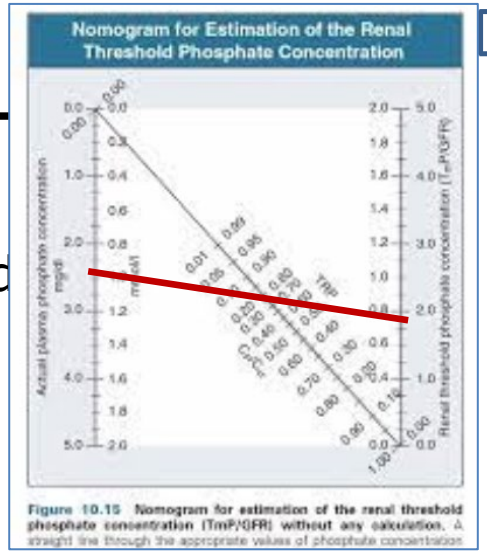


Figure 10.15 Nomogram for estimation of the renal threshold phosphate concentration (TmP/GFR) without any calculation. A straight line through the appropriate values of phosphate concentration

RTA

Acid load — Ur pH

Alk load — U-B CO2, FeHCO3

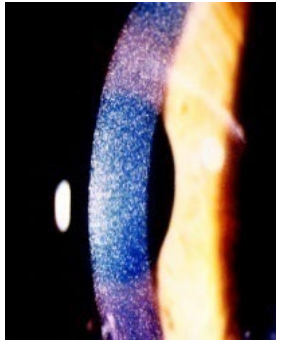
25

23

pRTA

2

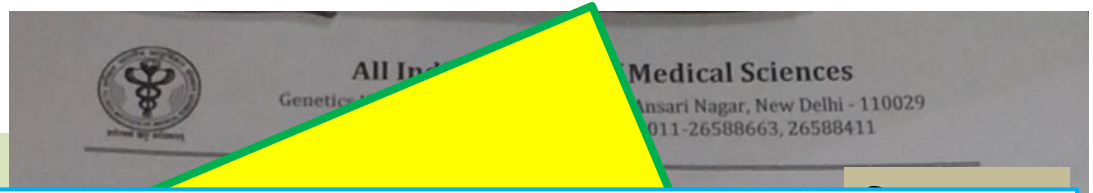
no family H/O
CKD/urolith



3 diagnostic tools:
Cystine crystals in cornea
Genetic mutation of *CTNS* gene
Leucocyte cystine estimation

Case: 1

Started on Cap **cysteamine**



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Stem Cell Gene Therapy for Cystinosis

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03897361

Recruitment Status : Recruiting
First Posted : April 1, 2019
Last Update Posted : October 21, 2022

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Sponsor:
University of California, San Diego

Collaborators:
California Institute for Regenerative Medicine (CIRM)
Cystinosis Research Foundation

Information provided by (Responsible Party):
Stephanie Cherqui, University of California, San Diego

Original Article

Infantile Nephropathic Cystinosis: Clinical Features and Outcome

Sumantra Raut, Priyanka Khandelwal, Aditi Sinha, Ritu Thakur, Mamta Puraswani, Thirumurthy Velpandian[1], Pankaj Hari, A

Division of Nephrology, Department of Pediatrics, All India Institute of Medical Sciences, [1]Department of Ocular Pharmac
All India Institute of Medical Sciences, New Delhi, India

Abstract

Background: Nephropathic infantile cystinosis, the most common cause of renal Fanconi syndrome, presents in early
growth, polyuria and polydipsia, and progresses to end stage renal disease during the first decade. Diagnosis is based o
for cystine crystals, leukocyte cystine content and genetic testing of the *CTNS* gene. Information on clinical features a
children with cystinosis is limited. **Methods:** We describe clinical features, renal outcomes and genetic variants in the
children with cystinosis. **Results:** We included 19 patients with cystinosis from 17 families predominantly presenting wi
polyuria (84%) and refractory rickets (74%). Cystine crystals were present in 84%. Fanconi syndrome was common; two
and 9 prese d 8 varian
pathogeni nclusion:
variant, co ed on the
Studies wi teamine i

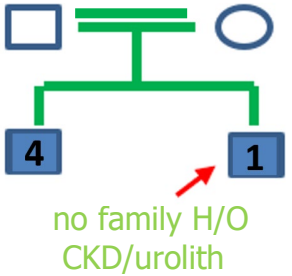
Cystine accumulation starts in utero but clinical symptoms are **absent at birth**

Kidney: 1st affected organ

6-12 months: full-blown Fanconi syndrome

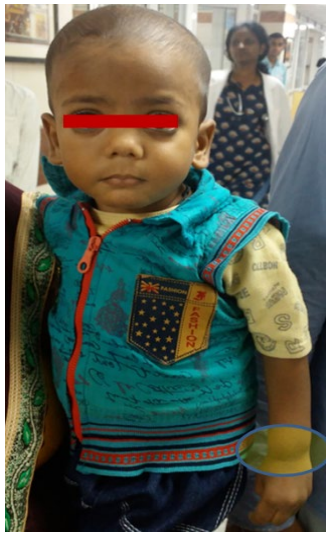
N= 19 patients (17 families)	
Median age:	9m (6.5, 15.5)
Poor growth:	95%
Polyuria:	84%
Refractory rickets:	74%
Cystine crystals:	84%
Hypothyroid:	42%
Nephrocalcinosis:	2/11
CKD-3/4/5:	9
Genetic variants:	8/12
Oral cysteamine:	42%

Case: 2



1y old boy Yuvi admitted for FTT, persistent diarrhea and polyuria, polydipsia - since last 4m

Excl breast fed till 5m, supplementary food after that (home based)
No H/O vomiting, dehydration, LUTS, A/N polyhydramnios
In due course: salt craving



Lab: UO 6.7ml/kg/hr
Ur/Cr: 32/0.9 mg/dl
Na/K/Cl: 137/2.3/111
pH/HCO_3: 7.25/14
PTH/ VitD: 612 / 17 ng/dl
Stool RE: WNL
Up: trace, spot PCR: 0.7,
USG KUB: B/L sizes OK,
no cyst/ NC
Rest workup: not done

D/D: RTA (?cystinosis), $NPHP_2$, PH
Eye exam : no cystine crystal
WBC cystine assay: not feasible

Not a Lab plan if CKD ensues:
urine electrolytes/biochemistry
Acidosis challenge, urine pH, Renal Bx

Next step of tests for CKDu:
MCU: reflux nephropathy
Eye check: cystine crystal, drusen BERA
Genetic workup

MedGenome Labs Ltd.
3rd Floor, Narayana Nethralaya Building, Narayana Health City,
#258/A, Bommasandra, Hosur Road, Bangalore - 560 099, India.
Tel : +91 (0)80 67154989 / 990, Web: www.medgenome.com

MEDGENOME

DNA TEST REPORT - MEDGENOME LABORATORIES

Full Name / Ref No:	SA[redacted]	Order ID/Sample ID:	1211[redacted]
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	1 year	Date of Sample Collection:	21st June 2019
Referring Clinician:	[redacted]	Date of Sample Receipt:	23rd June 2019
		Date of Order Booking:	24th June 2019
		Date of Report:	2nd August 2019
Test Requested:	Clinical Exome		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

B[redacted], born of a consanguineous marriage, presented with clinical indications of polyuria and polydipsia. He is suspected to be affected with renal tubular disorder or nephrogenic diabetes insipidus or Bartter syndrome or renal tubular disorders and has been evaluated for pathogenic gene variations.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
CTNS (+) (ENST00000381870.3)	Exon 10	c.771_793del **(p.Gly258SerfsTer30)**	Homozygous	Nephropathic cystinosis	Autosomal recessive	Pathogenic

Case: 3

11m
dou
No
Can

Mx:
- Genetic testing helps in differentiating phenocopies
- And also in reverse phenotyping

CLINICAL DIA

Baby P[redacted], born of a non-consanguineous marriag… of failure to thrive, recurrent diarrhea with metabolic acidosis and high cy… with cystic fibrosis or renal tubular acidosis or fibrilopathy or prim… thogenic gene variations.

RESULTS

…NOTYPE WAS IDENTIFIED

Gene (Tran…		Zygosity	Disease (OMIM)	Inheritance	Classification
EPCAM (+) (ENST0000026…)	…4insC (p.Arg125ThrfsTer8)	Homozygous	Diarrhea-5 with congenital tufting enteropathy	Autosomal recessive	Pathogenic

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely

Lab:
Ur/C
Na/k
pH/H
Stoo
Up:1
USG
Rest

Mx:
- Cystagon - stopped
- Fluid and electrolyte management
- Diet
- Counseling for next pregnancy
- Prior counseling regarding future chances of ESRD and renal transplant at early age was pacified

Thank you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14 - 15, 2023
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Indian Society of Pediatric Nephrology
WB Chapter
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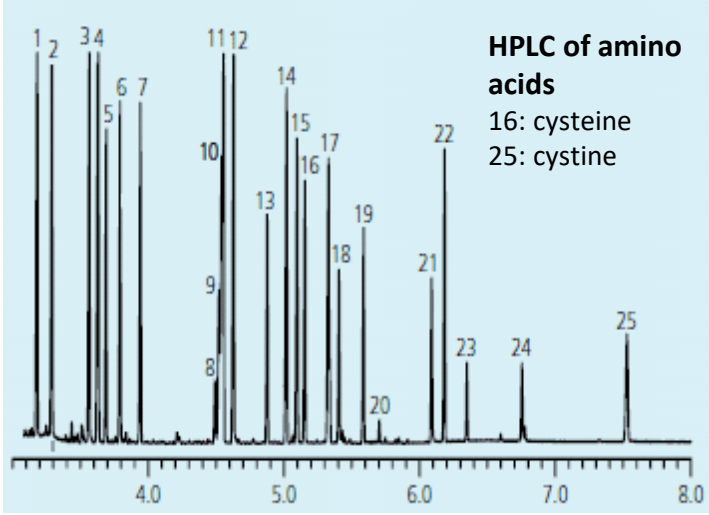
Leucocyte cystine level

Cystine from WBC is labelled with isotope 35-S

Quantitated by LC- MS/MS

✓Assay using the cystine binding protein (gold standard, more sensitive, permits detection of heterozygous but high radiation and cost); amino acid chromatography; HPLC



WBC cystine content (nmol of half-cystine/mg protein**)**
5 to 15 : infantile form (10-50 times of normal)
3 to 6 : intermediate form
<1 : heterozygous carriers
< 0.2 in normal individuals

Target on therapy: <1

Currently not available in Asian subcontinent

Eye exam

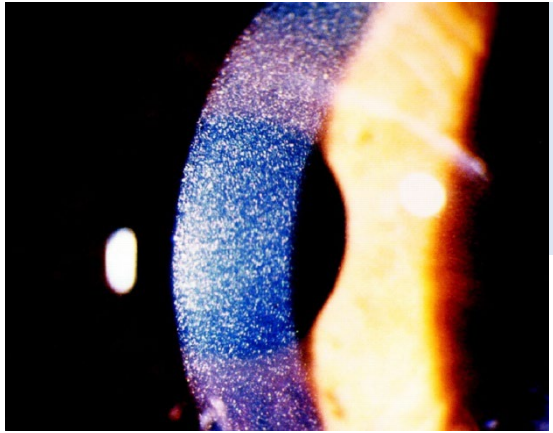
Demonstration of cystine corneal crystals by the slit lamp/ confocal lens examination

Earliest at the age of 1 year;

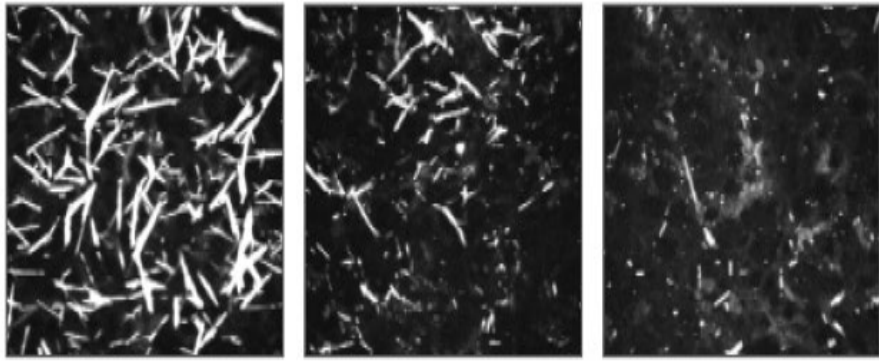
> 2years age its absence rule out cystinosis

Painful corneal erosions, band keratopathy

- Visual impairment: **2nd decade**



Slit-lamp photograph of infantile cystinosis (oblique slit)



Change in
In Vivo Confocal Microscopy
total score from day 0, 30, 90
(scale 0-28)

79% pt (11/14) has crystal at onset, 2 developed during FU and **1 didn't have till 30 months** of FU

Case discussion

Dr Georgie Mathew

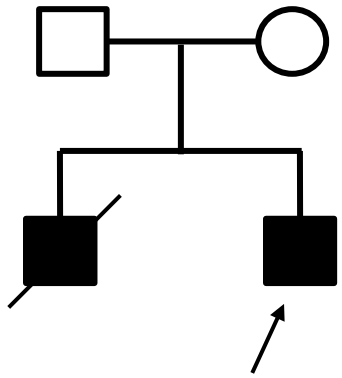
4 years/M, recurrent gross hematuria

Recurrent episodes of painful gross hematuria – from 2 years of age

? Passes gravel in urine

No polyuria or polydipsia or salt craving

No history of recurrent urinary tract infections; occasional lower abdominal pain



Developmentally normal

Drinks 400-600 ml per day and passes urine 3-4 times a day

Prefers salty snacks 3 times a day

History of sibling death at 8 years of age with unexplained chronic kidney disease

4 yr old/M, recurrent gross hematuria

Examination

Height 92 cm (-3.1 Z)

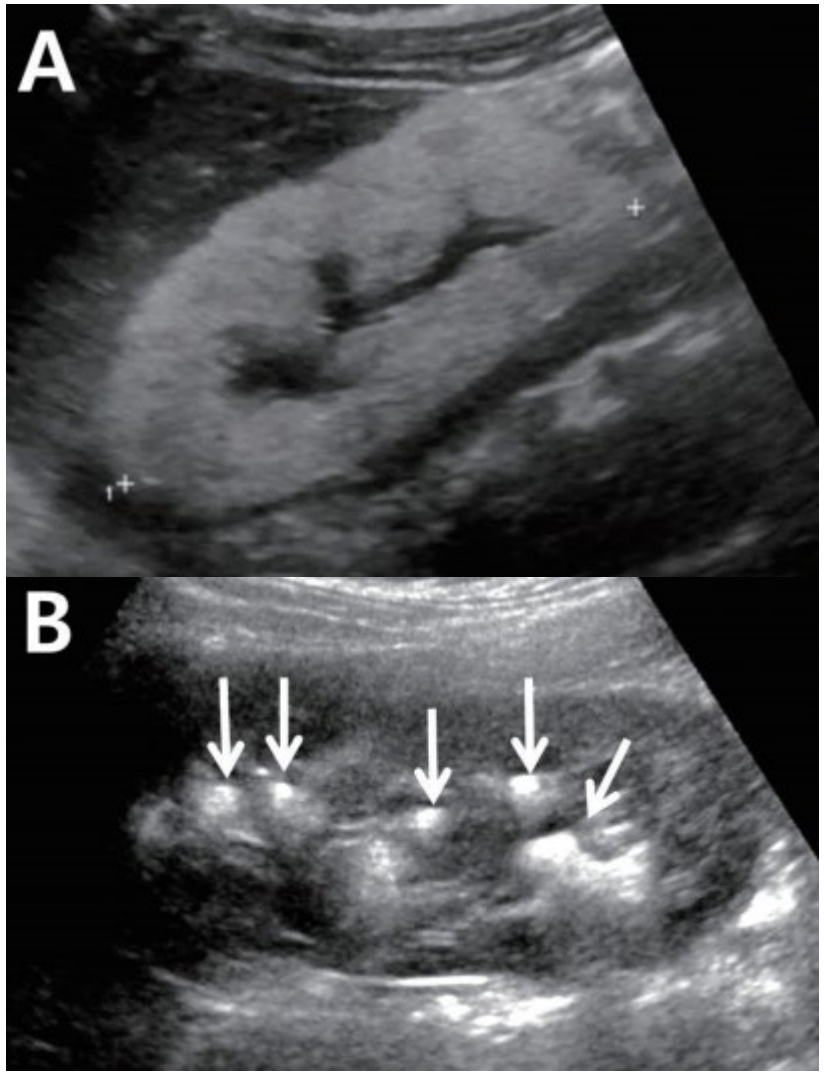
Weight 10.2 kg (-2.9 Z)

Pallor present

Systemic examination normal

Ultrasound – (A) Right kidney with lost corticomedullary differentiation (CMD)

(B) Left kidney with multiple calculi



Possibilities?

	Positive	Negative
Hyperoxaluria		
Dent disease		
Hypercalciuria		
Severe reflux dysplasia		

Blood tests

Parameter	Value
Creatinine eGFR	0.9 mg/dL 42 ml/min per 1.73 m^2
Electrolytes	137/4.2/19 mEq/L
Mg^{2+}	2.0 mg/dL
Ca/PO_4	9.5/4.2 mg/dL
Parathormone	25 pg/mL
25-OH vitamin D	35 ng/mL

24 hour urine tests

Parameter	Value (mg)	Interpretation
Volume	600 ml	937 ml/m^2
Creatinine	180	18 mg/kg
Calcium	26	2.6 mg/kg
Oxalate	106	286 mg/1.73 m^2
Citrate	212	572 mg/1.73 m^2

Low fluid intake, hyperoxaluria

10 yr/F, end stage kidney disease

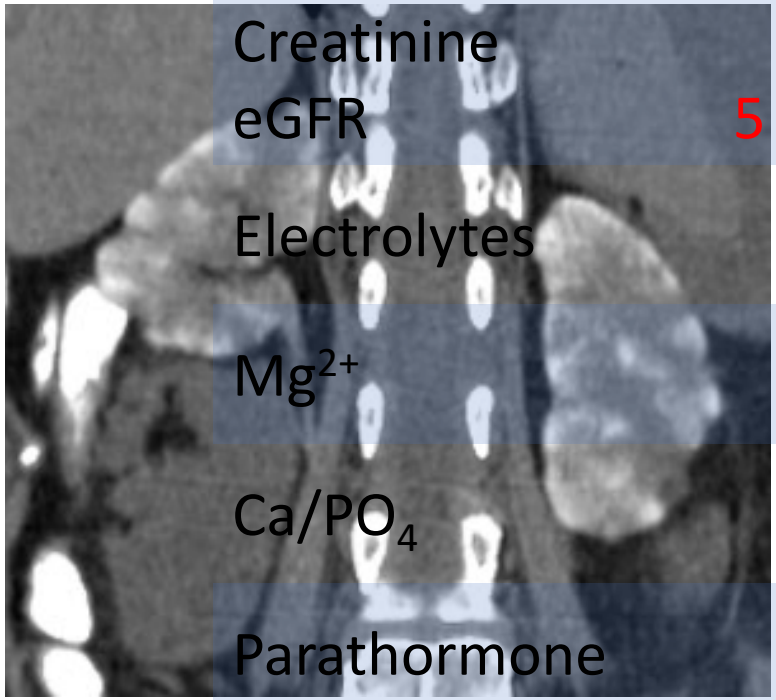
First born to consanguineously married parents

Uncle had ESKD with stone disease at age 25 yrs

Asymptomatic till now

CT scan performed elsewhere

Cortical nephrocalcinosis with shrunken kidneys



Parameter	Value
Creatinine	5.9 mg/dL
eGFR	5 ml/min per 1.73 m^2
Electrolytes	137/5.1/16 mEq/L
Mg^{2+}	2.2 mg/dL
Ca/PO_4	9.0/6.5 mg/dL
Parathormone	225 pg/mL
25-OH vitamin D	35 ng/mL

Clinical exome sequencing results

Patient 1

AGXT gene, exon 4, homozygous **c.508G>A** (p.Gly170Arg)

Chromosome 2:g.240871433; Depth:96x

Previously reported variant

Pathogenic as per ACMG

Patient 2

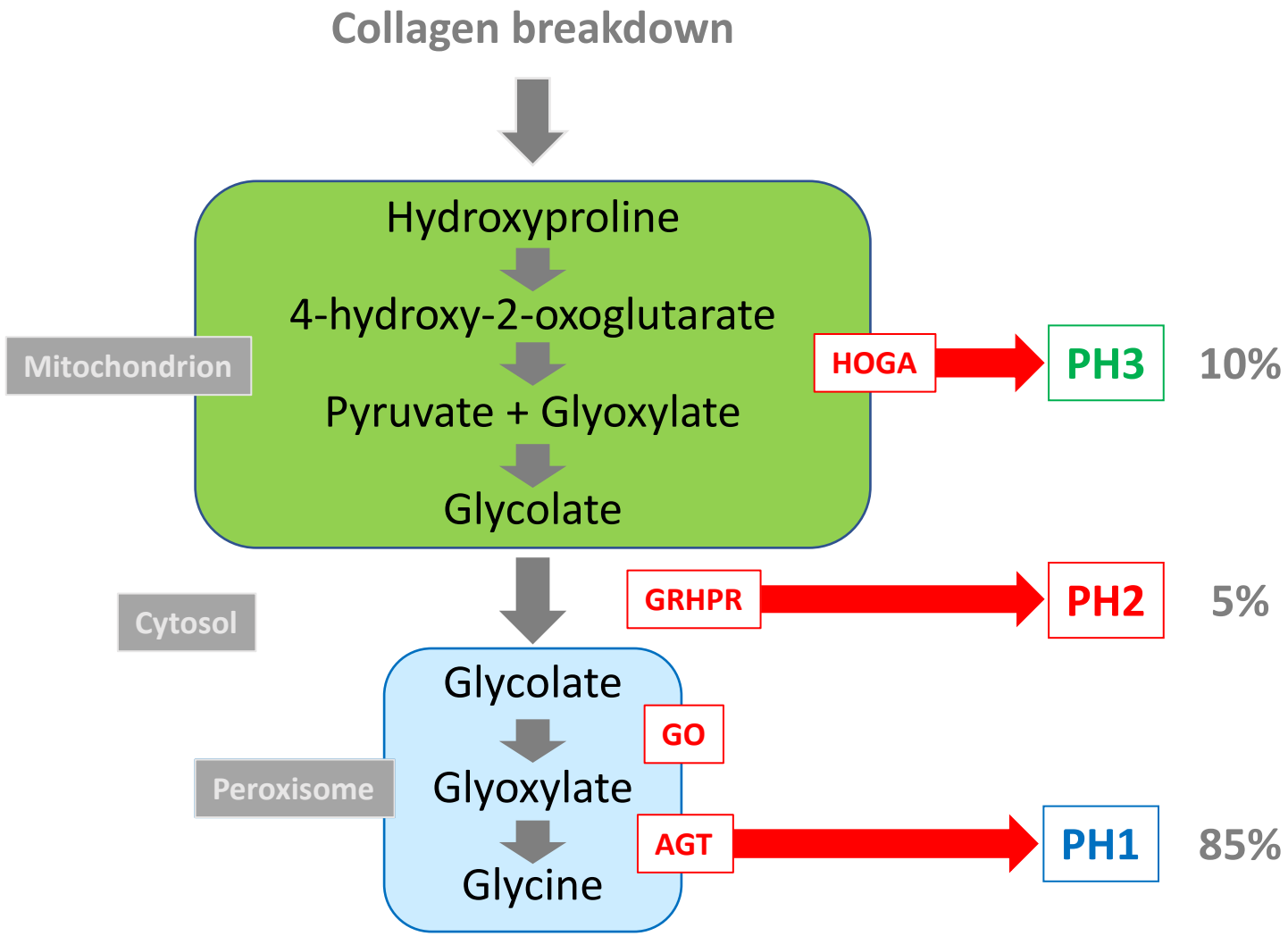
AGXT gene, exon 1, homozygous **c.33dup** (p.Lys12insfsTer156)

Chromosome 2:g.240868898dup; Depth:136x

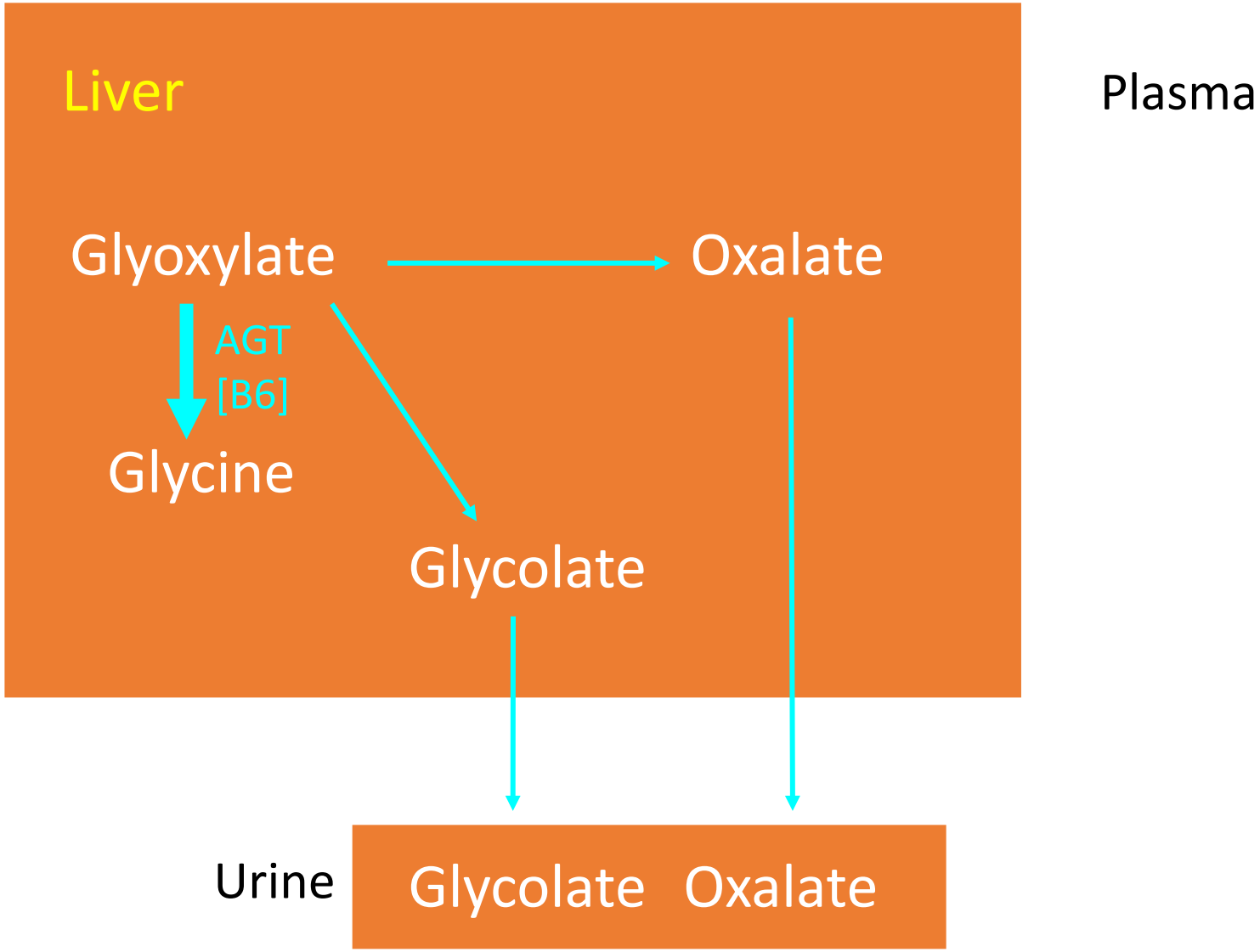
Previously reported variant

Pathogenic as per ACMG

Pathogenesis of hyperoxaluria



Healthy subjects



PH1 – Stage 1

Plasma

Liver

Glyoxylate → Oxalate

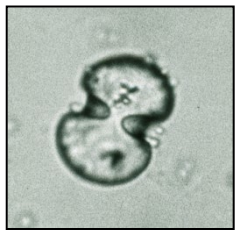
AGT
[B6]

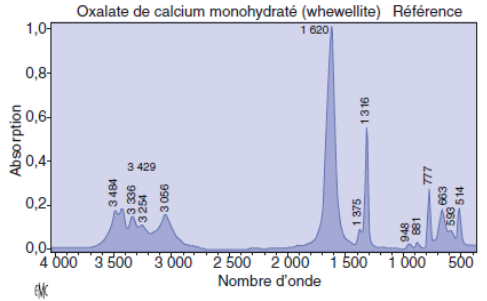
Glycine

Glycolate

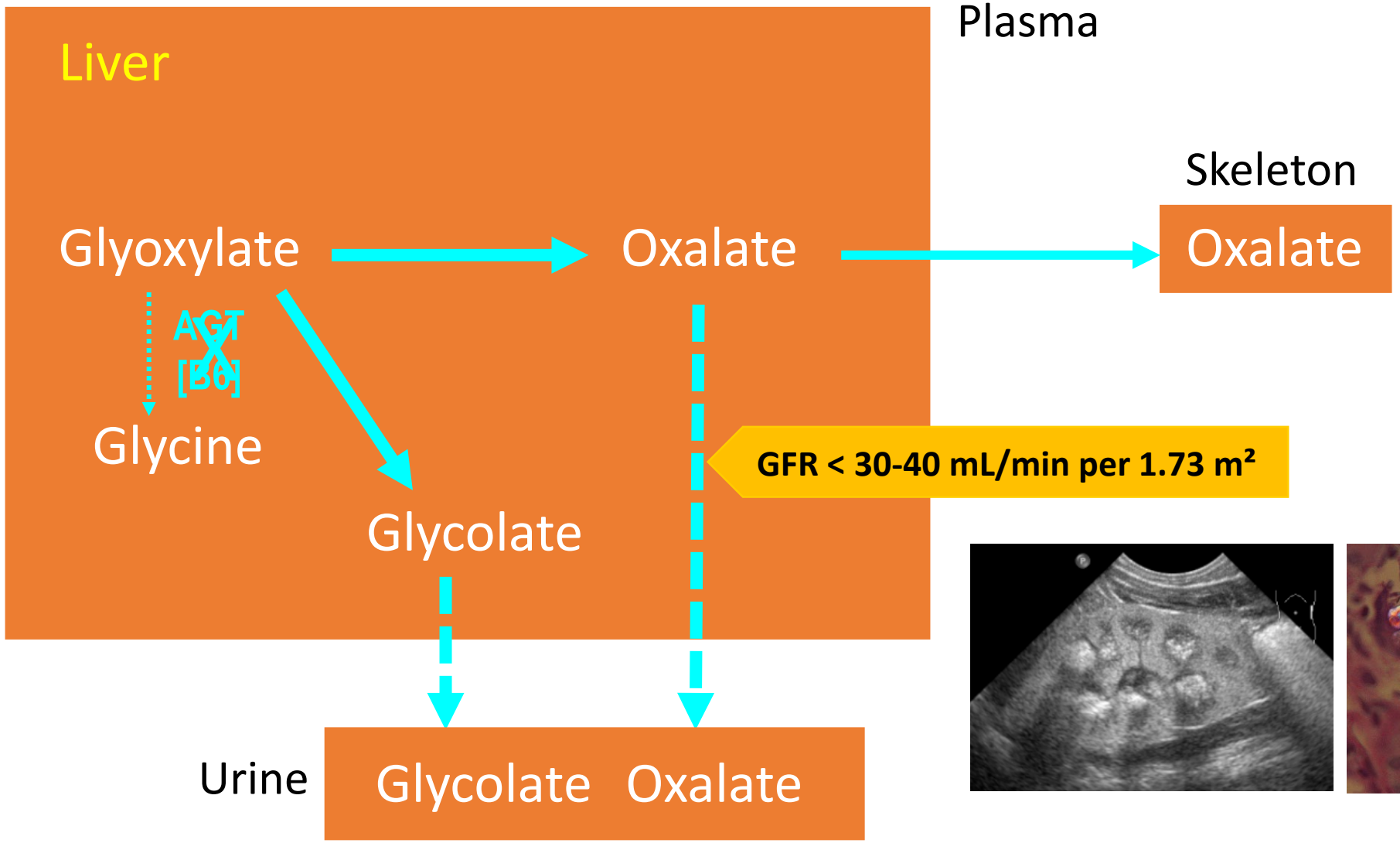
Urine

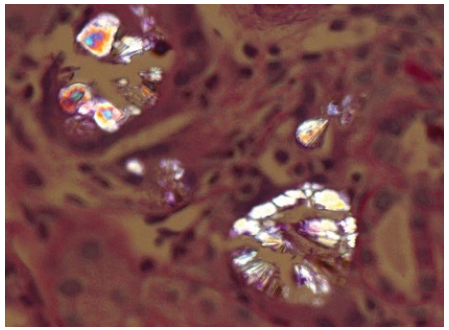
Glycolate Oxalate





PH1 – Stage 2


Liver
Plasma
Glyoxylate
Oxalate
Skeleton
Oxalate
AGT
[B6]
Glycine
Glycolate
GFR < 30-40 mL/min per 1.73 m²
Urine
Glycolate
Oxalate



PH1 – Stage 3

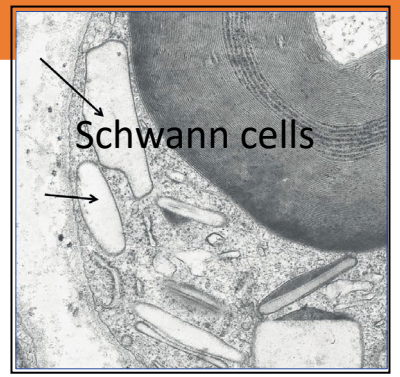
Liver

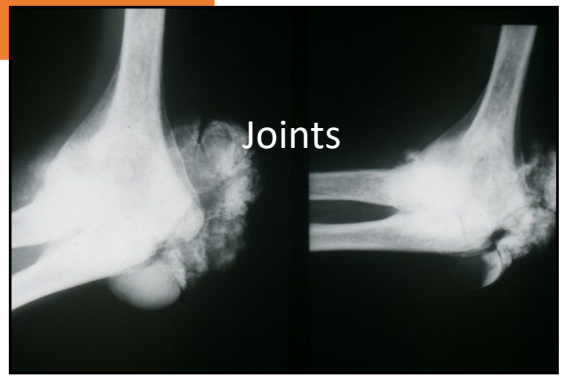
Glyoxylate → Oxalate → Skeleton: Oxalate

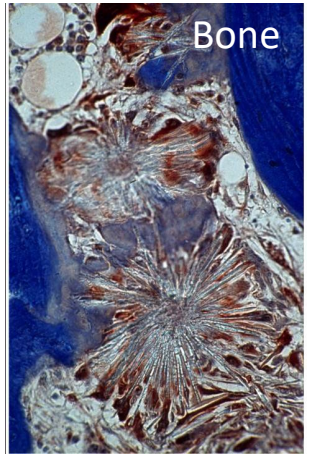
Glyoxylate → Glycine (AGT [Bc])

Glyoxylate → Glycolate

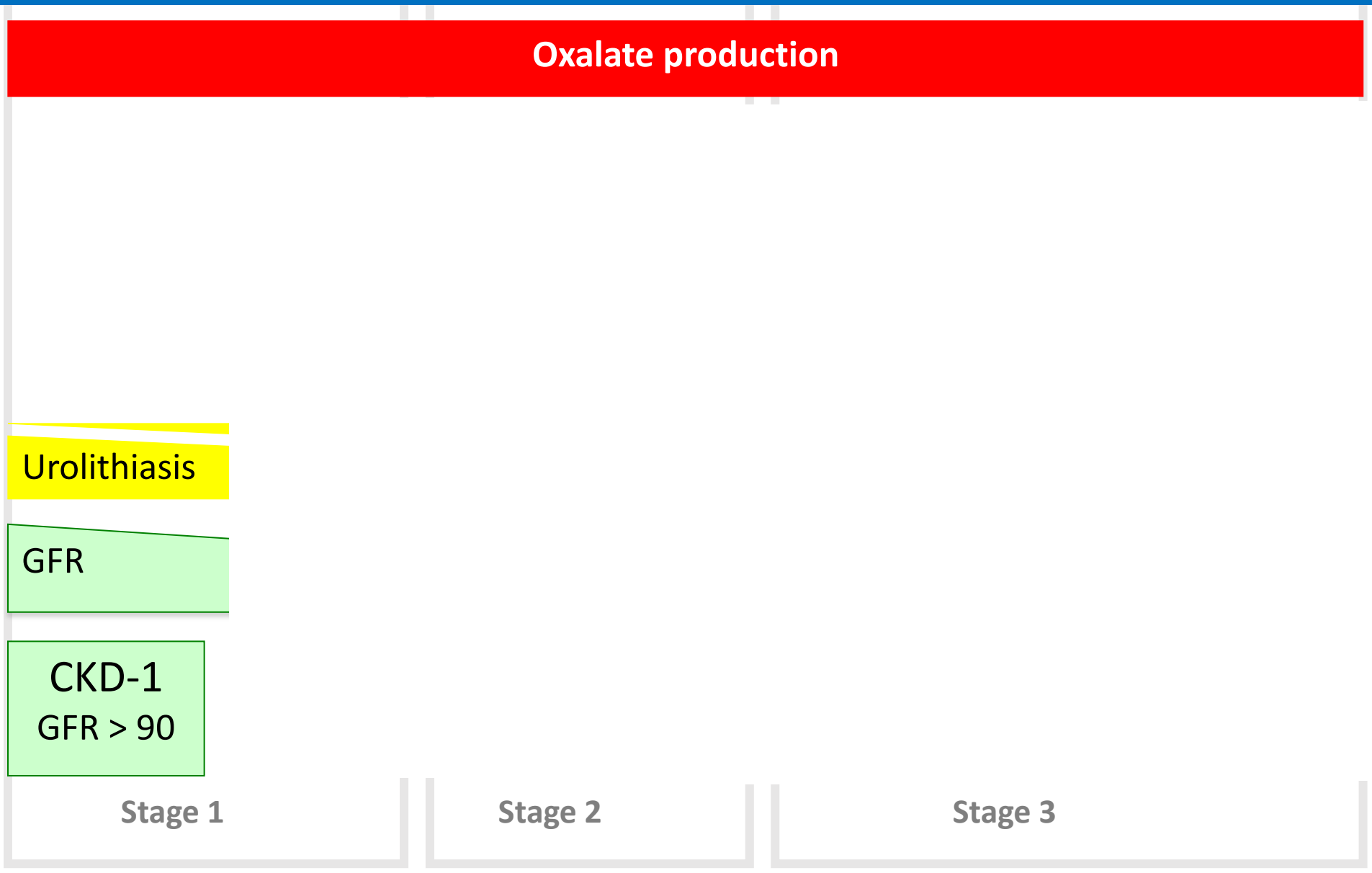
ESKD/KRT







PH1 disease profile



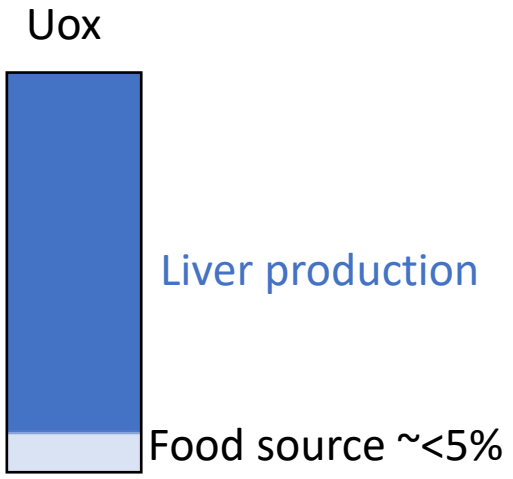
Management – general principles

Hydration ~3 L/m^2 (tube feed/ gastrostomy in young children)

Low salt diet

Calcium ox. crystallization inhibitors – citrate (0.1-0.15 g/kg/day, as long as GFR is preserved)

Limited benefit of restriction of oxalate containing food

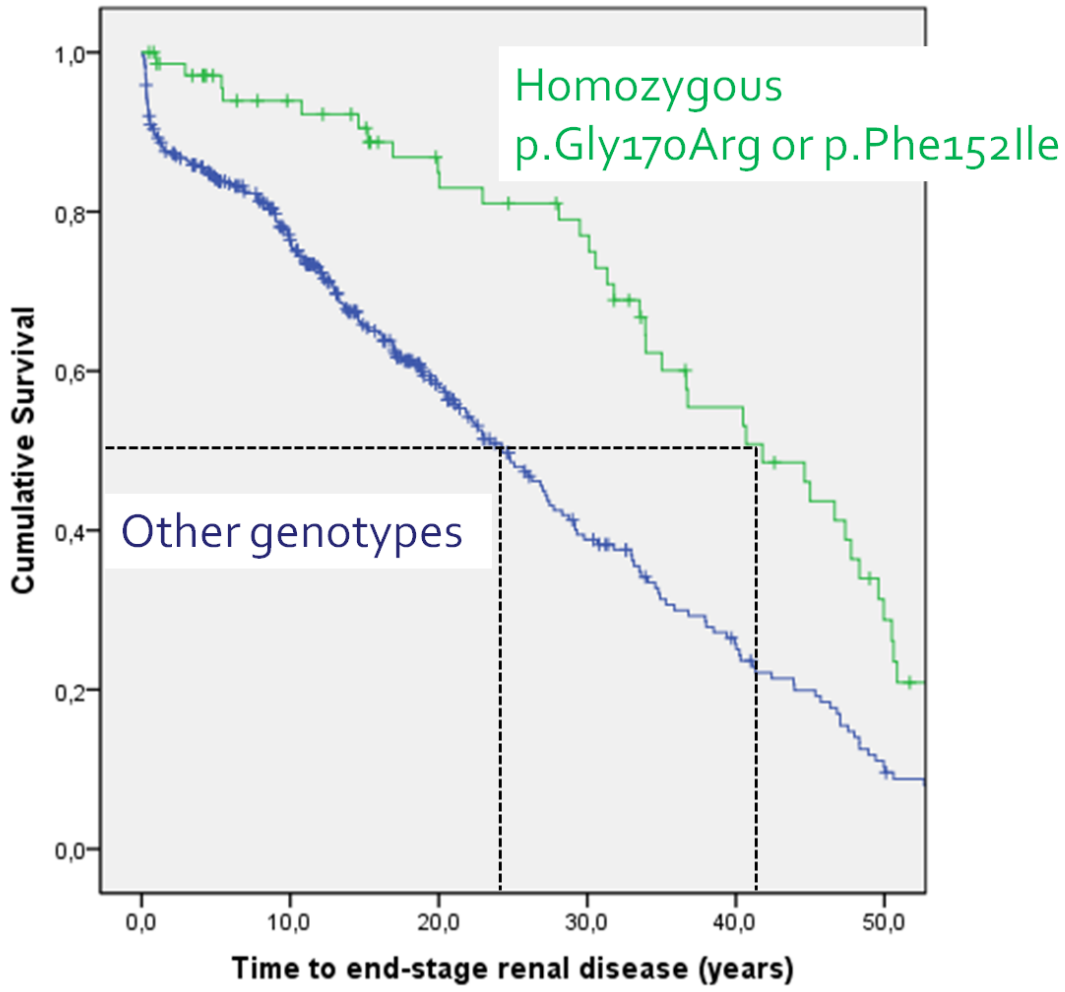


Avoid extra-corporeal shock wave lithotripsy

Avoid open surgery unless obstruction, infection or recurrent

Genotype-phenotype correlation

OXALEUROPE 512 PH1 patients



p.Gly170Arg *or* p.Phe170Ile
+
"minor allele" **p.Pro11Leu**

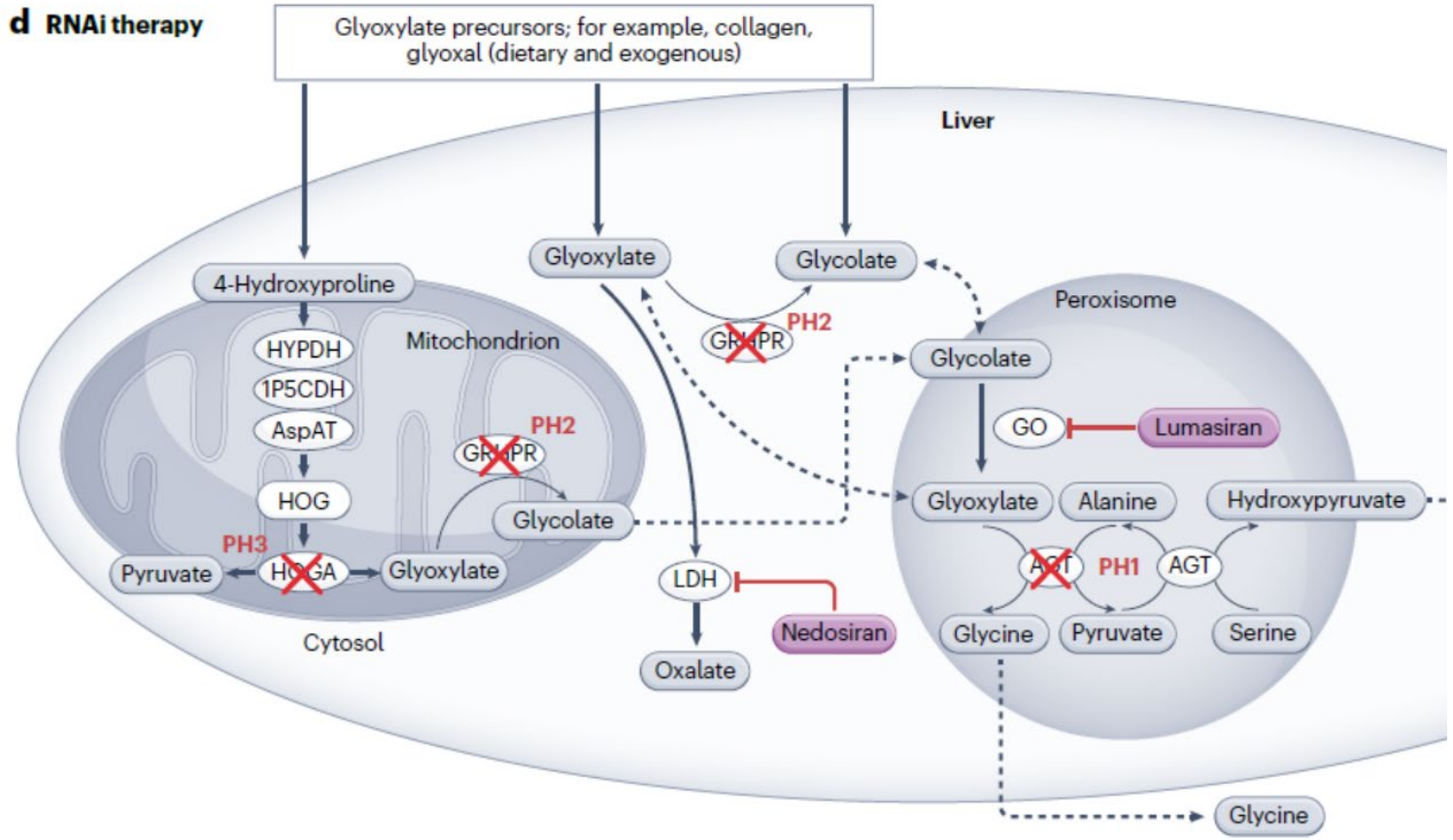
Vitamin B6 (pyridoxine)

- Starting dose: 5 mg/kg,
- Using steps, max. 20 mg/kg per day
- Aim: Uox reduction >30%

Stop Vitamin B6 if no response at 6 mo

Mandrile et al, *Kidney Int,* 2014

Small interfering RNA therapy



ILLUMINATE-C (n=21 PH1;>1 yrs)
CKD 3b or below (KRT group B)
Lumasiran sc q1mo*3→1 or 3 mo

Mean 33 – 42% reduction Uox

PHYOX2 (n=35 PH1 or PH2)
eGFR≥ 30 ml/min per 1.73 m^2
Nedosiran *vs* placebo

Mean 50-64% reduction Uox

Lumasiran inhibits production of glycolate oxidase (GO).
Nedosiran inhibits production of l-lactate dehydrogenase (LDH).

Micheal et al, *Am J Kid Dis,* 2022
Baum et al, *Kidney Int,* 2023
Groothoff et al, *Nat Rev Nephrol*, 2023

ERKnet and OxalEurope expert consensus 2023

Genetic testing as early as possible (A, strong)

Test pyridoxine responsiveness in all patients (stop at 6 mo *if* Uox <30% reduction *or* Uox > 1.5* upper limit) (A, strong)

Screen eyes and cardiac function

Transplantation (Tx)

Remove liver completely

Liver and kidney Tx (LKTx)– simultaneously or sequentially – personalised

CLKtx in PH1 with eGFR <30 , no B6 response and no access to RNAi therapy

PH1 with B6 response – isolated KTx (B, strong)

Groothoff, *Nat Rev Nephrol*, 2023

Case discussion

Dr Sudarsan K

Assistant Professor

Department of Paediatrics

JIPMER, Pondicherry

Case 1

4 y old girl brought for evaluation of short stature and bony deformities

No h/o polyuria, polydipsia, night blindness, salt craving

No h/o urinary disturbances or recurrent UTI

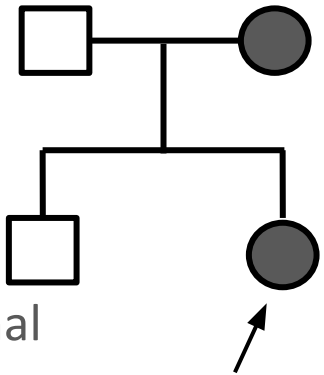
No h/o recurrent resp tract infections, chronic diarrhea

Received multiple doses of Vit D in the past but no improvement

No h/o tooth ache or hearing defect

Vaginal delivery, 2.75 kg, no antenatal polyhydramnios, develop normal

No family h/o short stature, bony deformities or kidney disease



On Examination

Weight 10.6 (-3.2 Z)

Height 85 cm (-4.1 Z)

US:LS ratio 1.36

Frontal bossing +

Wrist widening +

Rachitic rosary +

Genu valgum +

No pallor

Head to toe: No Bitot's spots or e/o vitamin deficiencies

Teeth: Normal

BP: 104/56 mm Hg

CVS: S1S2 normal, no murmur

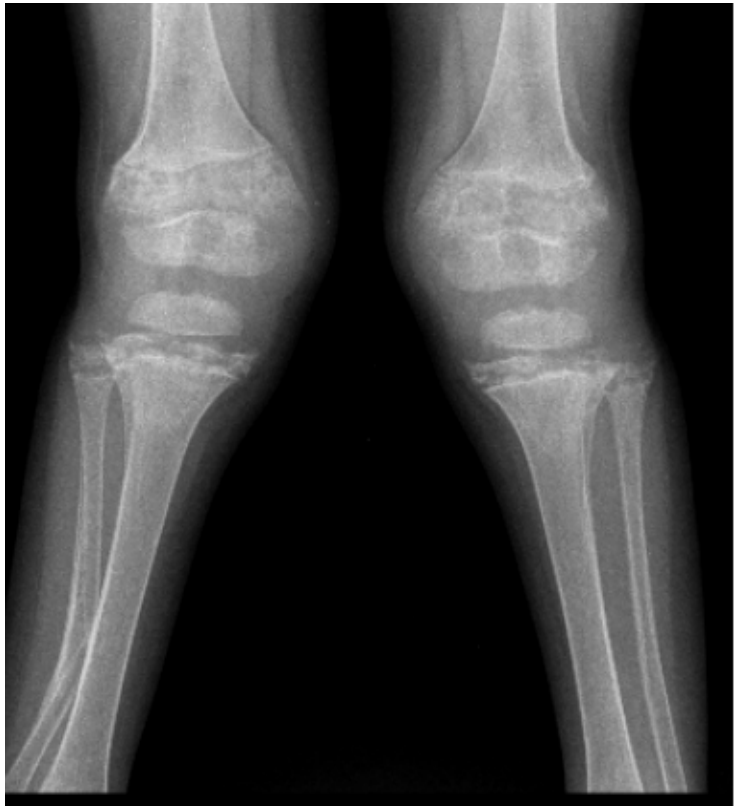
RS: B/L AEE, no crepts/wheeze

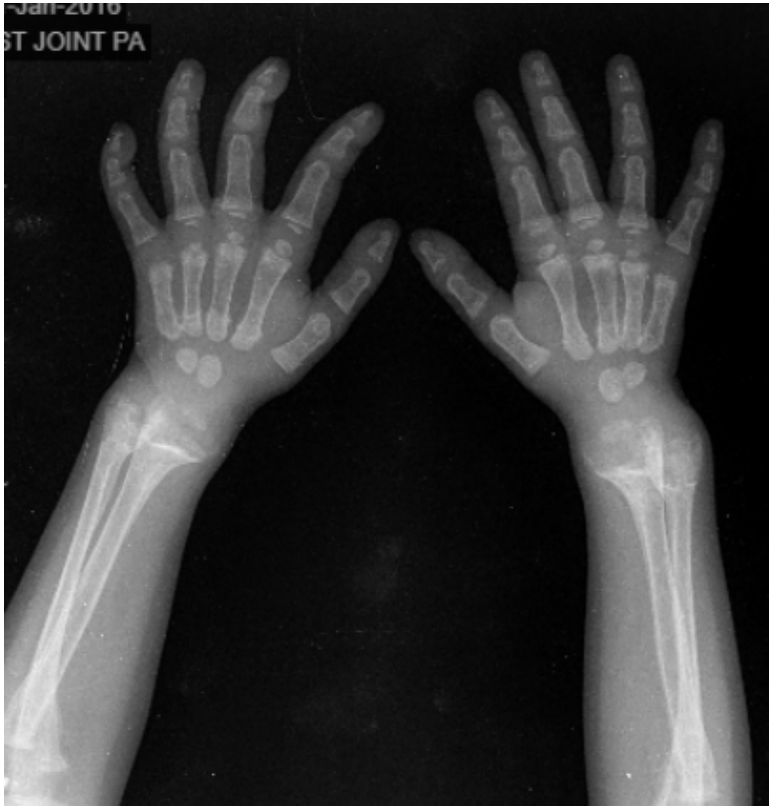
P/A: soft, non tender, no organomegaly

CNS: No FND

Impression: Refractory rickets under evaluation

X-ray





Blood investigations

Ca	9.1 mg/dL
P	**2.2** mg/dL
ALP	1085 IU/L
Vit D	82 ng/mL
iPTH	18.6 pg/mL
pH/ HCO3	7.39/22.4
Na/K	138/4.1
creatinine	0.36 mg/dL

Further evaluation

Urine ca/creat ratio 0.03

USG KUB: No nephrocalcinosis

Hearing assessment: Normal

Dental evaluation: Normal

Impression: Hypophosphatemic rickets

Treatment

Addphos 500 mg ¼ sachet QID (started at 50 mg/kg and titrated to 75 mg/kg/day)

Cap calcitriol 0.25 mcg OD

On follow up 1y later

6 cm ht gain

P: 3.2 mg/dL, ALP: 433 IU/L

Rickets healing, no nephrocalcinosis

Genetic testing on follow up

Gene	Gene/Locus MIM number	Disease (Inheritance)	Exon	Nucleotide change	Amino acid change	Zygosity	Type
PHEX	300550	Hypophosphatemic rickets, (XLD)	Ex3	c.345delG	p.K116fs*28	Heterozygous	Likely Pathogenic

Case 2

Case 2

2.5 y girl brought with bony deformities since 7 mo of age

No other significant history

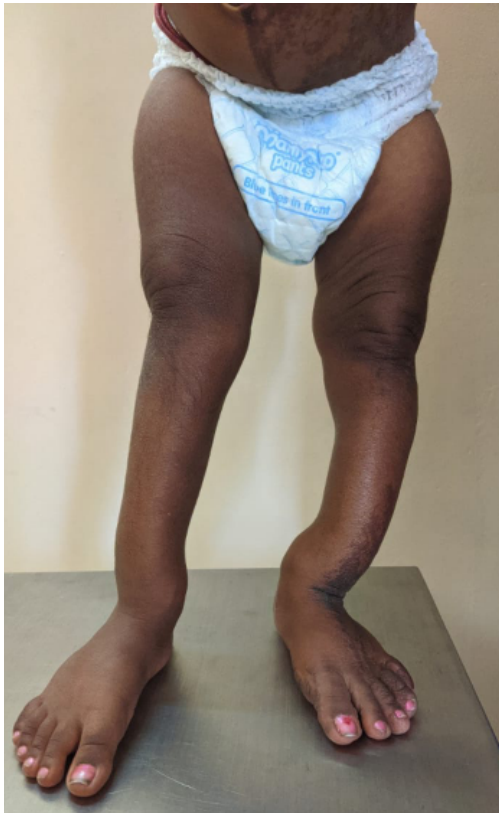
Weight 6.2 kg (-5.5 Z)

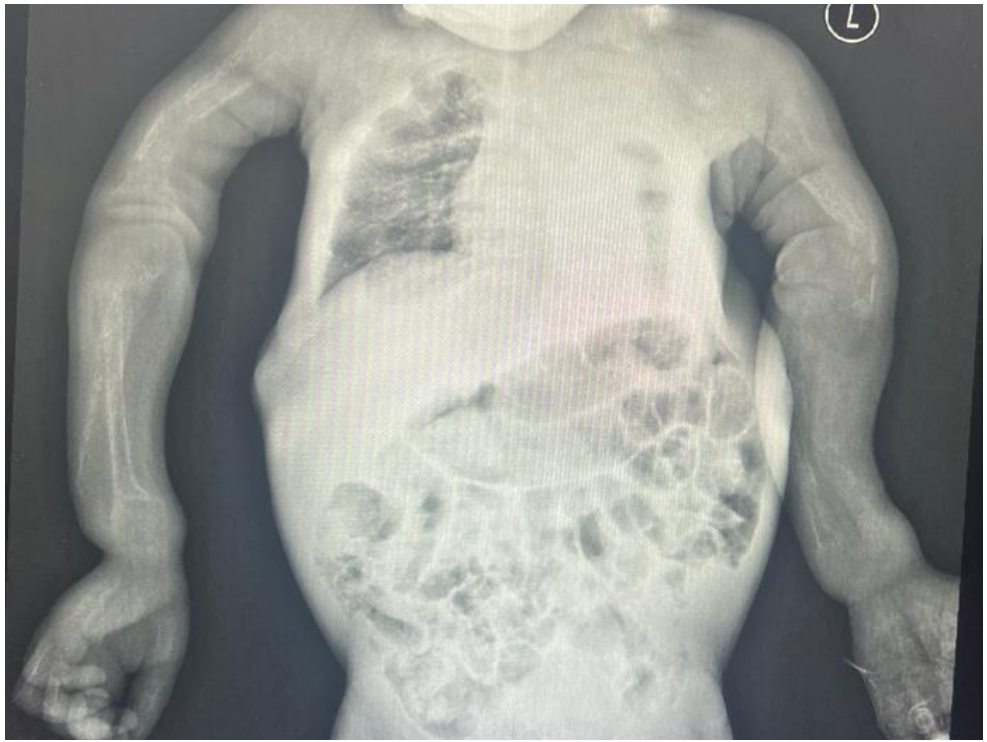
Height 69 cm (-6.1 Z)

Features of rickets +

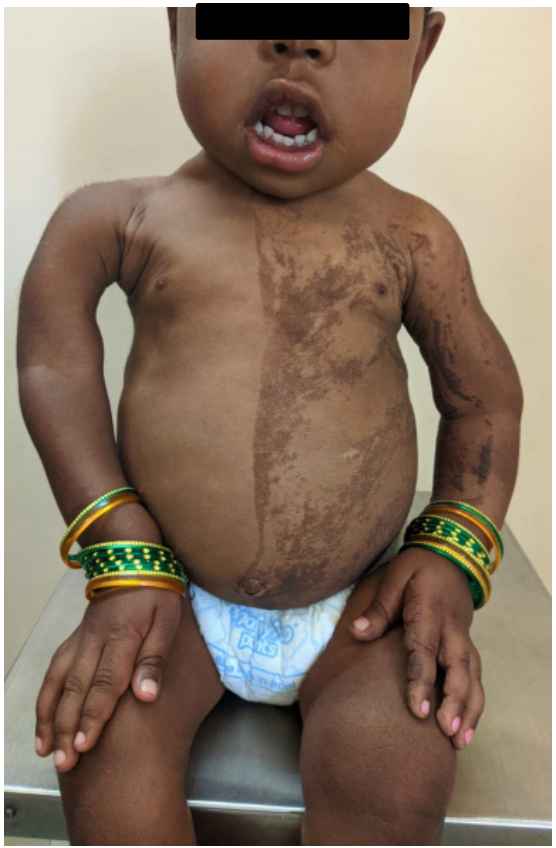
Ca	9.6 mg/dL
P	**1.3** mg/dL
ALP	2465 IU/L
Vit D	31 ng/mL
iPTH	24 pg/mL
pH/ HCO3	7.36/23.1
Na/K	136/3.9
creatinine	0.12 mg/dL

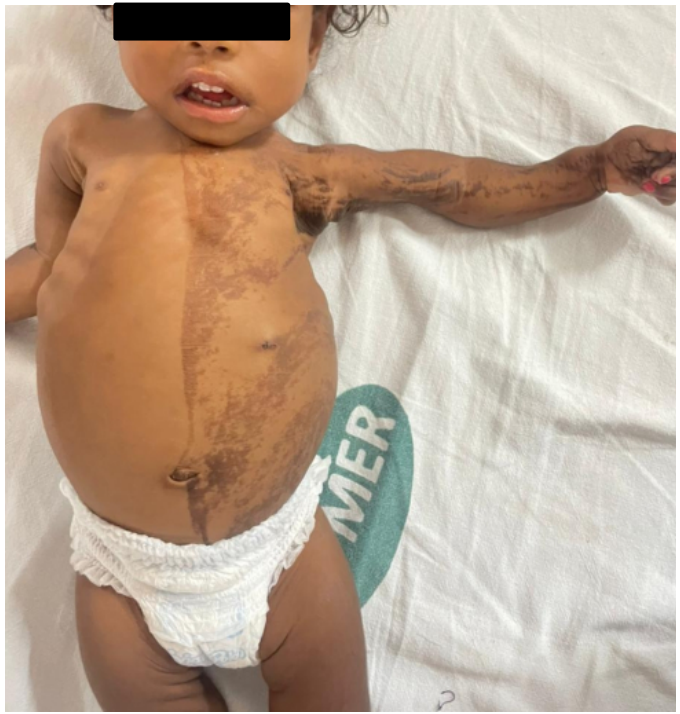
Florid rickets noted





Abnormal skin finding





Treatment and follow-up

Addphos 500 mg in 5 ml NS; 1 ml TDS (50 mg/kg/day)

Cap calcitriol 0.25 mcg OD

On follow up 6 mo later

2.5 cm ht gain, 2 kg weight gain

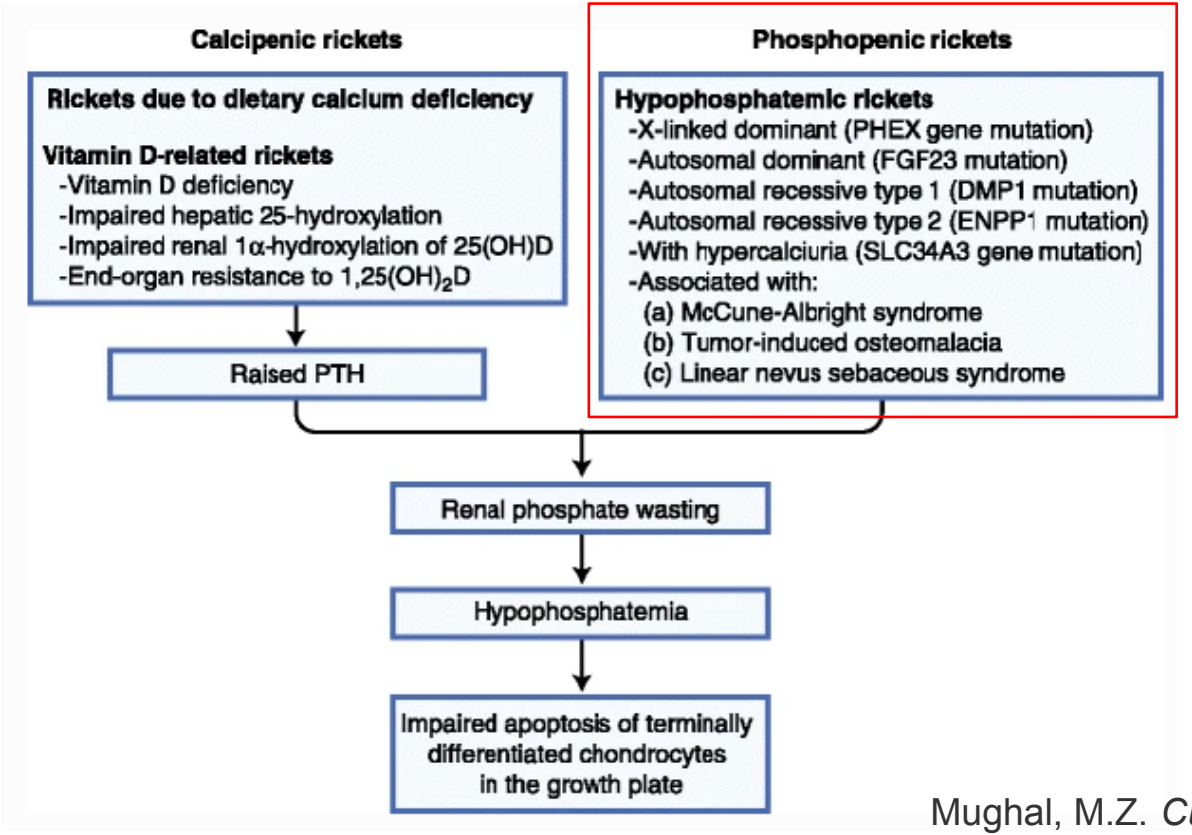
P: 2.1 mg/dL, ALP: 1245 IU/L

Rickets: some healing noted

Impression: Hypophosphatemic rickets due to epidermal nevus syndrome

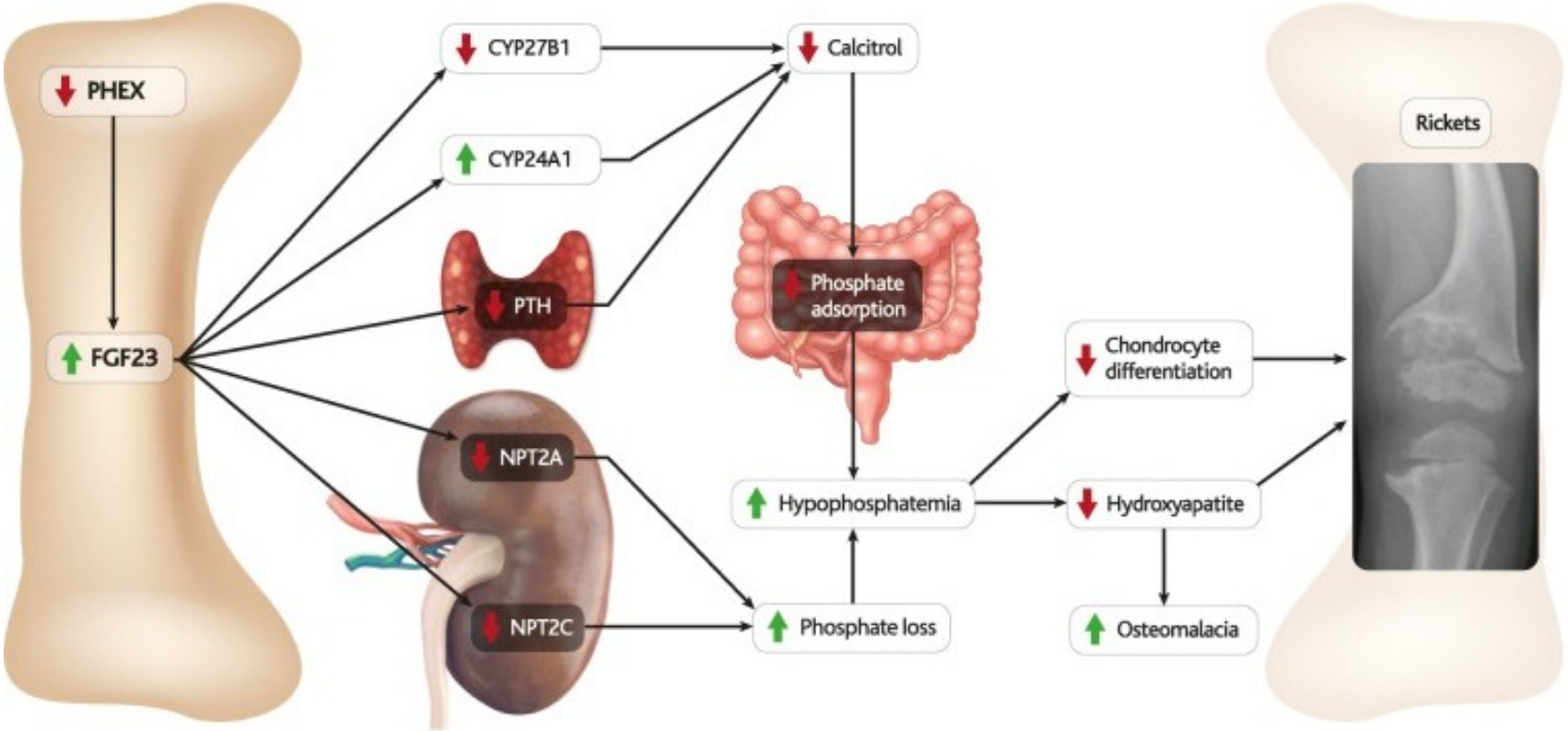
Hypophosphatemic rickets

Etiology of hypophosphatemic rickets



Mughal, M.Z. *Curr Osteoporos Rep* 2011

Pathophysiology



Beck-Nielsen. *Orphanet J Rare Dis*. 2019

Treatment

Phosphate: **20-60** mg/kg per day, max 80 mg/kg (neutral PO4/ Joulie's solution)

Early treatment; 4-6 times a day

Aim to normalize ALP not serum phosphate levels

Calcitriol **20-30** ng/kg per day– adjust for serum ALP, PTH and calcium

Routine calcium supplementation not required

Burosumab- promising role

Elevated PTH: ↓ PO4 dose, ↑ calcitriol

Monitor for nephrocalcinosis, hearing loss, dental defects

Haffner. *Nat Rev Nephrol*. 2019

Thank you


50
1964 - 2014
Breaking Boundaries...
Finding Frontiers...
JAWAHARLAL INSTITUTE OF
POST - GRADUATE MEDICAL
EDUCATION AND
RESEARCH

Management of Hypertensive Crisis

MD, FACEE (PEM), MNAMS
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Learning Objectives

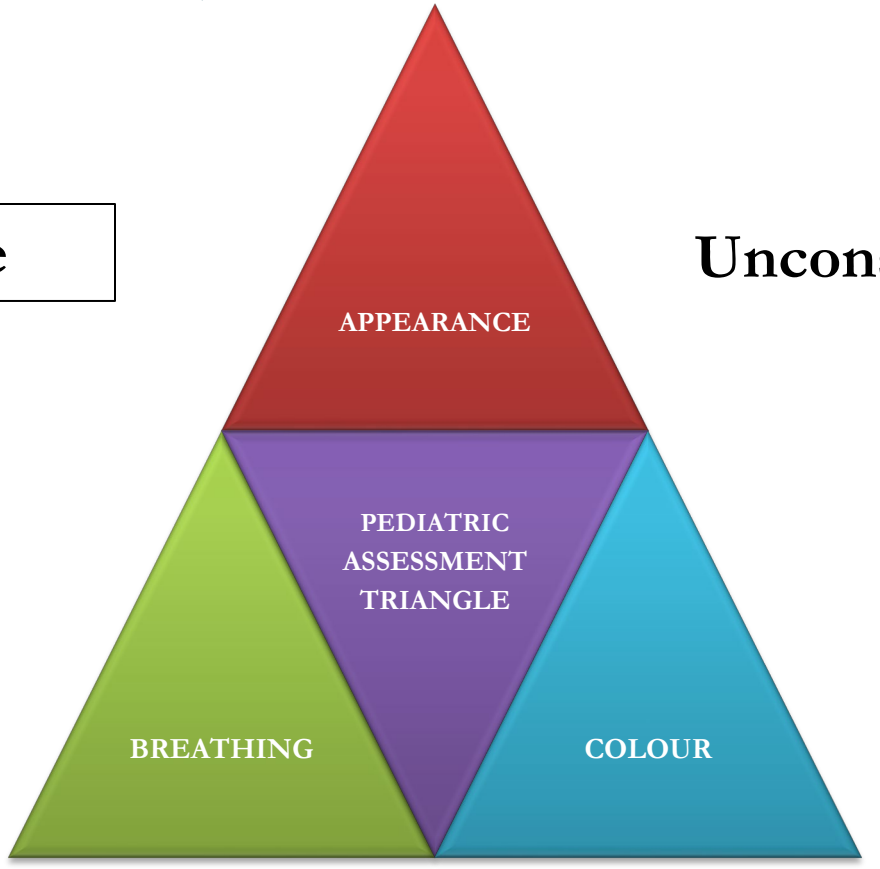
- Definitions
- Clinical Presentation
- Evaluation
- Investigations
- Management

Case 1

Initial Impression; Pediatric Assessment Triangle

7 years, Male

Unconscious



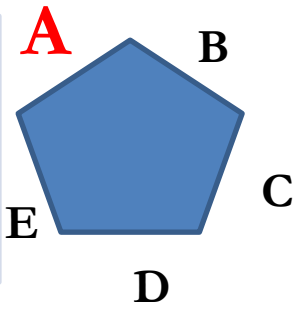
Tachypnoeic

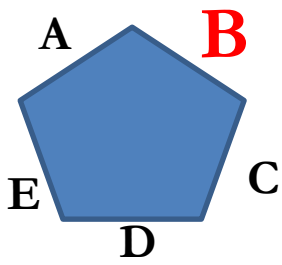
Pink

Intervention- Attached to monitor; Humidified oxygen

Primary Survey

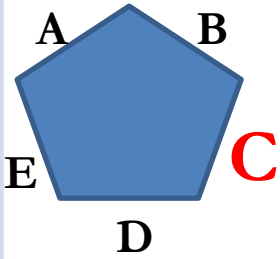
A **AIRWAY**	• Open and maintainable
B **BREATHING**	• RR- **40/ minute** • B/L chest moving equally with respiration • B/L breath sounds vesicular; creptitations+ B/L infra mammary, infra axillary regions • SpO2 **92%** at room air





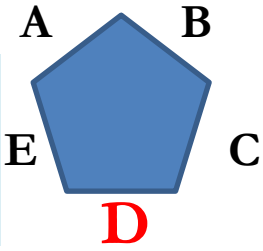
C
CIRCULATION

- HR - 118/minute, regular
- Peripheral pulses well palpable
- BP-190/120 mmHg (Stage II) , Temp- 98 ^{0}F
- CRT < 3 secs



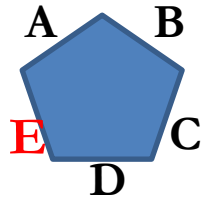
D
DISABILITY

- **Unconscious**
- GCS – E3V3M4, Dextrose- 110 mg/dL



E
EXPOSURE

- Facial puffiness +
- Post pyoderma pigmentation+



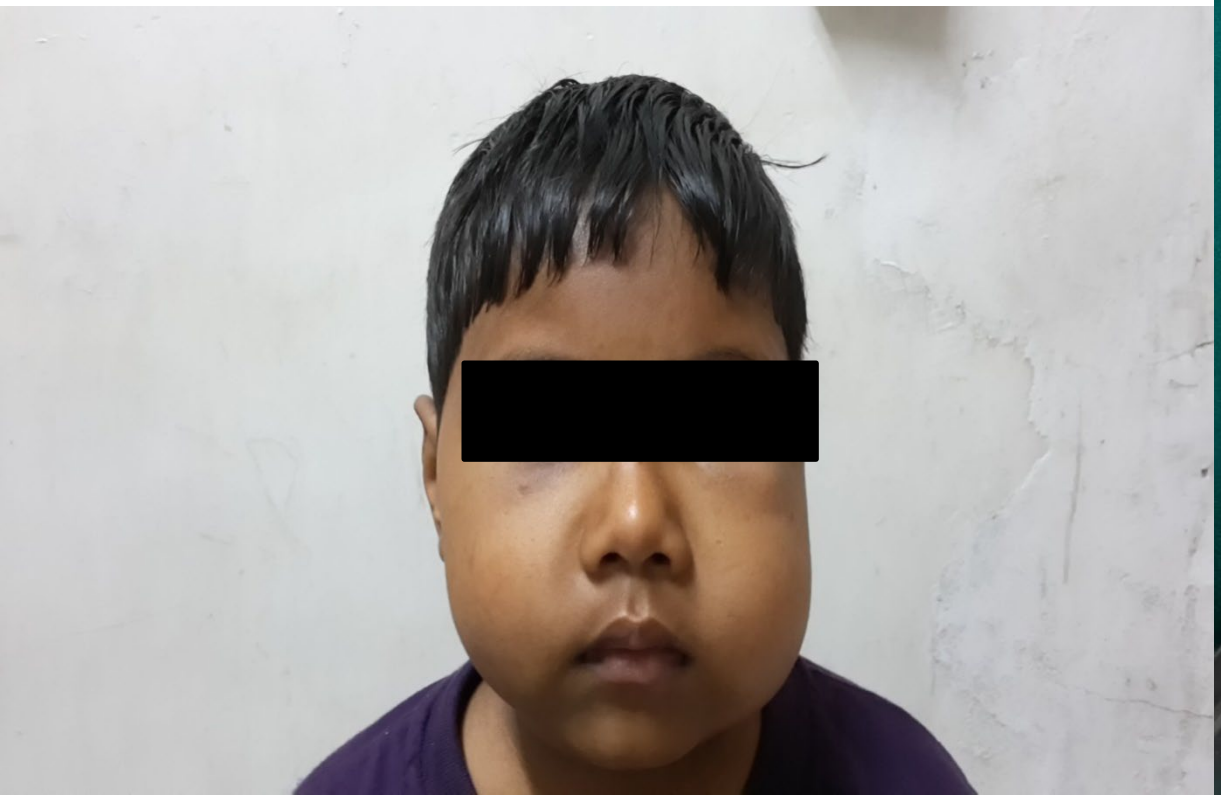
ER Evaluation and Intervention

Evaluation and Identification	Intervention
Respiratory distress	Put on oxygen by nasal prongs at 2 L /min
	IV access secured; blood samples taken Catheterised to monitor urine output
Suspected fluid overload	
Hypertensive Crisis	Started on IV Frusemide 1mg/kg, IV Nitroprusside

Focused History

- Sign and symptoms:
- Mild periorbital puffiness, headaches for 4 days, alteration of sensorium for 6 hours
- History of oliguria, Cola colored urine for 1 day
- There was no history of fever, rash, joint pains
- Pyoderma 2 weeks back
- Papilledema +

Cola Colour Urine



Clinical Practice Guidelines for Screening and Management of High Blood Pressure in Children and Adolescents

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

TABLE 3 Updated Definitions of BP Categories and Stages

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 mmHg, 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

Pediatrics 2017 Sep;140(3). pii: e20171904

- **Hypertensive crisis**: Sudden and abrupt severe elevation in BP from baseline, with life- threatening potential to cause rapid end-organ damage
- **Hypertensive emergency:** BP elevation is accompanied by evidence of severe symptoms and end-organ damage
- **Hypertensive urgency:** minor or no symptoms of end organ damage

- **Acute Severe Hypertension**

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

TABLE 6 Screening BP Values Requiring Further Evaluation

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

Investigations

- Urinalysis: Urine protein 2+, full of RBC's
  30% dysmorphic RBC's, few WBC's
- Urea 65 mg%, Cr 1.2 mg%, Na+ 138 mEq/L,

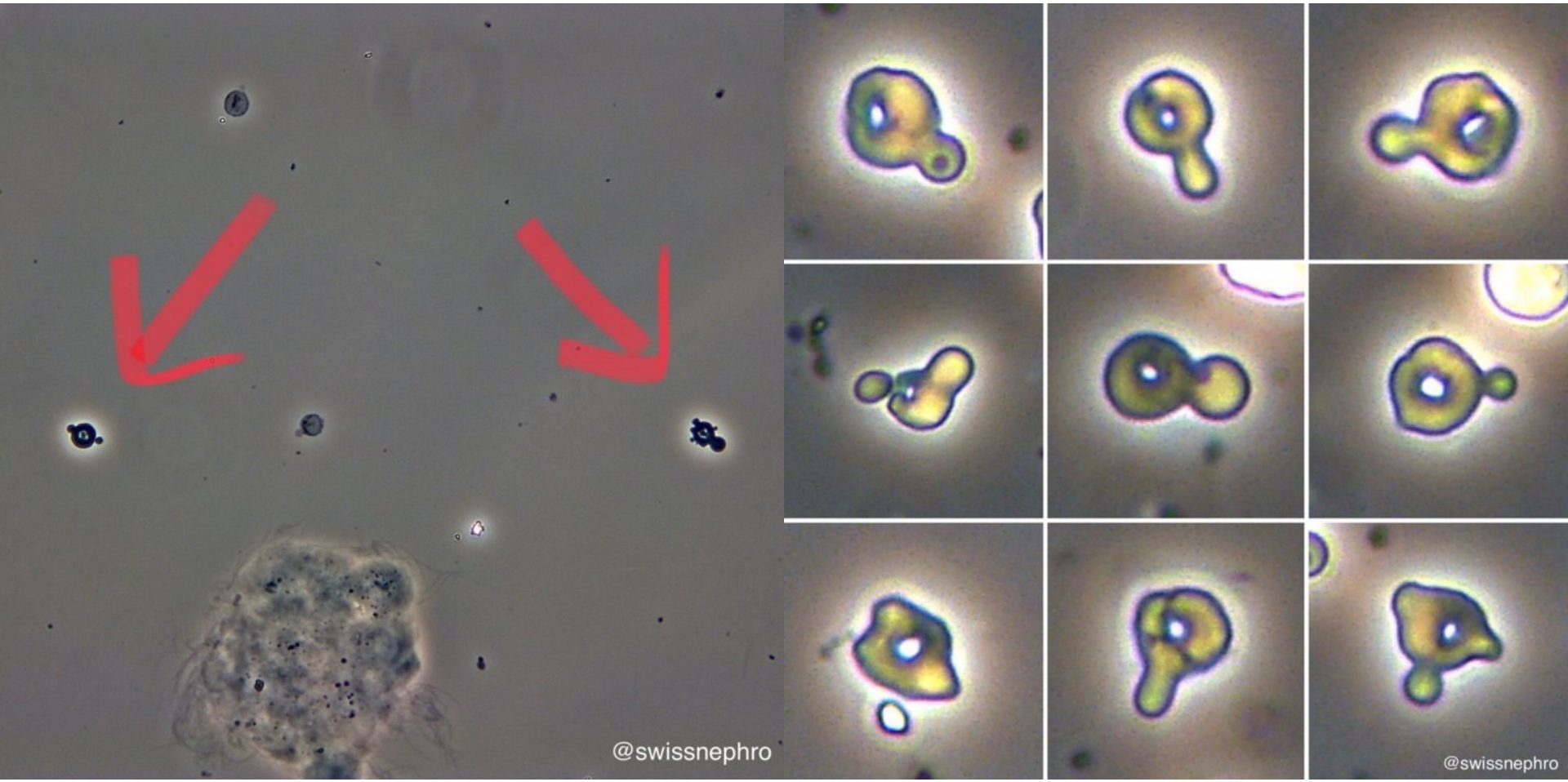
  K+ 4.0 mEq/L, albumin 3.4 gm%

  Cholesterol 180mg/dl, ASLO 400 IU/L

  C_3 34 mg/dL , Anti DNAs B 2000 Units/ml

Diagnosis: *Hypertensive emergency, Encephalopathy, AKI, (PSGN)*

Dysmorphic RBCs



PSGN: Atypical Clinical Presentations

- Seizures
- Acute hypertensive crisis
- Acute pulmonary edema
- Acute kidney injury
- Reversible posterior leukoencephalopathy syndrome
- Autoimmune hemolytic anemia

Ped Neph 2011; 26:165-180

Causes of Hypertensive Crisis

AGE	CAUSE
Infant	Coarctation of the aorta Renal parenchymal disease Renovascular causes
Young child	Renal parenchymal disease Renovascular causes Endocrine causes (eg, thyrotoxicosis) Coarctation of the aorta
School age	Renal parenchymal disease (eg, hemolytic uremic syndrome, Henoch-Schönlein purpura, acute poststreptococcal glomerulonephritis) Renovascular causes Endocrine causes Coarctation of the aorta
Adolescent	Renal parenchymal disease Renovascular causes Endocrine causes Medication and recreational substances

'Red flag' for Possible End-organ Dysfunction

Nausea and vomiting Headaches Upper motor neuron signs Hemiparesis or monoparesis, Bell's palsy Loss of vision or blurred vision Seizures Altered sensorium Drowsiness/reduced Glasgow Coma Scale	Hypertensive encephalopathy
Acute and chronic hypertensive changes on funduscopy Papilloedema	Hypertensive vascular changes, retinal bleeding and cotton wool lesions Increased intracranial pressure
Cardiomegaly Gallop rhythm Breathlessness Pulmonary oedema	Cardiac failure

Arch Dis Child Educ Pract Ed 2017;**102**:2–7

History, Physical Examination, Relevant Studies

ETIOLOGIC ORIGIN	HISTORY	PHYSICAL EXAMINATION FINDING	STUDIES
Renal parenchymal disease	Swelling Gross hematuria Urinary tract infections Polyuria Nocturia History of oligohydramnios Failure to thrive Muscle weakness Family history of renal disease	Edema Short stature Palpable mass Pallor	Complete blood cell count Serum creatinine level Blood urea nitrogen level Electrolyte levels Urinalysis Renal ultrasonography Consider genetic testing for monogenetic forms of hypertension
Renovascular disease	Neonatal history of an umbilical artery catheter	Carotid or abdominal bruit Abdominal mass Café-au-lait spots Adenoma sebaceum Ash leaf spots Neurofibromas	Renal ultrasonography with Doppler Serum renin level Serum aldosterone level CT angiography, MR angiography Angiography
Endocrinopathies	Weight loss Flushing Tremor Heat intolerance Muscle weakness	Acne Moon facies Striae Tachycardia Goiter Hirsutism Virilization	Free thyroxine, thyrotropin Serum renin level Serum aldosterone level Cortisol level Corticotropin Adrenal imaging Plasma and urine steroids
Primary hypertension	Smoking Family history of cardiovascular disease Sedentary behavior Weight gain Daytime fatigue Snoring	Increased body mass index Acanthosis nigricans	Hemoglobin A_{1c} Fasting lipids Polysomnography
Iatrogenic origin	Prior medical history Decongestants Stimulants Immunosuppressants Contraceptive pills		Drug screen
Cardiac origin	History of congenital cardiac disease Shortness of breath	Decreased pulses in lower extremity Leg blood pressure 10 mm Hg lower than arm blood pressure	Echocardiogram

Hypertensive crisis in children: an experience in a single tertiary care center in Korea

Clinical Hypertension

Lee *et al. Clinical Hypertension* (2016) 22:10

Table 2 Comparison of basal characteristics of the patients with hypertensive emergency and urgency

Characteristics	Hypertensive emergency (N = 31)	Hypertensive urgency (N = 20)	*P* value
Age (year)	8.46 ± 5.20	5.56 ± 4.71	0.051
Sex			
Male (%)	18 (58.1)	10 (50.0)	0.572
Female (%)	13 (41.9)	10 (50.0)	
Etiology			
Renal origin (%)	10 (32.3)	5 (25.0)	0.95
Renal disease (%)	5 (16.1)	3 (15.0)	1.000
Postrenal disease (%)	2 (6.4)	1 (5.0)	1.000
Renal artery stenosis (%)	3 (9.8)	1 (5.0)	1.000
Cancer (%)	16 (51.7)	8 (40.0)	0.267
Sepsis (%)	2 (6.4)	2 (10.0)	0.640
Hypoxic brain injury (%)	1 (3.2)	5 (25.0)	0.029
Cardiogenic (%)	2 (6.4)	0 (0.0)	0.514

Table 3 Target organ damage of various organs in patients with hypertensive crisis

	Hypertensive emergency (N = 31)	Hypertensive urgency (N = 20)	*P* value
EYE			
Visual symptom (%)	7 (22.6)	2 (10.0)	0.454
Retinopathy (%)	7/14 (50.0)	0/6 (0.0)	0.034
CNS			
Seizure (%)	10 (29.0)	0 (0.0)	0.004
PRES on brain MRI (%)	10/16 (62.5)	0/11 (0.0)	0.004
HEART			
LVH, RVH, BVH (%)	13/30 (43.3)	0/15 (0.0)	0.002
Abnormal EchoCG (%)	9/22 (40.9)	0/10 (0.0)	0.002
Ejection fraction	68.7 ± 9.70	68.1 ± 5.34	0.434
Kidney			
Anuria (%)	14 (45.2)	8 (40.0)	0.778
Cr elevation (%)	15 (48.4)	9 (45.0)	1.000

Suspected Genetic Disorder in a Child With Hypertension

Physical Examination Finding	Genetic Syndrome	Genetic Abnormality Involved
Café-au-lait-spots, axillary, or inguinal freckling	Neurofibromatosis type 1	*NF1*
Hypomelanotic macules, facial angiofibroma, shagreen patch	Tuberous sclerosis complex	*TSC2* > *TSC1*
Female with short stature, webbed neck, widely spaced nipples, short 4th metacarpal	Turner syndrome	46, XO
Retinal angioma, spinal or cerebellar hemangioblastoma, adrenal or extra-adrenal pheochromocytoma	Von Hippel-Lindau syndrome	*VHL*
Ambiguous genitalia	Congenital adrenal hyperplasia (11β-hydroxylase deficiency or 17α-hydroxylase deficiency)	*CYP11B1, CYP17A1*
Short metacarpal bones, short stature	Autosomal dominant hypertension with brachydactyly syndrome	*PDE3A*

Adv Chronic Kidney Dis. 2017;24(6):372-379

Management

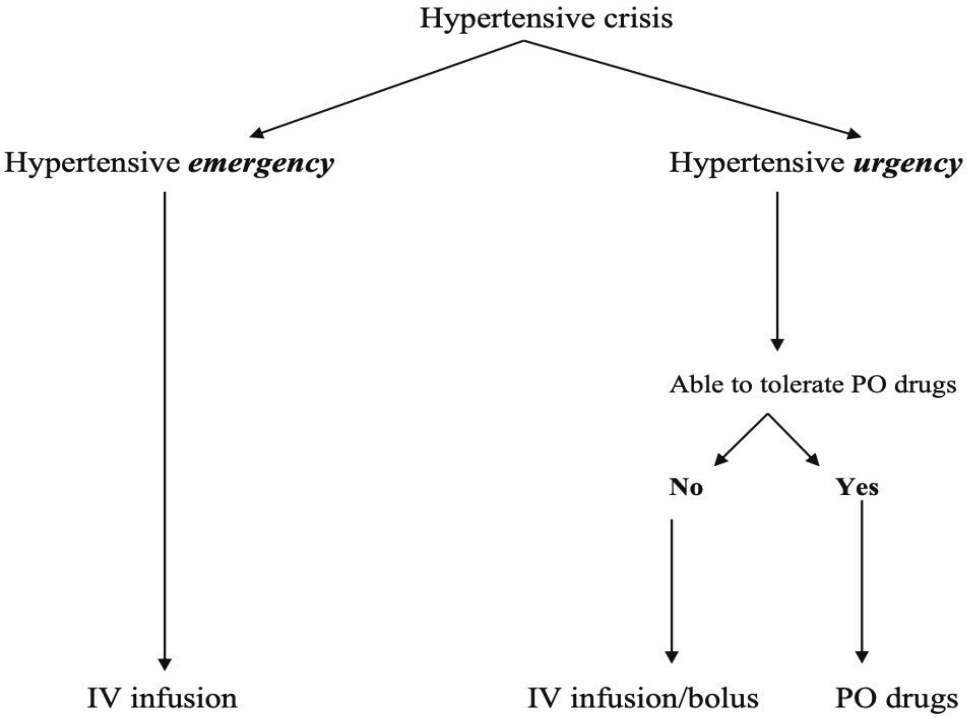
- Stage II HTN with acute target organ damage: Encephalopathy, Pulmonary oedema, AKI - Hypertensive Emergency
- Initial BP Reduction by Principle of Quarters: only by one quarter of the planned reduction during the first quarter of the day.
- Second Phase: Further gradual reduction of BP over the next 24–48 h to BP values around the 95th percentile
- Third Phase: To <95th centile
- Rapid reduction can result in ischemia to brain, retina, spinal cords & kidneys
- IV continuous infusion preferred- nitroprusside, nicardipine, labetalol, NTG

Hypertensive Emergency

- SBP of 190 mmHg, the overall goal was to reduce BP by 60 to about 130 mmHg over next 24–48 h.
- Over the first 6 h, BP was reduced by 15 mmHg (25% of planned 60 mmHg).
- In the next 42 h, the BP was gradually reduced from 175 to about 130 mmHg.
- Nitroprusside infusion-0.5 μgm/kg/min & later increased to 2.0 μgm/kg/min
- Frusemide
- Ped Neph. ICU: After 12 hours of infusion, Amlodipine added in doses of 0.5 mg/kg/day

Seminar Nephrol. 2005; 25: 272-80

Decision Making Tree



1st step: first 6 hours: decrease BP only by 25% of the planned BP decrease

↓

2nd step: next 24 – 48 hours: decrease BP gradually to BP around 95th percentile

↓ Add PO drugs

3rd step: >48 hours: decrease BP <95th percentile

Ped Neph. 2019; 34:2523-2537

AAP 2017 Update

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Severe Hypertension With Life Threatening Symptoms

- Esmolol
- Hydralazine
- Labetalol
- Nicardipine
- Sodium nitroprusside

Severe Hypertension With Less Significant Symptoms

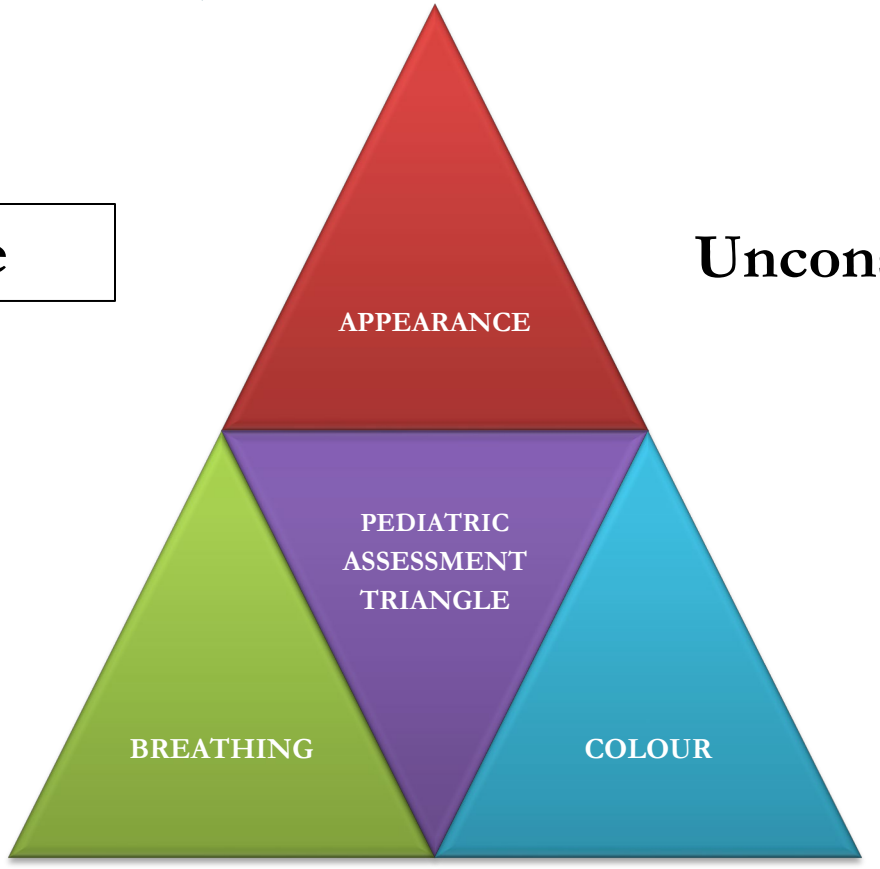
- Clonidine
- Fenoldopam
- Hydralazine
- Isradipine
- Minoxidil

Case 2

Initial Impression; Pediatric Assessment Triangle

9 years, Male

Unconscious, Seizures



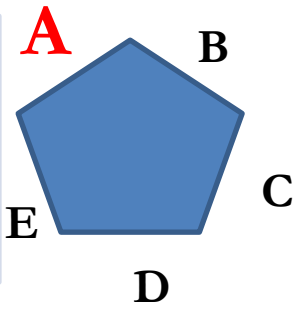
Normal

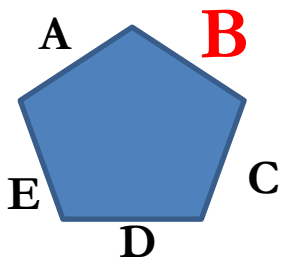
Pink

Intervention- Attached to monitor

Primary Survey

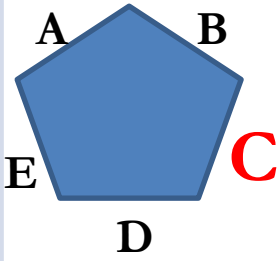
A **AIRWAY**	• Open and maintainable
B **BREATHING**	• RR- 20/ **minute** • B/L chest moving equally with respiration • B/L breath sounds vesicular • SpO2 **97%** at room air





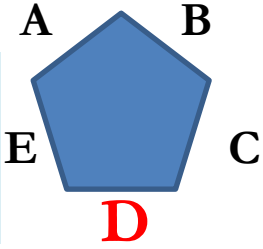
C
CIRCULATION

- PR - 92/minute, regular
- Peripheral pulses well palpable
- BP-170/120 mmHg (Stage II) , Temp- 98 ^{0}F
- CRT < 3 secs



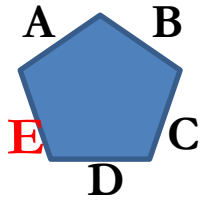
D
DISABILITY

- **Unconscious**
- GCS – E3V3M5, Dextrose- 110 mg/dL



E
EXPOSURE

- Normal



ER Evaluation and Intervention

Evaluation and Identification	Intervention
Unconscious	Lateral Position
	IV access secured; blood samples taken Catheterised to monitor urine output
Hypertensive Crisis	
Encephalopathy	Started on IV Midazolam 0.1mg/kg IV Phenytoin

Focused History

- Sign and symptoms:
- Headache for 4 days
- Multiple episodes of GTCS with loss of consciousness (status epilepticus)
- BP – 170/120mm Hg

  Rt UL – 160/118; Lt UL – 156/114

  Rt LL – 164/114; Lt LL – 160/114
- Papilledema

Investigations

	At admission
Hb	14.4 gm%
TLC	28900/mm3
DLC (N/L/E)	87/13/-
Platelet count	3 lacs/mm3
RBS	94 mg%
Urea	29mg/dl
Creatinine	0.5mg%
Sodium	135meq/L
Potassium	3.8meq/L
Calcium	9.4mg%
Phosphorus	4mg%
LFT	WNL
Lipid Profile	WNL

Further Course

- IV Nitroprusside followed by oral medications

  BP maintained between 50th -90th centile

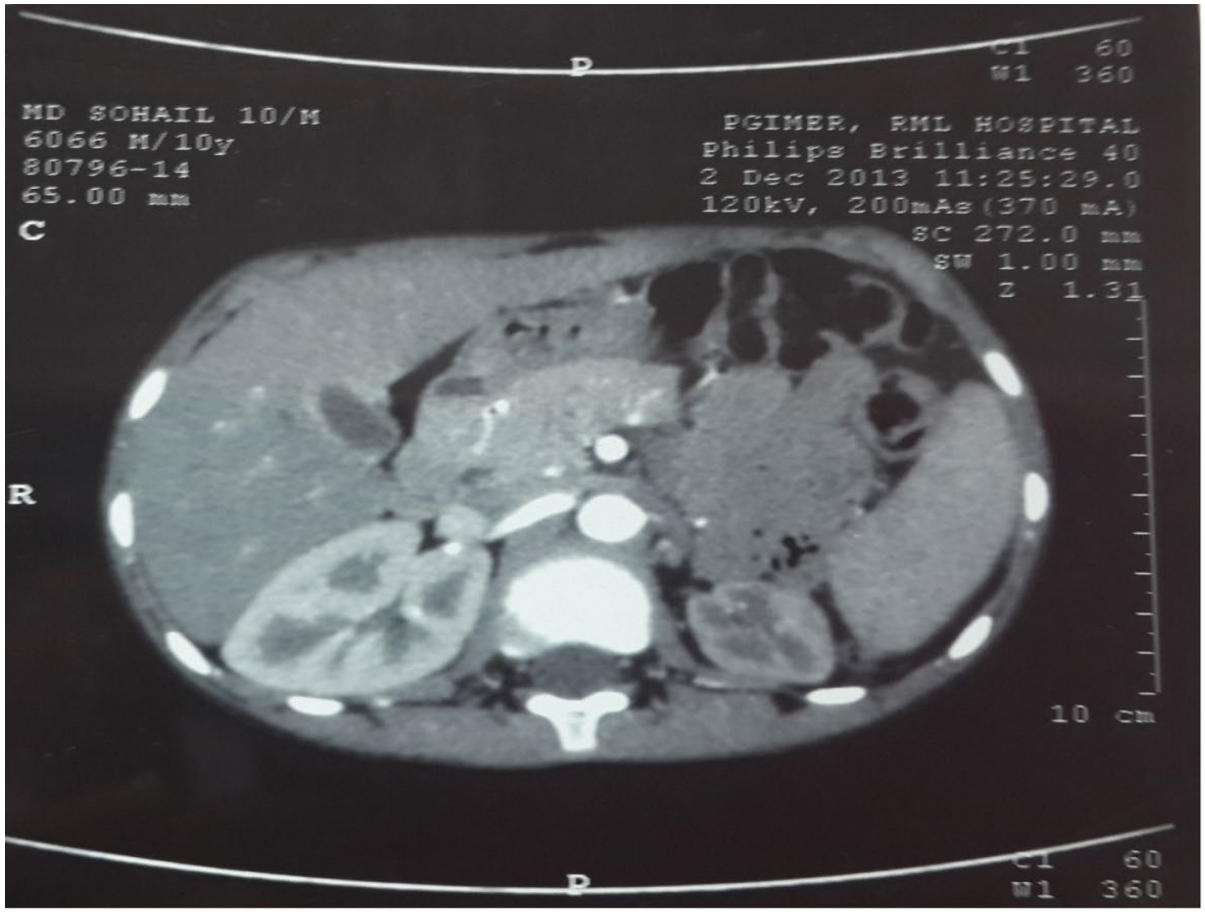
  Amlodipine @ 0.6mg/kg/day

  Clonidine@ 15mcg/kg/day

  Atenolol @ 1mg/kg/day
- USG KUB – Small left kidney with maintained CMD

  (RK - 9.6 * 3.8 cms, LK – 7.4 * 2.8 cm)
- Plasma Renin Activity – 31.62 ng/ml/h (1.9 – 5.2)
- Aldosterone – 81.65 pg/dl (12 - 340)

CT Angiography of Renal Vessels



Renovascular Hypertension: Left Renal Artery Stenosis

Renovascular Hypertension

Panel 1: Causes of renovascular hypertension in children

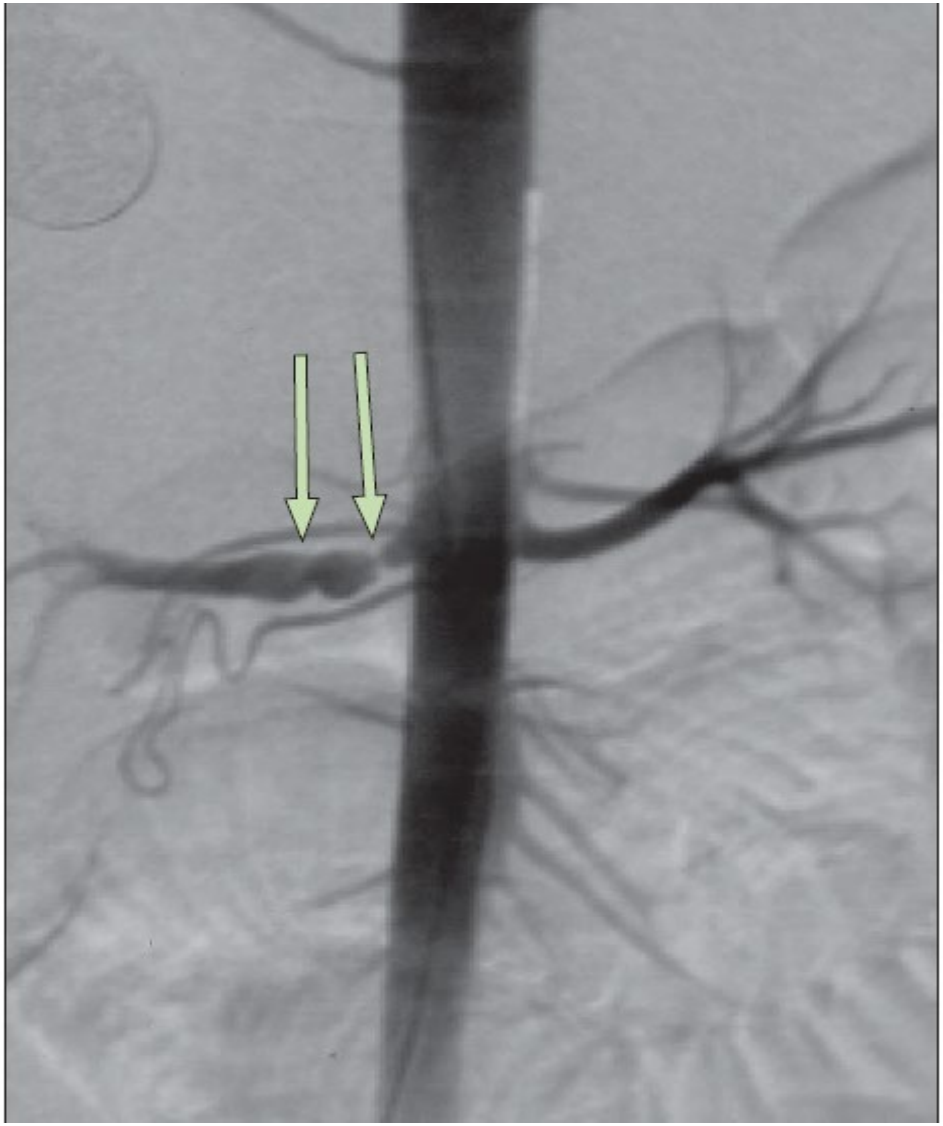
Fibromuscular dysplasia

Syndromic
- Neurofibromatosis type 1
- Tuberous sclerosis
- Williams' syndrome
- Marfan's syndrome
- Other syndromes

Vasculitis
- Takayasu's disease
- Polyarteritis nodosa
- Kawasaki disease
- Other systemic vasculitides

Extrinsic compression
- Neuroblastoma
- Wilms' tumour
- Other tumours

Other causes
- Radiation
- Umbilical artery catheterisation
- Trauma
- Congenital rubella syndrome
- Transplant renal artery stenosis



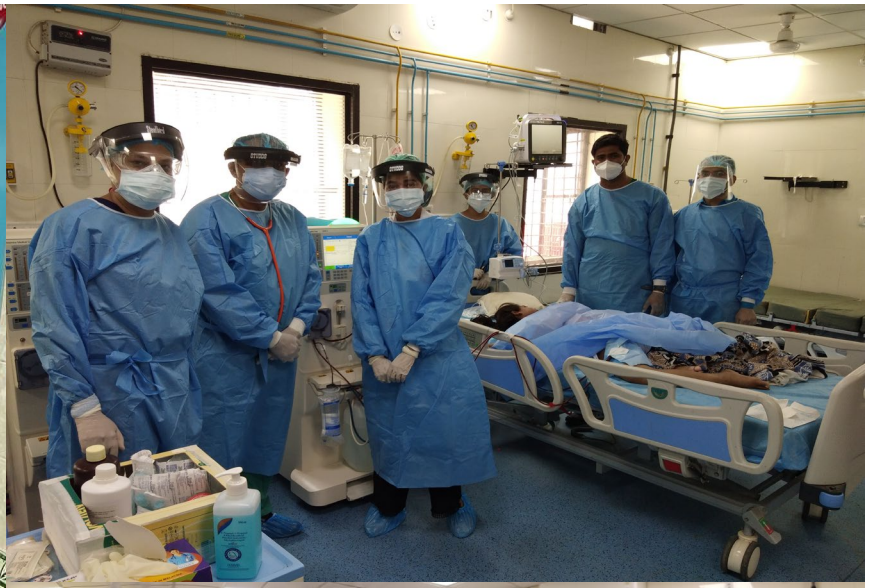
When to Suspect Renovascular Hypertension ?

- Very high BP, Cerebral symptoms, Cardiac failure, Facial palsy
- Hypertension not controlled with two or more drugs
- Diagnosis of a syndrome with a high risk of vascular disease
- Signs of vasculitis : Takayasu's disease
- Renal artery thrombosis or umbilical artery catheterization
- Transplanted kidneys
- Bruit heard over renal artery or arteries
- Raised peripheral plasma renin or moderate hypokalemia

Summary Slide

Red flags	End-organ dysfunction
Nausea and vomiting Headaches Upper motor neuron signs Hemiparesis or monoparesis, Bell's palsy Loss of vision or blurred vision Seizures Altered sensorium Drowsiness/reduced Glasgow Coma Scale	Hypertensive encephalopathy
Acute and chronic hypertensive changes on funduscopy Papilloedema	Hypertensive vascular changes, retinal bleeding and cotton wool lesions Increased intracranial pressure
Cardiomegaly Gallop rhythm Breathlessness Pulmonary oedema	Cardiac failure


DIVISION OF PEDIATRIC NEPHROLOGY
DEPARTMENT OF PEDIATRICS
KALAWATI SARAN CHILDREN'S HOSPITAL, NEW DELHI



Thanks!

Specific Investigations

- **CT renal angiography**

  -RK 9.8 * 4.32cms -LK 8.0 * 2.8cms

  -Rt renal artery measures 5.3mm at ostium

  -Extramural thickening in descending abdominal aorta just proximal to origin of left renal artery involving 25mm of length, extending to lt renal artery.

  -Thin streak of contrast visualized in LRA due to marked reduction of caliber leading to lesser contrast opacification of left kidney.

Investigations

- DTPA Renography

	LK	**RK**	**Total**
Differential function:	4.0 %	96.0 %	100 %
GFR (ml/min):	3.01	66.5	69.6

- DSA

  Rt renal artery normal

  Lt renal artery hypoplastic with one small accessory artery

Final Diagnosis

- Stage 2 hypertension with hypertensive encephalopathy (Cause – Hypoplastic left renal artery)

Anti-FH antibody associated typical hemolytic uremic syndrome in children

Aditi Sinha

Additional Professor, Division of Nephrology
Department of Pediatrics, All India Institute of Medical Sciences, New Delhi

Atypical hemolytic uremic syndrome: Ultra-rare but severe disease

Incidence of HUS

0.7–8 cases/100,000 population/yr

Atypical HUS (aHUS): Annual incidence

6.3/million <18 yr

2-7 per million children per year

12% of all HUS, which was 15.7 per million <5-yr

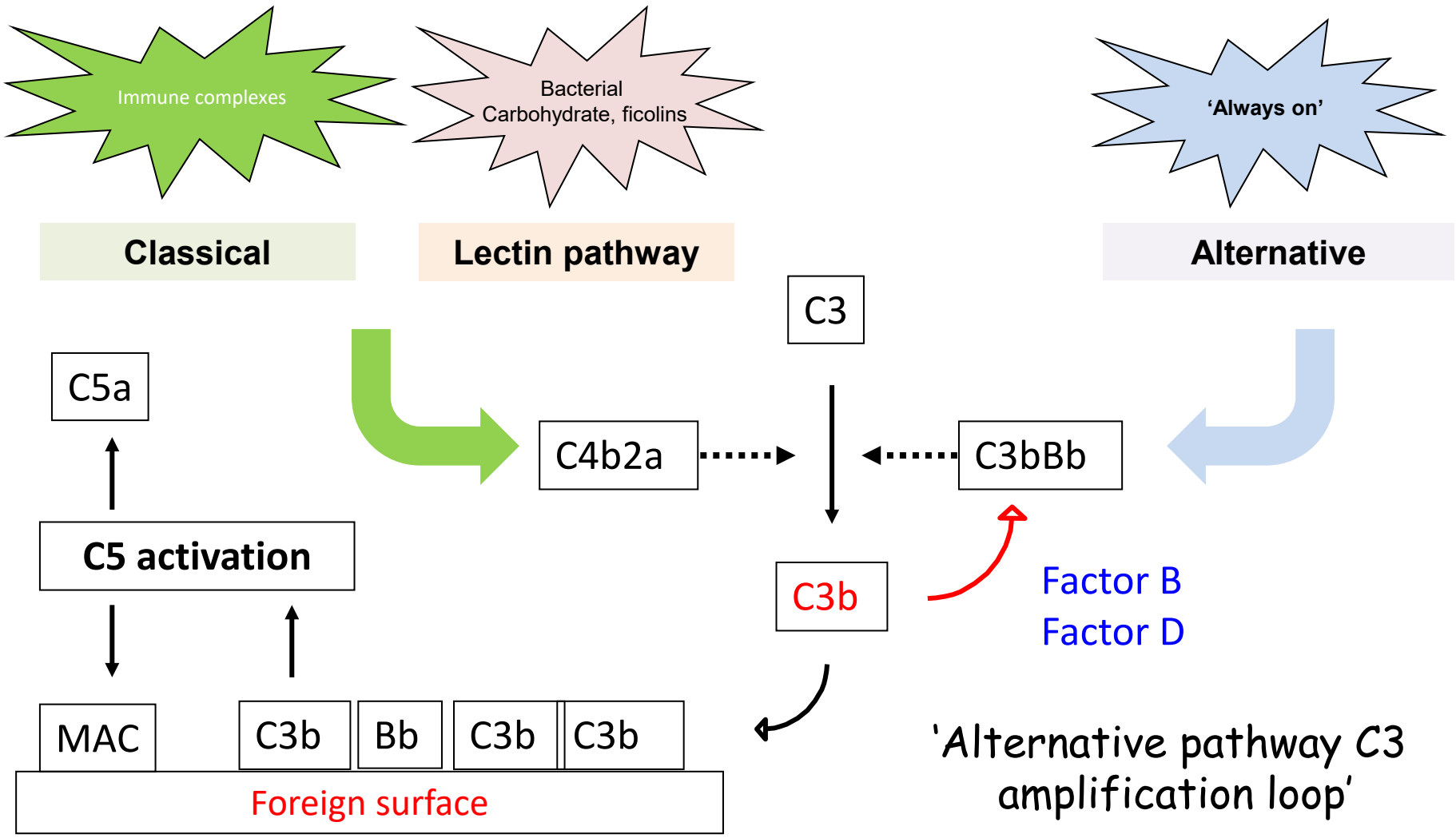
1-yr prospective UK study: 0.4 patients/million population

Leading cause of community acquired severe AKI

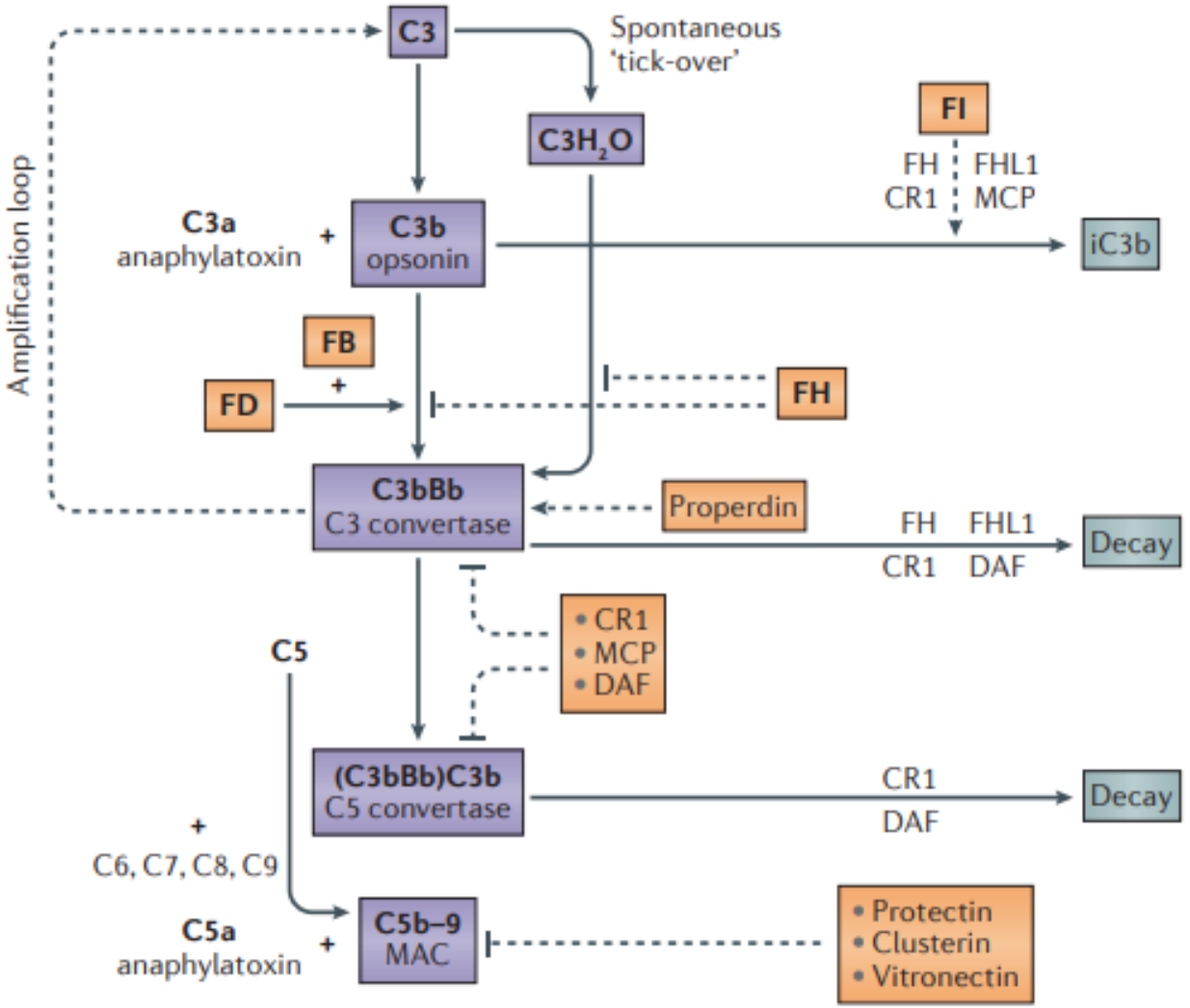
Mortality 4% (3.4% STEC-HUS; 8.3% aHUS)

10-years; North Italian network. Eur J Pediatr 2016; 175: 465-73

Complement activation



Alternate Pathway Complement Regulation



Nat Rev Nephrol 2016; 12: 563-78

Complement profiles in atypical HUS

Low levels of C3, CH50, AH50, and CFB
Increased levels of C5a, C5b-9, Bb

Biomarker	Unit	aHUS subjects					Reference range^
		Sample size	No. of studies	Mean (SD)	Median (IQR)	Range (Min - Max)	
C3*	**mg/dl**	**752**	**51**	**72.11 (35.04)**	**70.5 (52 - 99.78)**	**1.1 - 221.3**	**75 - 175**
C4$	mg/dl	343	34	20.41 (9.54)	20.5 (14 - 28)	2 - 45	14 - 40
C4d$	µg/ml	108	5	7.2 (6.49)	4.75 (2.94 - 8.35)	1.4 - 20.8	≤9.8
C5a+	**mg/dl**	**117**	**6**	**54.89 (32.94)**	**48.8 (34.98 - 64.53)**	**4.96 - 148.7**	**10.6 - 26.3**
C5b-9+	**ng/ml**	**174**	**14**	**466.03 (401.42)**	**317 (186 - 569.77)**	**44 - 1840**	**≤250**
CH50*	**U/ml**	**63**	**9**	**28.25 (32.09)**	**24.25 (3.5 - 53.25)**	**3 - 154**	**30-75**
AH50*	**%**	**23**	**2**	**27.61% (30.24%)**	**10% (10% - 38.5%)**	**10% - 93%**	**≥46%**
Bb+	**µg/ml**	**77**	**4**	**2.63 (2.1)**	**1.9 (1.16 - 3.21)**	**0.7 - 7.386**	**≤1.6**
CFB*	**mg/dl**	**19**	**6**	**13.08 (6.58)**	**12.4 (12.05 - 20.75)**	**5 - 28.6**	**15.2 - 42.3**
CFH$	mg/dl	123	7	40.2 (132.34)	24.45 (19.45 - 48.03)	10.2 - 467	23.6 - 43.1
CFI$	mg/dl	38	6	8.05 (5.01)	6.55 (5.93 - 6.88)	4.4 - 18.1	NA
D-Dimer+	**ng/ml**	**2**	**2**	**246 (65.05)**	**246 (223 - 269)**	**200 - 292**	**<2.2**

Pediatr Nephrol 2022; 37:1479–93

Pediatric Atypical HUS*

%	Bacchi* N=89	Noris* N=152	Schaefer n=387	Adults N=693
CFH	**21.3**	**25.6**	**21**	**21-32**
MCP (CD46)	13.5	9.2	14	3.8-6.4
CFI	6.7	2.6	3	5.7-10
C3	7.8	3.9	5	5.7-8.8
CFB	1	-	2	0.4-2.4
Anti-FH	**11**	**3.9**	**24** [45% 6-17 yr]	**1.9-19**
THBD	-	7.8	-	0.9
Complement	**64.7**	**53**	**43**	**43-67**
None defined	**27.4**	**47**	**57**	**33-57**
DGKε	-	-	**8**/101	

French. CJASN 2013;8:554; **Europe**. CJASN 2010;5:1844 JASN 2018; **93 genes; N=400**

Global aHUS (n=851): 45% had mutation, antibody KI 2018;94:408 ALEXION

Mutations in various complement proteins in aHUS

Mutation	No. of studies	Total aHUS patients	Pooled estimate (95% CI)
CFH	12	2,295	21.41% (16.60–26.64%)
CFI	12	2,295	6.89% (5.01–9.05%)
C3	9	2,193	5.29% (3.74–7.09%)
THBD	6	1,176	1.74% (0.47–3.8%)
MCP	11	2,177	9.98% (7.15–13.22%)
CFB	5	1,469	1.55% (0.99–2.32%)[a]
DGKE	4	558	6.57% (0.93–16.76%)
Combined	7	1,922	3.06% (1.26–5.61%)
Others	4	691	19.29% (1.34–50.78%)
CFH Ab	6	1,142	6.89% (3.39–11.52%)

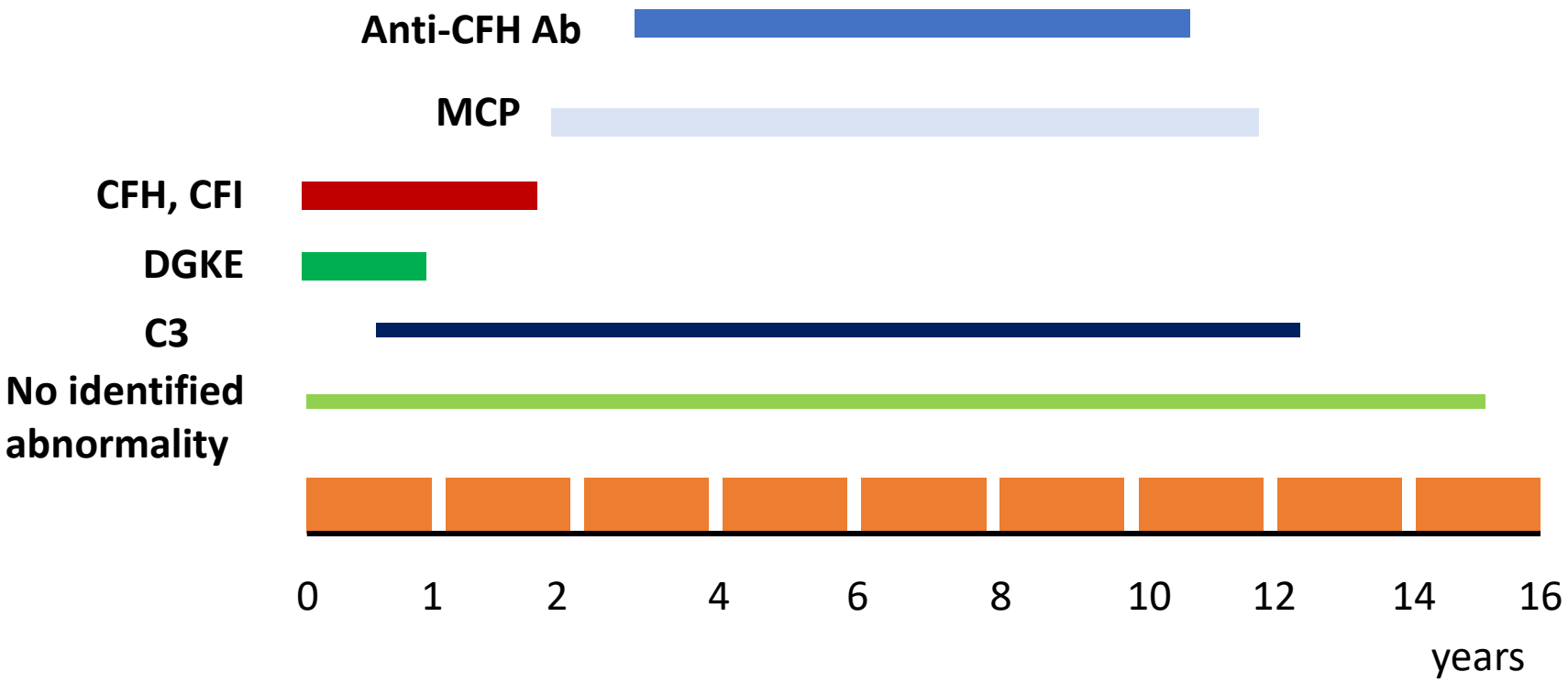
Pediatr Nephrol 2022; 37:1479–1493

Genotype phenotype association

	%	Onset	Low C3 %	ESRD %	Relapse %	Recurrence %
C3	2-10	>1-yr	**70-80**	60	50	40-70
Factor H	**20-30**	>1 mo	30-70	**50-70**	50	**75-90**
Factor I	4-10	>1 mo	20-40	50	10-30	**60-80**
MCP (CD46)	**5-15**	>1-yr	**0-25**	0-10	**70-90**	<20
Factor B	1-4	<1-yr	**100**	50	Common	100
CFH antibody	**6-50**	5-15 yr	**40-60**	**30-40**	20-50	Low
Thrombomodulin	3-5	>1-mo	50	50	30	1 patient
Diacylglycerol kinase ε	**25%** <1-yr	<1-yr	**20**	**80-100**	Yes	Low

***No abnormality detected in 30-40% cases; low risk of recurrence**

Atypical HUS: Age at onset



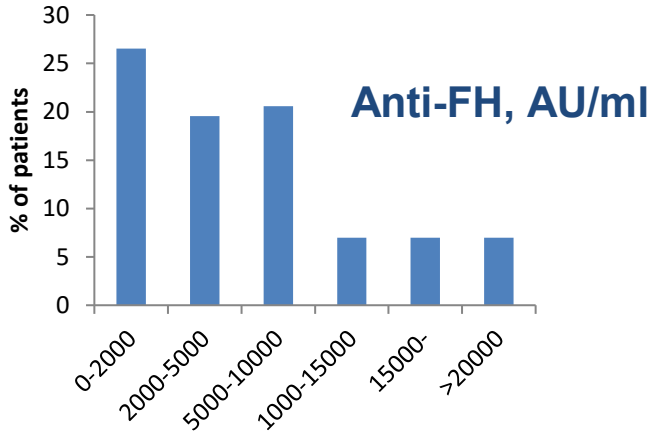
Fremeaux-Bacchi CJASN 2013

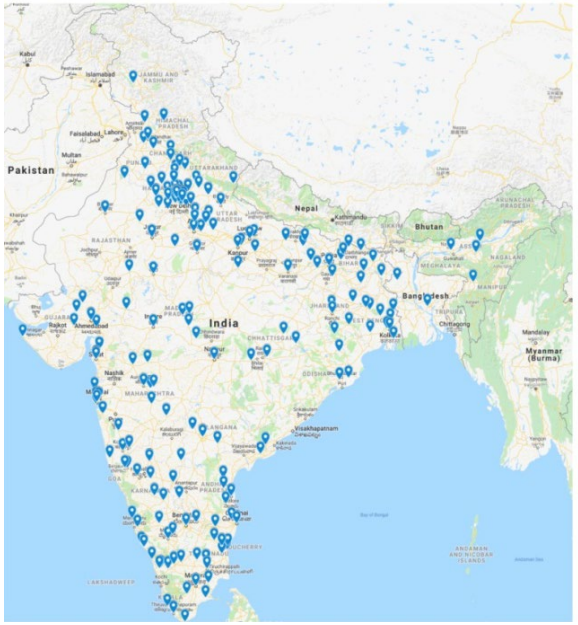
CLINICAL RESEARCH www.jasn.org

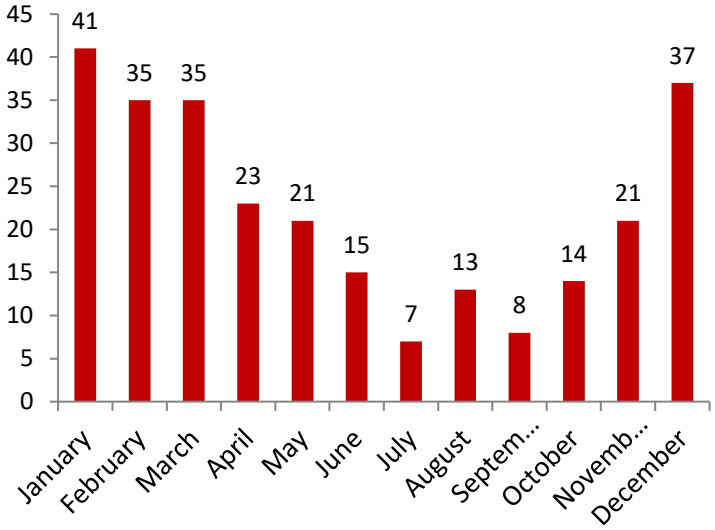
J Am Soc Nephrol 21: 2180–2187, 2010.

Clinical Features of Anti-Factor H Autoantibody–Associated Hemolytic Uremic Syndrome

Marie-Agnès Dragon-Durey,*†‡ Sidharth Kumar Sethi,§ Arvind Bagga,§ Caroline Blanc,† Jacques Blouin,* Bruno Ranchin,‖ Jean-Luc André,¶ Nobuaki Takagi,** Hae Il Cheong,†† Pankaj Hari,§ Moglie Le Quintrec,‡‡ Patrick Niaudet,§§‡ Chantal Loirat,‖‖ Wolf Herman Fridman,*†‡ and Véronique Frémeaux-Bacchi*†





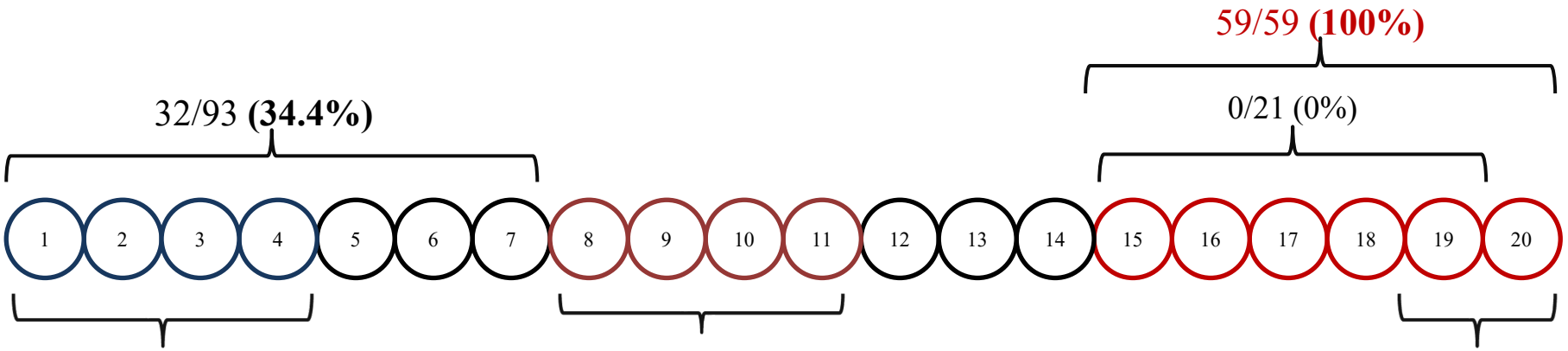


Positive threshold: 150 AU/ml (n=250)

Nation wide database, 72 centers

Anti-FH antibodies: 573/1017 (**56%**)

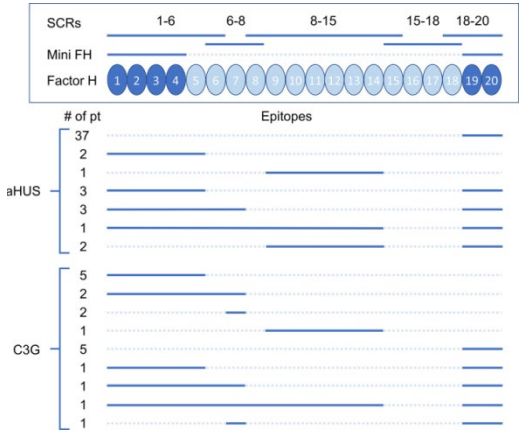
Antibodies (IgG3) bind multiple FH epitopes

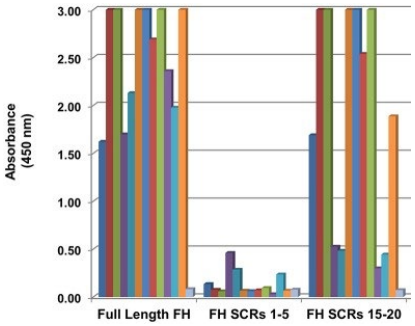


Author	SCR 1-4	SCR 1-7	SCR 8-11	SCR 15-19	SCR 15-20	SCR 19-20
Blanc	13/14	17/18	5/18		18/18	8/17
Bhattacharjee		5/10			10/10	10/10
Moore	1/12					7/12
Jozsi		0/16	4/16	0/16	16/16	16/16
Jozsi		0/5	1/5	0/5	5/5	5/5
Strobel	0/2				2/2	2/2
Guo **China-TMA**	4/36	6/36				12/36*
Puraswani **AIIMS**	**3/8**	**4/8**	**7/8**		**8/8**	

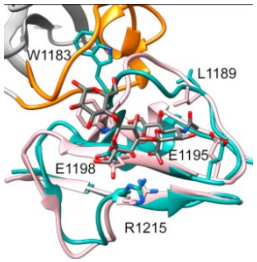
Front Immunol June 2019

*No epitope in 50%
Pediatr Nephrol (2019) 34:269





Bergamo. Front Immunol 2019



Antibodies IgG3

Bind multiple epitopes on FH

Leu1181 - Leu1189$_{CCP20}$

J Biol Chem 2022; 298(6):101962

Iowa. Front Immunol 2020

Copy number variations in *CFHR1/3*

Multiplex-ligation dependent probe amplification

SALSA MLPA P236-A3 ARMD, MRC Holland

CFH, *CFHR3*, *CFHR1*, *CFHR2* & *CFHR5* (not *CFHR4*)

Patient group	Gene	−/− (%)	−/+ (%)	+/+ (%)
aHUS; with anti-FH antibodies, n=96	*CFHR1*	**78 (81%)**	11 (12%)	7 (7%)
	CFHR3	**72 (75%)**	19 (20%)	5 (5%)
aHUS; without anti-FH antibodies, n=68	*CFHR1*	**15 (22%)**	25 (36%)	28 (41·2%)
	CFHR3	**13 (19%)**	25 (37%)	30 (44·1%)
aHUS patient family members[a], n=65	*CFHR1*	**30 (46%)**	29 (45%)	6 (9%)
	CFHR3	**28 (43%)**	33 (51%)	4 (6%)
Healthy volunteers[a], n=84	*CFHR1*	**8 (10%)**	30 (36%)	46 (55%)
	CFHR3	**8 (10%)**	30 (36%)	46 (55%)

Odds of anti-FH HUS with *CFHR1* del

155 (95% CI 93-265; *P* <0.0001)

Anti-CFH Ab ~ 12% worldwide

More common in India

Study	Event/sample size	Estimate (95% CI) %
Puraswani M et al., 2019	436/781	55.83 (52.26–59.35)
Valoti E et al., 2019	30/305	9.84 (6.74–13.74)
Bernabéu-Herrero et al., 2015	14/367	3.82 (2.1–6.32)
Lee et al., 2015	15/51	29.41 (17.49–43.83)
Fremeaux-Bacchi et al., 2013	14/214	6.54 (3.62–10.73)
Hofer et al., 2013	30/116	25.86 (18.18–34.82)
Noris et al., 2013	1/60	1.67 (0.04–8.94)
Noris et al., 2010	8/273	2.93 (1.27–5.69)
Durey M et al., 2009	14/177	7.91 (4.39–12.92)
Leban N et al., 2009	0/4	0 (0–60.24)
Moore I et al., 2009	13/142	9.16 (4.97–15.15)
Józsi M et al., 2008	16/147	10.88 (6.35–17.07)
Durey M et al., 2005	3/48	6.25 (1.31–17.2)
Total (random effects)	594/2685	11.82 (3.56–24.01)

Pediatr Nephrol 2022; 37:1479–1493

Prevalence varies; not *FHR1* deficiency in population

	AI-HUS of aHUS	*CFHR1* deficiency, %	
	%	AI-HUS	Controls
Germany (147)	**10.9**	87.5	2
France (214)	**6.5**	92.9	2.8
Spain (151)	**4.6**	71.4	1.7
UK (175)	**9.7**	82.4	3.0
Italy (149)	**0.7**	90	ND
India (518)	**56.0**	88.2	**9.5**
Austria; Europe (100)	**25**	85.7	2.5
Korea (51)	**29.4**	73.3	1
Belgium (45)	**13.3**	71.4	9.7
USA (448)	**10.9**	76	NA

High prevalence: Egypt (2021; 28) **43%**; China (2021; 59) **65%**

Children & adults	**7.5** (5.8-9.5)	145/171	40/1164
Children alone	**44.7** (39.9-49.5)	**84.8 (79-90)**	**3.4 (2.5-4.6)**
Outside south Asia	**23.5** (18.1-29.9)		

Variants in relevant genes in anti-FH HUS

Next-Generation sequencing: Customised panel of 27 genes

8 whole genes: *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *DGKE*, *THBD* and *PLG*

Only exons (±25 bp flanking introns): *ADAMTS13*, *CFHR1-5*, *C1*, *C5*, *C6*, *C7*, *C8A*, *C8B*, *C9*, *FCN1*, *FCN2*, *FCN3*, *MASP1*, *MASP2*, *MBL2*

77 consecutive
21 relapses; **9** ESKD

Homo del *CFHR1*

92% patients

9.8% controls

Only 1 in 107 patients had a pathogenic variant

Variants, chiefly VUS: **7 (6.5%)**, chiefly VUS: **7 (6.5%)**

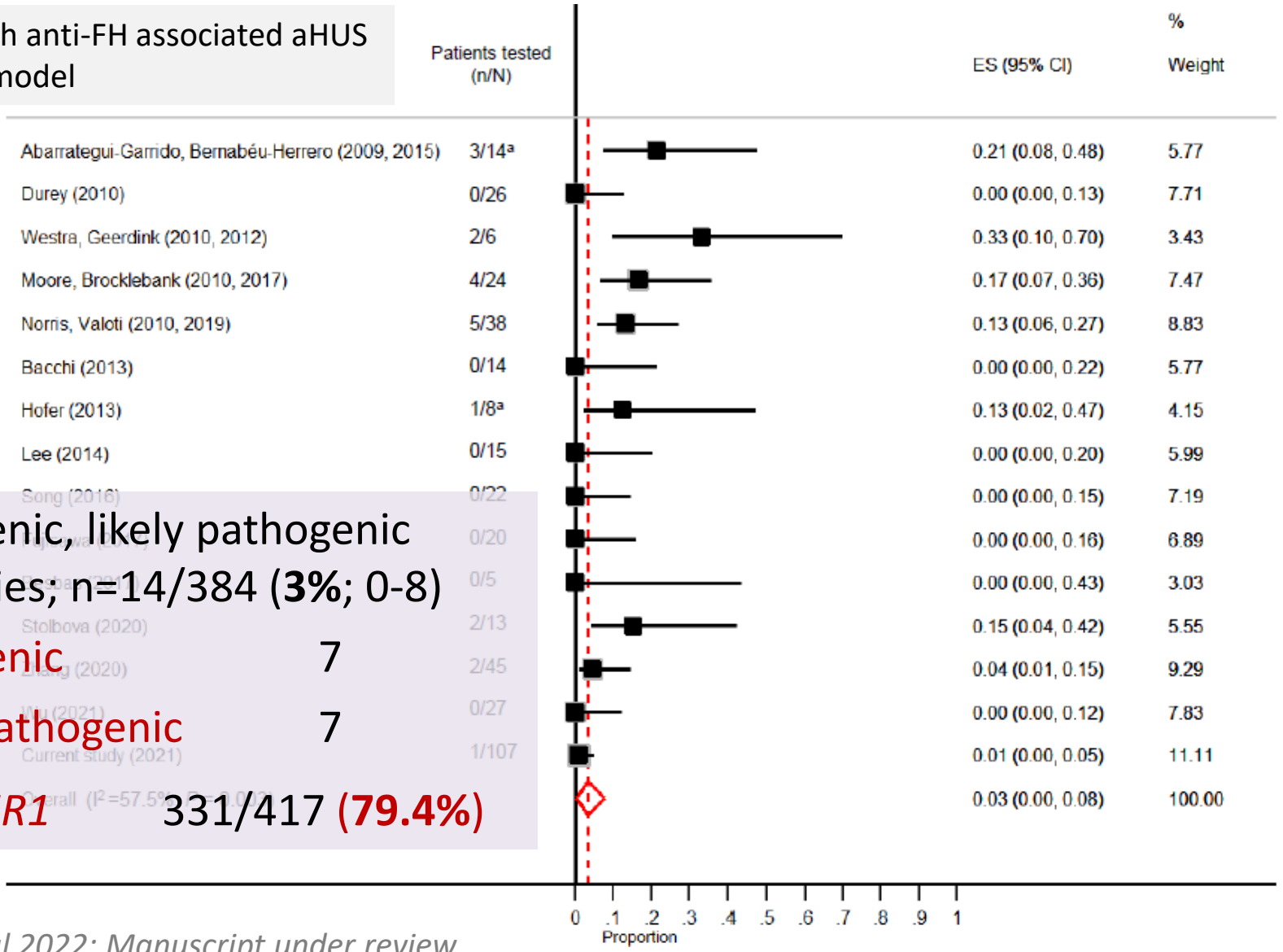
	Gene	Chromosomal position (hg19)	cDNA position, protein change	Zygosity	Population frequency[a]	In-silico prediction[b]	Novelty	Association with aHUS	ACMG classification[criteria]
	Variants in genes causative for aHUS								
1	*CFI*	chr4:g.110687890G>C	c.148G>C, p.Pro50Ala	Heterozygous	0.0002; 0.0001	1; D; 24.9; 5.68	In [26-28]	Yes; $P<0.001$[d]	Pathogenic [PS3[c], PS4, PM2, PP3]
2	*CD46*	chr1:g.207934726T>C	c.608T>C, p.Ile203Thr	Heterozygous	NA; NA	0.96; D; 23.9; 4.85	In [7, 29]	No; $P<0.025$[d]	Unknown significance [PM2, PP3]
3	*CFI*	chr4:g.110687845A>G	c.193T>C, p.Tyr65His	Heterozygous	NA; <0.0001	1; D; 27.2; 5.68	In [45]	Not reported	Unknown significance [PM1, PM2, PP3]
4	*C3*	chr19:g.6711075C>T	c.1402G>A, p.Gly468Arg	Heterozygous	NA; <0.0001	0.98; D; 26.1; 5.03	Rare	Not reported	Unknown significance [PM2, PP3]
	Variants in genes associated with aHUS								
5	*THBD*	chr20:g.23029546G>T	c.596C>A, p.Ala199Asp	Heterozygous	NA; NA	0.97; P; 23.6; 2.07	Novel	Not reported	Unknown significance [PM2]
6	*THBD*	chr20:g.23030015C>T	c.127G>A,p.Ala43Thr	Heterozygous	0.003; 0.002	0.17; P; 10.4; 1.61	In [30]	No; $P<0.5$[d]	Unknown significance [PS3[c], BP4]
7	*PLG*	chr6:g.161152161G>T	c.1335G>T, p.Arg445Ser	Heterozygous	0.0004; 0.0005	0.96; D; 23.9;-5.5	Rare	Not reported	Unknown significance [PM2]

Coexisting variants increase risk of relapse

Khandelwal et al 2022; Manuscript under review

Low prevalence of pathogenic or likely pathogenic variants in relevant genes in anti-FH HUS

384 patients with anti-FH associated aHUS
Random effect model



Pathogenic, likely pathogenic
19 studies; n=14/384 (**3%**; 0-8)

Pathogenic 7

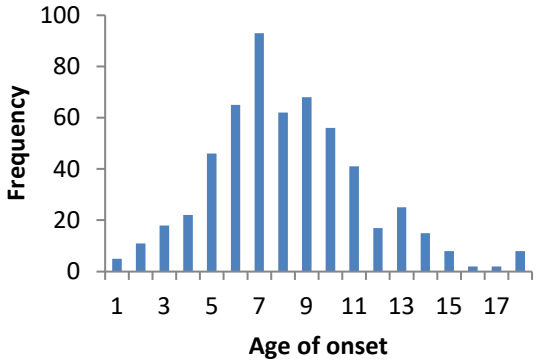
Likely pathogenic 7

Del *CFHR1* 331/417 (**79.4%**)

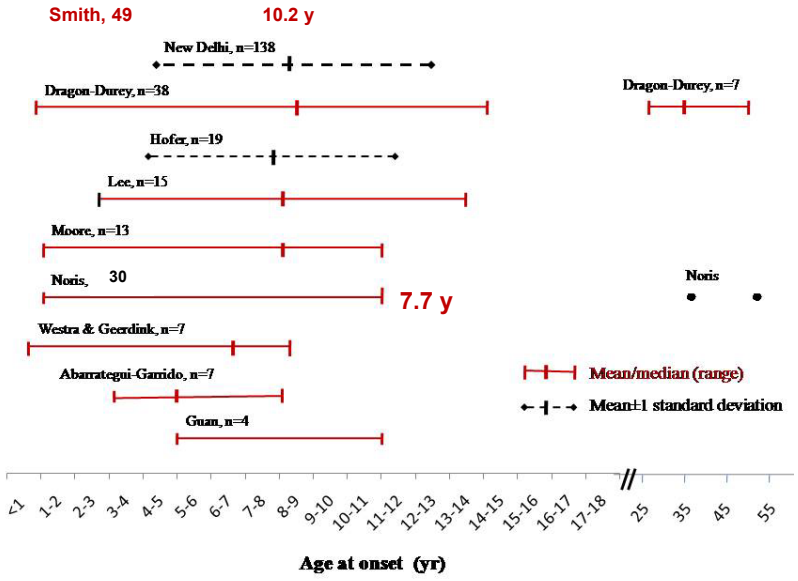
Khandelwal et al 2022; Manuscript under review

Severe clinical manifestations

	Anti-FH HUS, n=573
Age	7.8±3.4 years
Prodrome	
Febrile illness	300 (52%)
Diarrhea	37 (7%)
Duration of oligoanuria	8±10 days
Extrarenal symptoms	121 (33%)
Seizures	132 (23%)
Stage 2 hypertension	304 (**53%**)
Hemoglobin	5±2 g/dl
Platelets	61±40000/cu mm
Nephrotic proteinuria	327 (**58%**)
Creatinine	5.5±3 mg/dl
Complement C3	70±28 mg/dl
Anti-FH antibody	9567±769 AU/ml



Infancy (6); adults (5)



Anti-FH HUS : Clinical features

	Dragon-Durey 2010; 45	Hofer 2013; 19	India 2017; 386	Lee 2015; 15	Brocklebank 2017; 17
GI prodrome	84% abd. pain, diarrhea 53%	87% pain, diarrhea 13%	7.5% diarrhea	14%	53% pain, diarrhea 47%
Infections	9% varicella, URI STEC, norovirus	42% URI	54% fever	14% URI	24% fever
Dialysis	57%	74%	86%	67%	47%
CNS	24%	11%	29%	7%	24%
Pancreatitis	23%				12%
Hepatitis	50%	58%	34%	7%	6%
Cardiac	8%			33%	

Other autoantibodies in aHUS

IgM anti-FH: 7 of 186 (3.8%)
3/20 (15%) BMT associated HUS

No association: del *CFHR3-1*

Milan. JASN 2021

IgA anti-FH (~30%) in case series
Associated with IgG_{1-4} anti-FH

China-TMA group

Factor I antibodies: **3** of 175
No association with del *CFHR1/3*
Two had significant *CFH* variants

UK. CJASN Mar 2012

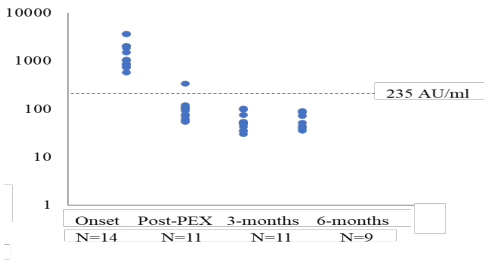
FI-antibodies: 11/35 **(31%) aHUS**

C3 low: 73%

Chandigarh. Immunobiology 2020

Anti-FB antibodies in ~9% aHUS

- 14/122 (11.5%) anti-FH associated HUS
- 0/28 genetic cause for aHUS
- 4/43 (9.3%) no anti-FH antibodies & no variants



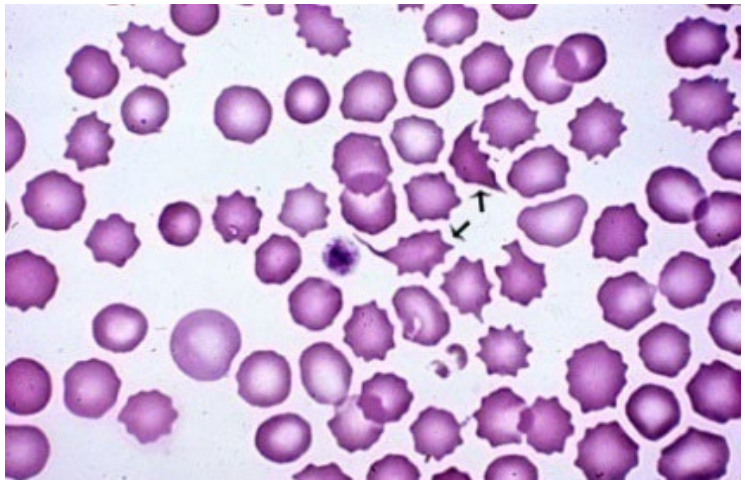
Pediatr Nephrol 2019; 34: 1465-82

Hemolytic uremic syndrome in a developing country: Consensus guidelines

An international consensus approach to the management of atypical hemolytic uremic syndrome in children

Lancet 2019

Thrombocytopenia, hemolysis & schistocytes



Shiga toxin-producing *Escherichia coli*, *Shigella dysenteriae* type 1, *Citrobacter*, *Campylobacter*

Pneumococcal HUS
Invasive infection with neuraminidase-producing *Streptococcus pneumoniae*

Infection-associated HUS
Triggered by influenza A, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, Coxsackie virus, echovirus, varicella virus, hepatitis A, B, and C, *Salmonella typhi*, *Bartonella*, leptospira, malaria, dengue, and rickettsia

Secondary HUS
Systemic lupus erythematosus; antiphospholipid antibody syndrome
Hematopoietic stem cell or solid organ transplant
Malignancy
Malignant hypertension
Drugs: quinine, mitomycin, ticlopidine, clopidogrel, calcineurin inhibitors, sirolimus, oral contraceptives, bevacizumab

Defective cobalamin metabolism
Homozygous or compound heterozygous mutation in *MMACHC*

Atypical HUS
Homozygous or heterozygous mutations in *CFH*,[a] *CFI*, *CFB*, *C3*, *CD46*, *THBD*, or *DGKE*
Autoantibodies to factor H
Unexplained

Consensus guidelines 2019

Hemolytic uremic syndrome in a developing country: Consensus guidelines

Diagnose in presence of all

- Microangiopathic hemolytic anemia — 1B

  Anemia, schistocytes >1%, LDH >450, undetectable haptoglobin
- Platelets <150000/µl

  15-20%: No thrombocytopenia; screen multiple time points
- Acute kidney injury

Evaluation for DIC, TTP if indicated — 1B

DIC: sepsis/ malignancy

TTP: persistent thrombocytopenia (<30,000/µl); mild or no AKI — 2C

Exclude infections mimic/trigger: malaria, leptospirosis, dengue

Differentiate from thrombotic thrombocytopenic purpura

Consider cobalamin associated HUS

Evaluation of HUS

Diagnosis

CBC; schistocytes; reticulocytes

LDH, haptoglobin; DCT

Creatinine, electrolytes, SGOT/PT

Complement C3

Urinalysis

Test: malaria, dengue; leptospirosis

Coagulation profile

Ultrasound abdomen

Echo, neuroimaging, amylase, troponin

Determine cause

Investigate: Infection, secondary HUS

Anti-FH; antinuclear antibodies

Flow cytometry CD46

Store: ADAMTS13 activity; homocysteine

Selected patients

Shiga toxin: Stool culture; PCR for Shiga toxin; LPS IgM antibodies

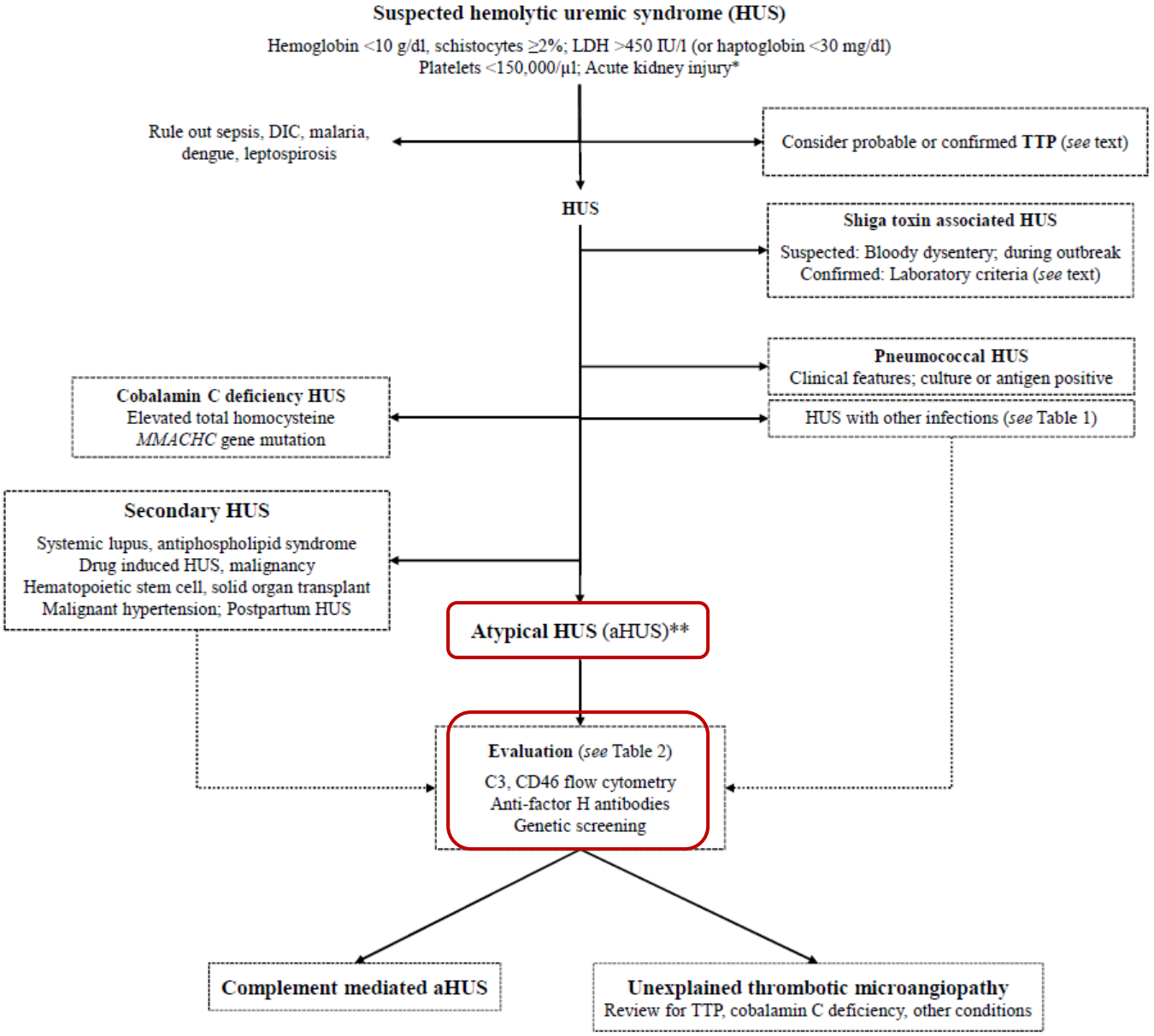
Pneumococcal: Culture, PCR or ELISA; peanut lectin agglutination

Next-gen sequencing *CFH, CFI, CFB, C3, CD46, DGKE; MMACHC*

MLPA: *CFHR1-5*, *CFH* (CNVs)

Indications for biopsy

Evaluation of HUS



Pediatric Nephrology
https://doi.org/10.1007/s00467-019-04233-7

CONSENSUS CONFERENCE

Hemolytic uremic syndrome in a developing country: Consensus guidelines

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- Microangiopathic hemolytic anemia — **1B**

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- Acute kidney injury

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DIC: sepsis/ malignancy

TTP: persistent thrombocytopenia (<30,000/µl); mild or no AKI — **2C**

Exclude infections mimic/trigger: malaria, leptospirosis, dengue

Shiga toxin associated HUS

Confirmed case HUS associated with infection with shiga toxin producing organisms confirmed by positive stool culture and either of:

(i) Detection of virulence genes (PCR) **1A**

(ii) Free fecal shiga toxin *or* O157 lipopolysaccharide antigen (ELISA)

(iii) Antibodies to LPS of prevalent serogroups (ELISA)

Suspected case HUS within 2-3 weeks of bloody diarrhea, and/or during outbreak of STEC-HUS in patients >6 months-old

Screen for STEC in all suspected cases of STEC-HUS on stool sample collected within 6-10 days of onset of diarrhea **2A**

Centers for Disease Control and Prevention (CDC) MMWR Recomm Rep 2009; 58
Japanese guidelines. Clin Exp Nephrol 2014; 18:525-557

Shiga toxin associated HUS

Hydration (isotonic fluids) from onset of bloody diarrhea to onset of HUS; monitor overload

1B

Antibiotics for bloody diarrhea

1A

Cefixime, fluoroquinolone for 3-5 days

High mortality with shigellosis

Do **not** suggest use PEX and/or eculizumab

ASFA guidelines: category IV

J Clin Apheresis 2016;31:149–62

Exception: Severe neurological or cardiac involvement

2D

Not recommend Infusions, heparin, urokinase, dipyridamole, steroids, toxin binders, antimotility agents

1B

Is it necessary to differentiate TTP from HUS?

Rare cause of TMA: Inherited 2.4%, acquired 4.6%

ADAMTS activity assay: Long turnaround time; not available

Fallacy of clinical diagnosis: **Severe AKI in 10-12% TTP**

Congenital TTP has **varied** phenotype

KDIGO 2017 "routine evaluation for ADAMTS13 activity not necessary in children"

Suggest storing plasma (3.2% sodium citrate at -20 to -80^{o} C)

FRET based assays: Fresh samples; stored plasma (up to 4-yr)

French national registry for TMA. Lancet Haematol 2016; 3:e537-e546
KDIGO Controversies Conference. Kidney Int 2017; 91:539-551
Standardization of TMA terminology. J Thromb Haemost 2017; 15:312-322

Cobalamin deficiency associated HUS

Sample stored; processed later if plasma total homocysteine not immediately available

2C

Probable Elevated total homocysteine (>50-100 µM/L; chromatography or immunoassay); normal B12, folate

Confirmed Homozygous or compound heterozygous mutation in *MMACHC* gene

1A

Patients with probable, confirmed cblC deficiency: Prompt therapy with parenteral hydroxycobalamin, oral betaine, folate

Other Atypical HUS

Plasma exchanges.....until recently

Supplement regulators, remove inhibitors

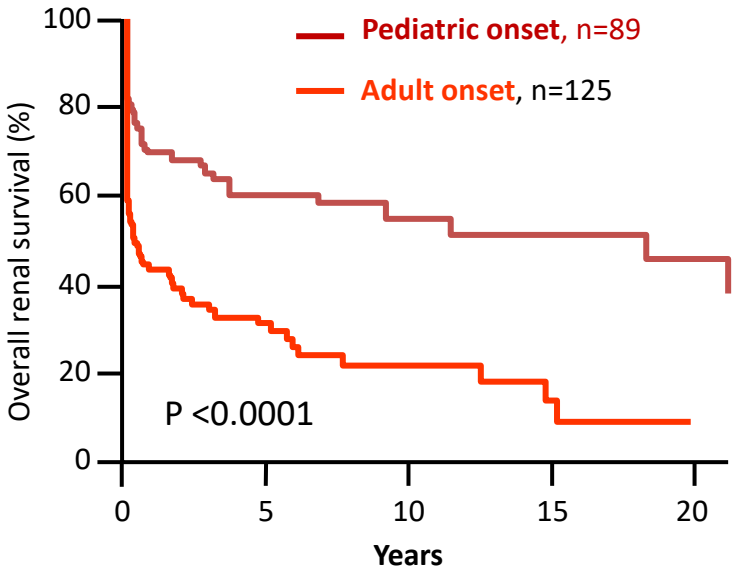
Anti-FH context: Remove anti-FH, immune complexes; provide free FH, 'decoy' FHR1

European HUS Study Group: Pediatr Nephrol 2009;24:687

Early (within 24 h) intensive PE

Audit Pediatr Nephrol 2014 (UK); J Clin Apheresis 2019 (India)

Unsatisfactory outcomes

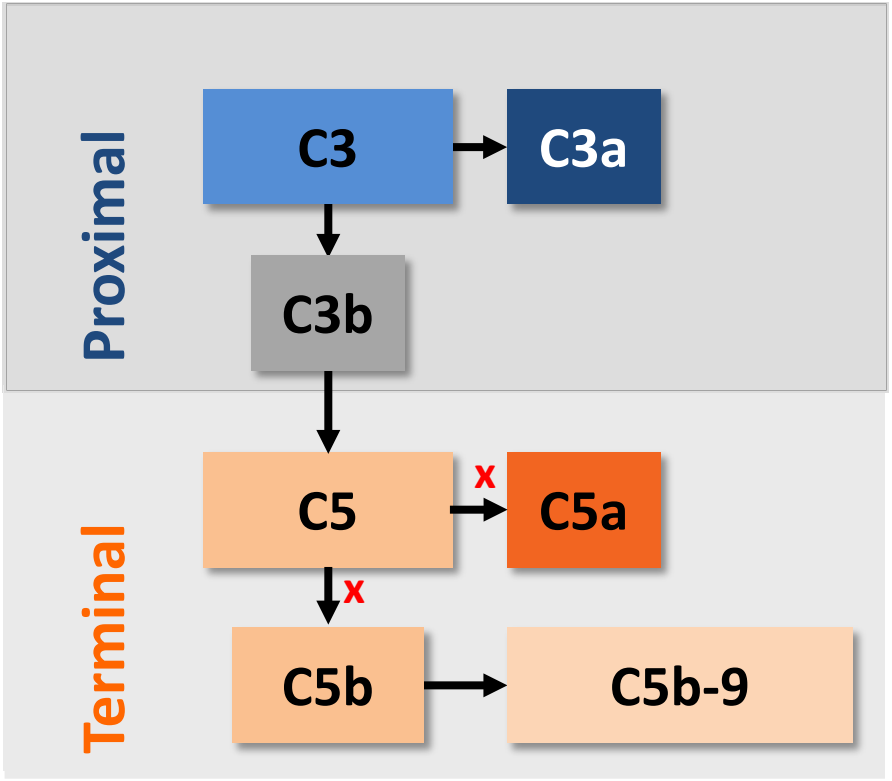


Safety of PEX

AIIMS: 2013-17; 1576 sessions

	Johnson N=29 PEX, 20 PI+PEX	AIIMS N=84 PEX, 6 PEX+PI
Age	~50% <5-yr	~80% >5-yr
Ventilation; cardiomyopathy	25%; 11%	12%; 28%
Seizures; altered sensorium	11%; 31%	14%; 52%
Catheter related complications	**31%**	**8%**
Infection	8	7 (2 <1-yr-old)
Thrombosis; ischemia	3; 1	0; 0
Catheter only for PEX	15/51 (29%)	12/90 (13%)
Withdrawal therapy	1/51 (2%)	4 (4%)
Outcomes		
Hematological remission	11 (8-21.5) days	7 (5-9) days
Relapse	11/59 **(19%)**	10/84 **(12%)**
Dialysis dependence @ day 30	12/71 (17%)	15/88 (17%)

Eculizumab binds to C5, blocks terminal complement



Renal, hematological,
CNS, cardiac recovery

Eculizumab in aHUS

aHUS in native kidneys
Post-transplant recurrence
Prophylaxis of recurrence

Availability

Expense

Duration of therapy….

Long term effects

Other complement blockers

Interventions for Atypical HUS

Cochrane Database Systematic Rev 2021; CD012862

Eculizumab (4; n=100); ravulizumab (n=58)

Single arm studies; high risk of bias

After 26 weeks ECZ: No deaths; 70% reduced dialysis need; TMA response 60% (26 weeks), 65% (2-yr)

After 26 weeks RVZ: 4 patients died; 59% reduced dialysis need; complete TMA response in 54%

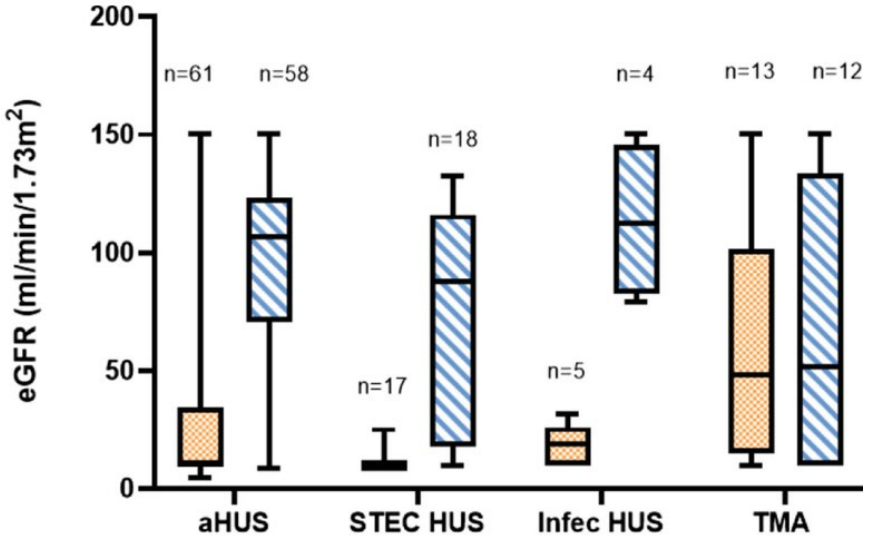
Improved eGFR & health-related quality of life

Serious adverse events 42%; meningococcal infection in 2

Future studies; longer follow-up

Efficacy and safety of eculizumab in children

N = 21 centers of PNRC
Retrospective data 2008-2015



Diagnosis	66	18	5	14
Paired N	54	17	4	12
Paired Difference eGFR*	73.8(15.1, 106.6)	73.3(65.9, 106.1)	86.4(70.4, 116.0)	0.0(-2.2, 28.5)

Almost ~35% of children experience infection following eculizumab

	aHUS	STEC	TMA
Bacterial infection	18 (25)	3 (16.7)	6 (40)
Viral infection	9 (13)	1 (6)	7 (50)
Non-infectious	15 (21)	1 (6)	2 (14)
Mortality	1 (1.5)	2 (11)	5 (35)

Pediatric Nephrology (2021) 36:2349–2360

Extended action with Ravalimumab

Eculizumab (Soliris), IV (FDA, EMA approved)

Body weight	Induction	Maintenance
≥40 kg	900 mg/wk×4 doses	1,200 mg (week 5), then 1,200 mg q 2 wk
30 to <40 kg	600 mg/wk×2 doses	900 mg (week 3), then 900 mg q 2 wk
20 to <30 kg	600 mg/wk×2 doses	600 mg (week 3), then 600 mg q 2 wk
10 to <20 kg	600 mg/wk×1 dose	300 mg (week 2), then 300 mg q 2 wk
5 to <10 kg	300 mg/wk×1 dose	300 mg (week 2), then 300 mg q 3 wk

Adverse effects	Cost
Headache, back pain, diarrhea, anemia, leukopenia, nasopharyngitis, vomiting; meningococcal infection	100,000/- per vial of 300 mg

Ravalimumab (Ultomiris), IV (FDA, EMA approved)

Body weight	Induction	Maintenance
≥40 kg	2400 mg	3000 mg q 8 wk
30 to <40 kg	1200 mg	2700 mg q 8 wk
20 to <30 kg	900 mg	2100 mg q 8 wk
10 to <20 kg	600 mg	600 mg q 4 wk
5 to <10 kg	600 mg	300 mg q 4 wk

Adverse effects	Cost
Similar as above, headache more common	180,000/- per vial of 300 mg

Studies on HUS, TMA in progress

EUCTR2017-001082-24	Cemdisiran (ALN-CC5)
EUCTR2014-001032-11; NCT03205995	Narsoplimab (OMS721)
NCT01757431	Eculizumab
NCT03131219	Ravulizumab
(children)	
EUCTR2017-000064-15; EUTCR2020-002475-35	Crovalimab (aHUS)
EUCTR2011-002691-17	Eculizumab (STEC-HUS)
EUCTR2016-000997-39; NCT02205541	ECUSTEC, ECULISHU
NCT04132375	INM004 (equine anti-
Stx antibodies)	
EUCTR2014-004261-24	Avacopan (C5aR, CD88
antagonist)	
NCT04889430	Iptacopan (FB
inhibitor)	

An international consensus approach to the management of atypical hemolytic uremic syndrome in children

Pediatr Nephrol 2016;31:15–39

Eculizumab within **24–48 h of onset**

ECZ not immediately available: start PE, or PI

Switch (to ECZ) when diagnosis confirmed

Exception: Anti-CFH associated HUS

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2016) **58**, 549–555 doi: 10.111

Clinical guides for atypical hemolytic uremic syndrome in Japan

Anti-FH HUS: Plasma exchange + immunosuppressants yield better outcomes

Eculizumab: Consider for patients with extra-renal injury

Eculizumab preferred for aHUS: KDIGO 2017

	Plasma therapy	Eculizumab
Ariceta, 2009	Prefer PEX to infusions	Not available
Japan, 2014	Prefer PEX to infusions; **anti-FH HUS**	First line
Spain, 2013	Second option: Prefer PEX to infusions	First line
Korea, 2015	PEX &/or infusions; **anti-FH HUS**	First line
Consensus, 2016	Second option; **anti-FH HUS**	First line
Australia, 2018	PEX for adults (TTP); **anti-FH HUS**	First line
Portugal, 2018	PEX if eculizumab NA; adults (TTP)	First line
IPNA, 2022-23		Awaited..

Kidney International (2017) 91, 539–551; Pediatr Nephrol 2016;31:15–39

Developing countries : Limited access to ECZ

HUS in developing country: Consensus *Pediatr Nephrol. 2019*

Atypical HUS without anti-FH antibodies

In absence of eculizumab, recommend prompt initiation of PEX. **1C**

Initial therapy: PEX preferred to plasma infusions

Suggest daily PEX until hematological remission; taper 3-4 weeks **2D**

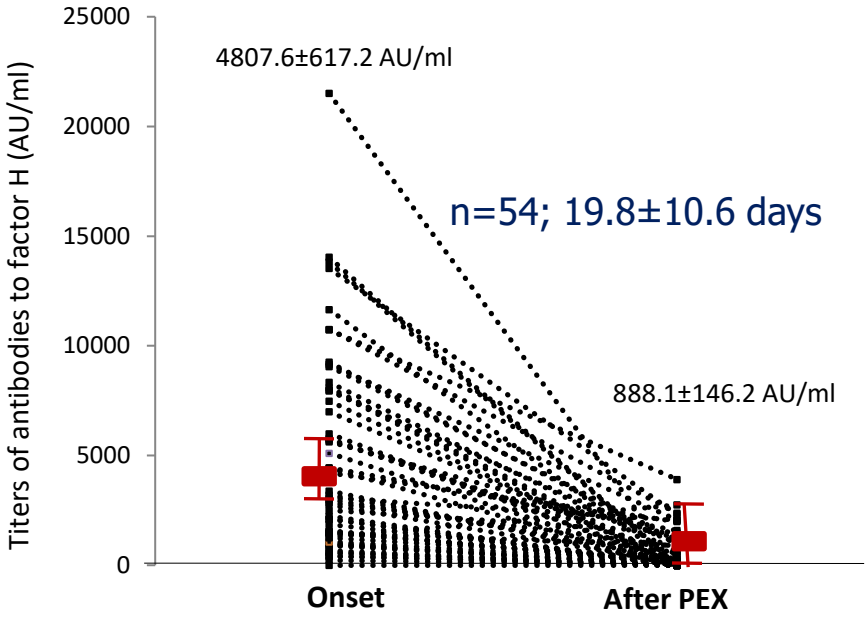
Monitor: Plasma, filter reactions; complications of catheter insertion, infection or thrombosis; blood borne infections **1C**

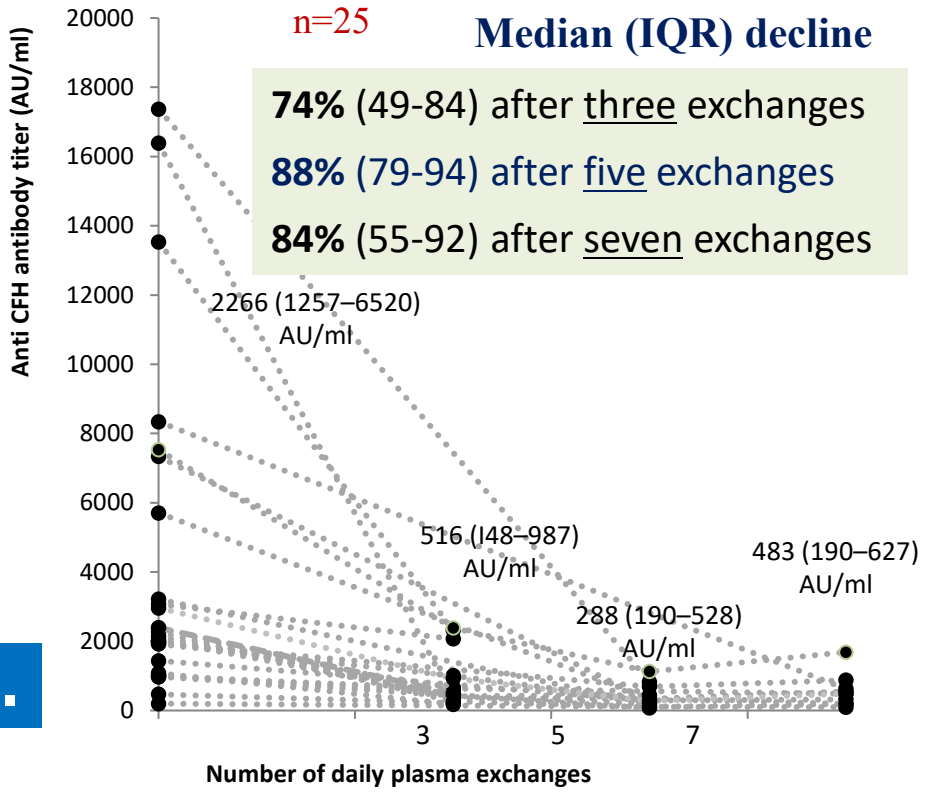
Recommend all efforts to enable therapy with eculizumab: **1C**

i. lack of remission despite 5-7 days of PEX
ii. life-threatening features (seizures, cardiac dysfunction)
iii. complications due to PEX or vascular access
iv. inherited defect in complement regulation

Plasma exchanges reduce antibody levels

IgG chiefly extracellular; 5-7 exchanges → 80-88% reduction



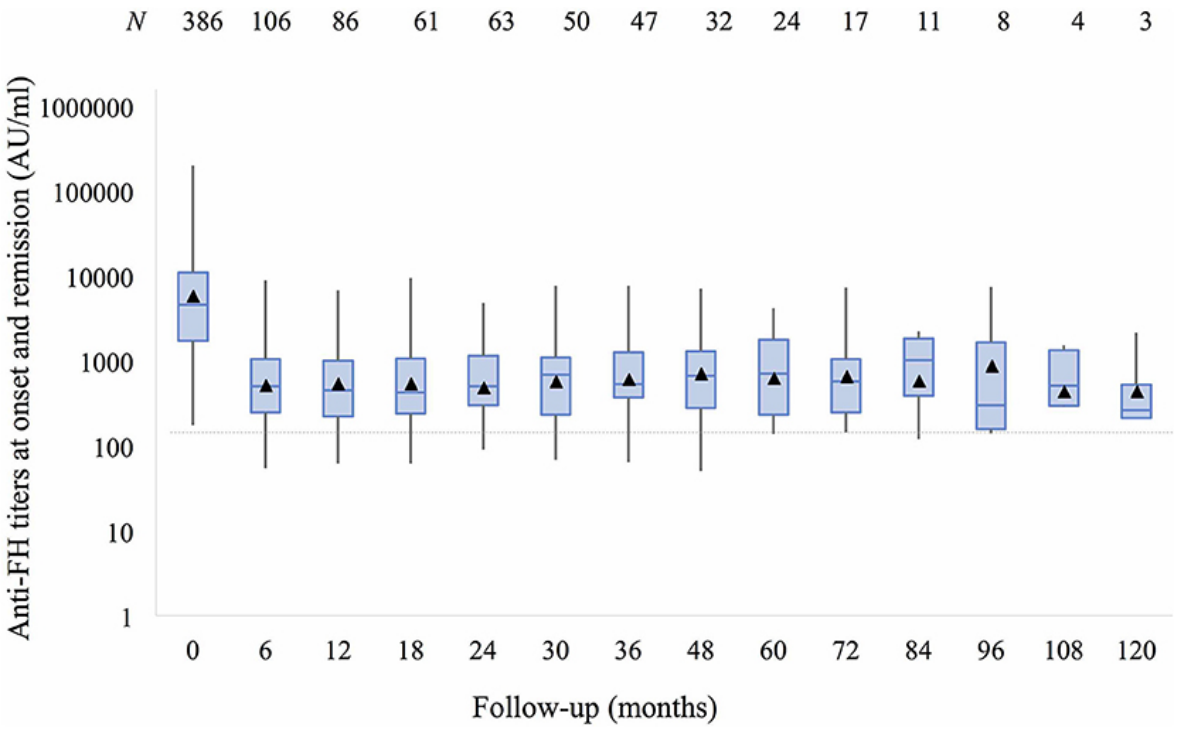


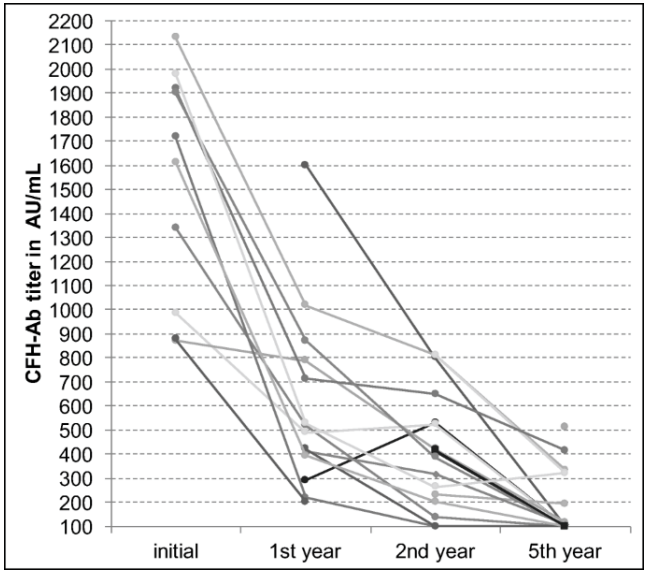
Additional IVIG does not help….

Kidney Int 2014;85:1151-60

Pediatr Nephrol 2015;30:451-7

Anti-FH titers decline, but stay relatively high….



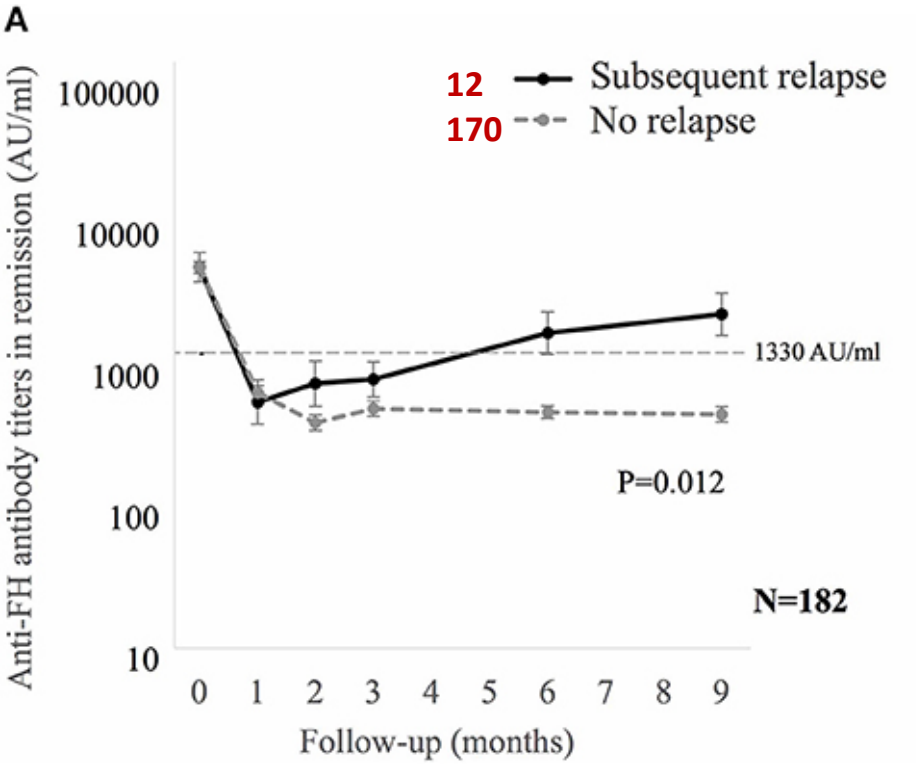


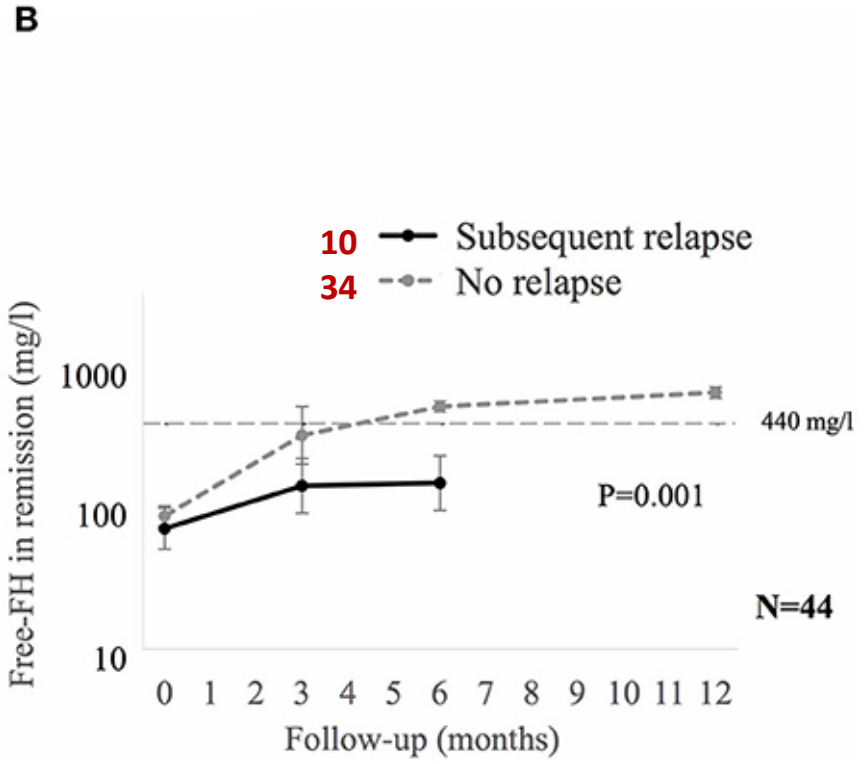
N=19 @ 5-yr, 55% patients had Ab titers <100 AU/ml

Innsbruck. Pediatr Nephrol 2021; 36: 917–25

High anti-FH & low free FH predict relapse

Anti-FH ≥1,330 @ 6-months: Sensitivity 75%, specificity 81%; AUC 0.86



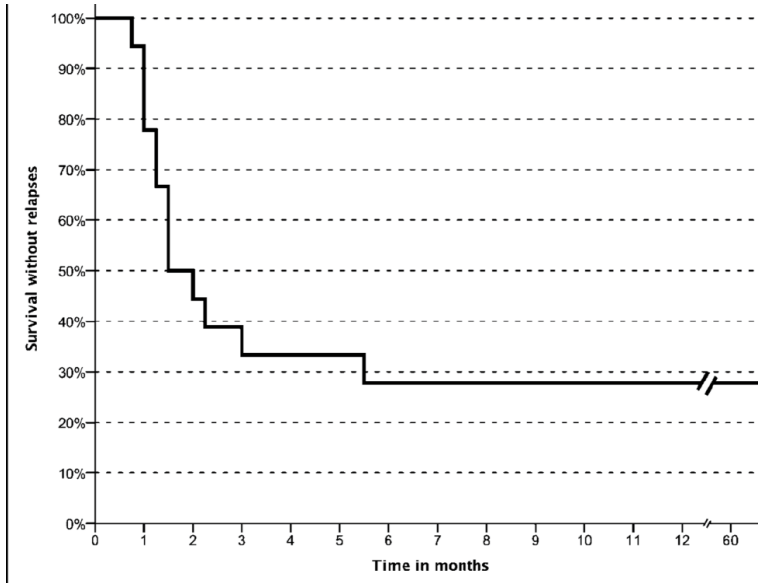


Free FH ≤440 mg/l @ 6-months: Sensitivity 70%, specificity 100%; AUC 0.91

Combined: Sensitivity 75%, NPV 91%; AUC 0.91; HR 6.3 (1.7, 24; *P* 0.018)

Relapses within 6-24 months of onset

	N
AIIMS	**83/443 (18.7%)**
Dragon-Durey	13/30 (43.3%)
Moore	3/13
Noris	3/7
Geerdink	3/6
Guan	0/4
Sana	1/4
Hofer	14/19 (74%)



Innsbruck. Pediatr Nephrol 2021;

SARS-CoV2

Mycoplasma pneumoniae

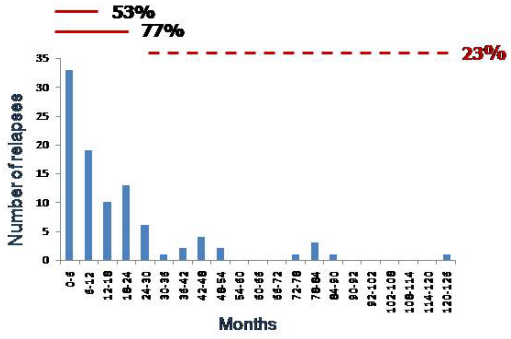
Pediatr Nephrol 2022

Nephron 2022

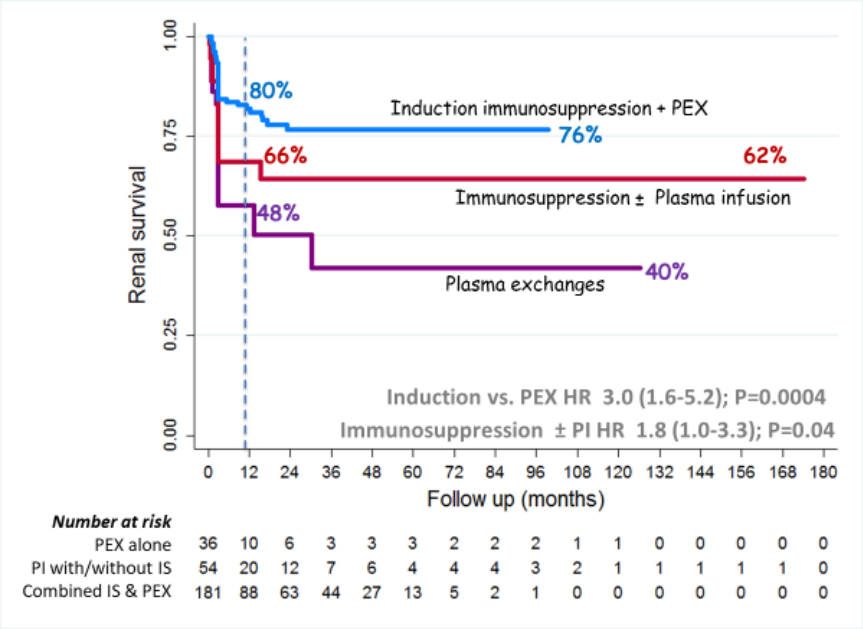
One-fourth relapses beyond 2-years

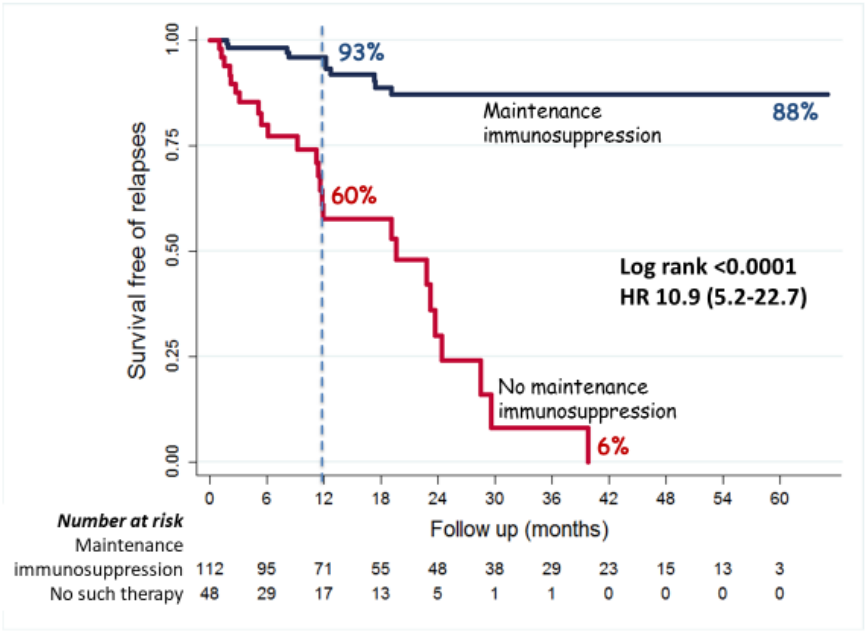
96 relapses in 83 (18.7%) patients (n=443)

Median time to relapse 11.3 (3-22.6) months



PEX + immunosuppression improve outcomes





Adverse outcome: 20% *vs.* 52% @ 1-yr with combined therapy vs. PEX

Relapse free: 88% *vs.* 6% with or without maintenance therapy

Kidney Int 2014;85:1151-60
Pediatr Nephrol 2015;30:451-7
Front Immunol 2019

Adverse outcome: Number needed to treat 2.6

Relapse: Number needed to treat 4.5

Improved outcomes in the past 8 years

Predicting adverse outcome: Prompt PEX & immunosuppression improves outcomes

Parameter (N=356)	Univariate		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, yr	1.02 (0.96, 1.1)	0.73	-	-
Duration of oliguria >7 days	2.47 (1.6, 3.9)	<0.001	1.74 (0.8, 3.8)	0.16
Neurological features	1.47 (0.96, 2.2)	0.07	1.89 (0.9, 4.0)	0.092
C3 <70 mg/dl	2.30 (1.4, 3.7)	0.001	1.66 (0.8, 3.6)	0.20
Anti-FH ≥8000 AU/ml	1.68 (1.1, 2.6)	0.021	2.23 (1.1, 4.5)	**0.024**
Requirement of dialysis	4.02 (1.8, 9.2)	0.001	1.68 (0.4, 7.6)	0.50
Plasma exchange <14 d	2.70 (1.5, 4.7)	0.001	2.60 (1.2, 5.7)	**0.017**
Time to PEX ≥14 d	1.64 (0.97, 2.8)	0.064	2.09 (0.9, 4.7)	0.071
Immunosuppression ± infusion	0.60 (0.2, 1.5)	0.27	-	-
PEX & immunosuppression	0.27 (0.2, 0.4)	<0.001	0.37 (0.2, 0.9)	**0.026**
Maintenance therapy*	0.07 (0.02, 0.3)	<0.001	0.02 (0.01, 0.4)	**0.011**

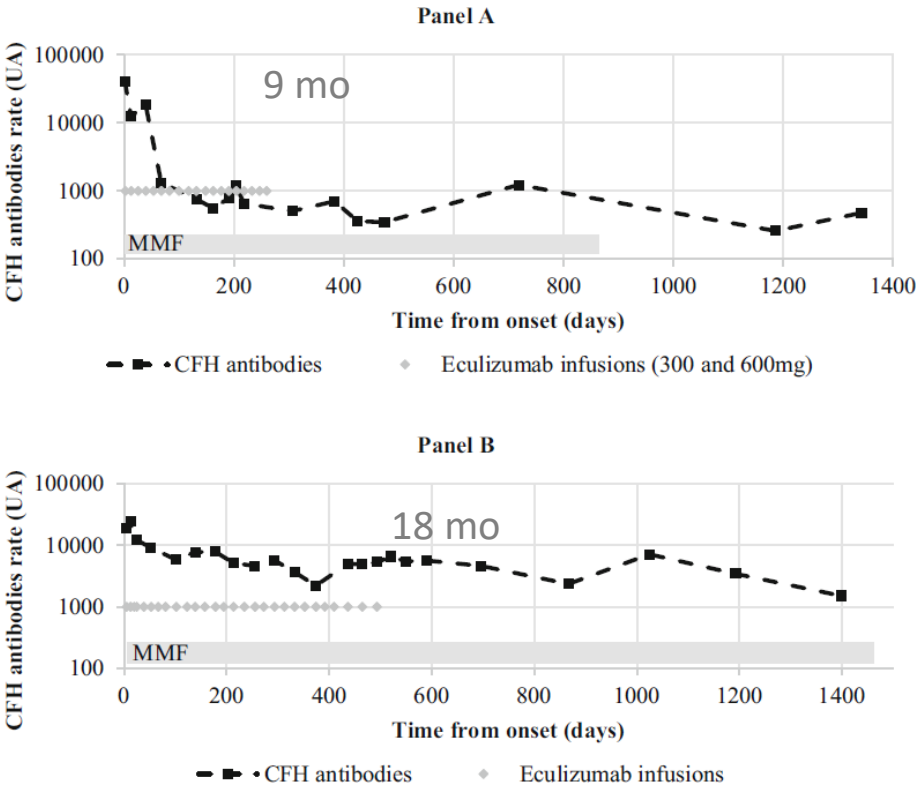
***Decreased risk of relapses**

Role of Eculizumab in anti-FH HUS?

Combining ECZ with immunosuppression

Two French children

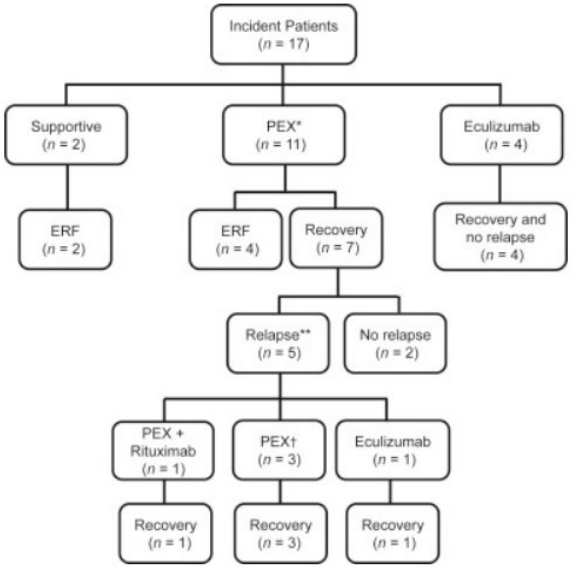
A. 4-yr-old boy; B. 10-yr-old girl

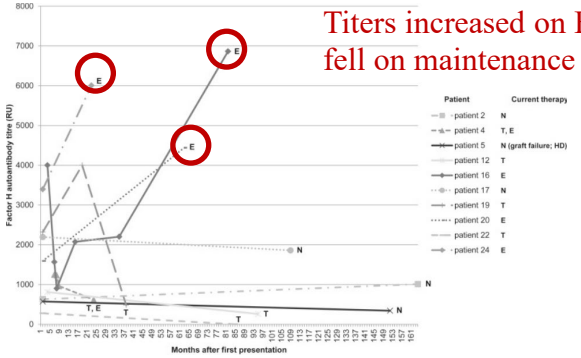


Pediatr Nephrol 2021; 36: 1647–1650

Therapy with ECZ alone

5 of 17 children in UK

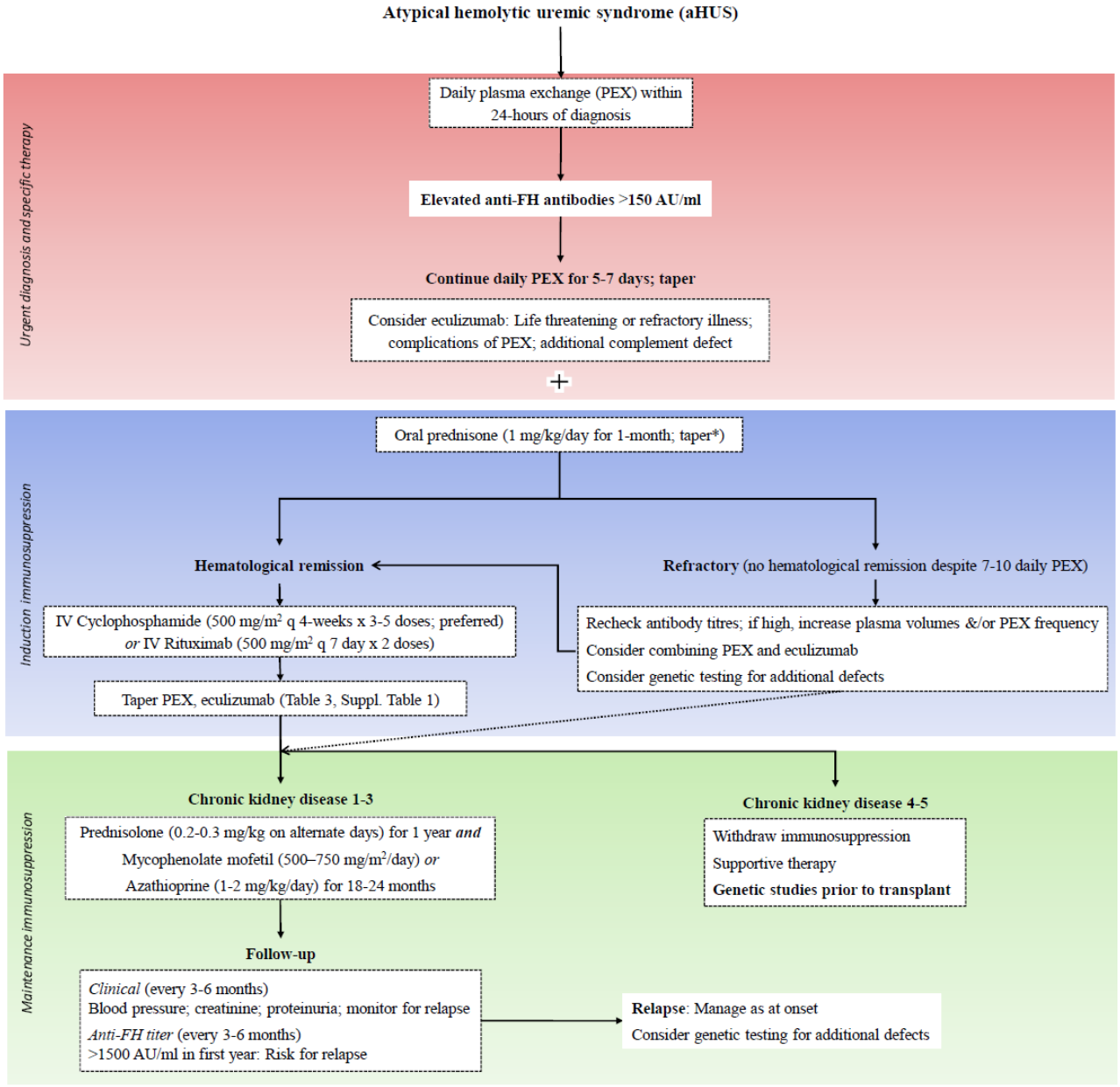




Titers increased on ECZ vs. fell on maintenance IS

Kidney Int 2017; 92:1261–1271

Anti-FH associated aHUS



Pediatric Nephrology
https://doi.org/10.1007/s00467-019-04233-7

CONSENSUS CONFERENCE

Hemolytic uremic syndrome in a developing country: Consensus guidelines

Anti-FH antibody associated HUS

Recommend PEX and immunosuppressive therapy — 1B

Do **not** recommend immunosuppressive agents without confirming presence of antibodies — 1D

Suggest PEX daily till hematological remission; taper 3-6 wk — 2D

Do **not** suggest infusions as substitute for PEX

Recommend frequent monitoring titers first 12-24 months — 1C

Therapy with eculizumab — 2C
- Lack of remission despite 5-7 PEX
- Life-threatening features
- Complications with PEX, access
- Defect in complement regulation

Therapy for anti-FH HUS

Plasma exchange

Initiate within 24-hr of diagnosis

1.5 *x* plasma volume for 5 days & until platelets >100,000/mm^3
Single volume PEX alternate days *x* 2 wk; twice weekly *x* 2-wk

Induction

Prednisone daily, alternate day

After daily PEX
IV Cyclophosphamide q 4-wk *x* 5

IV Immunoglobulin; IV Rituximab

Maintenance (1-2 yr)

Prednisone 0.1–0.2 mg/kg *x* 6-9 mo

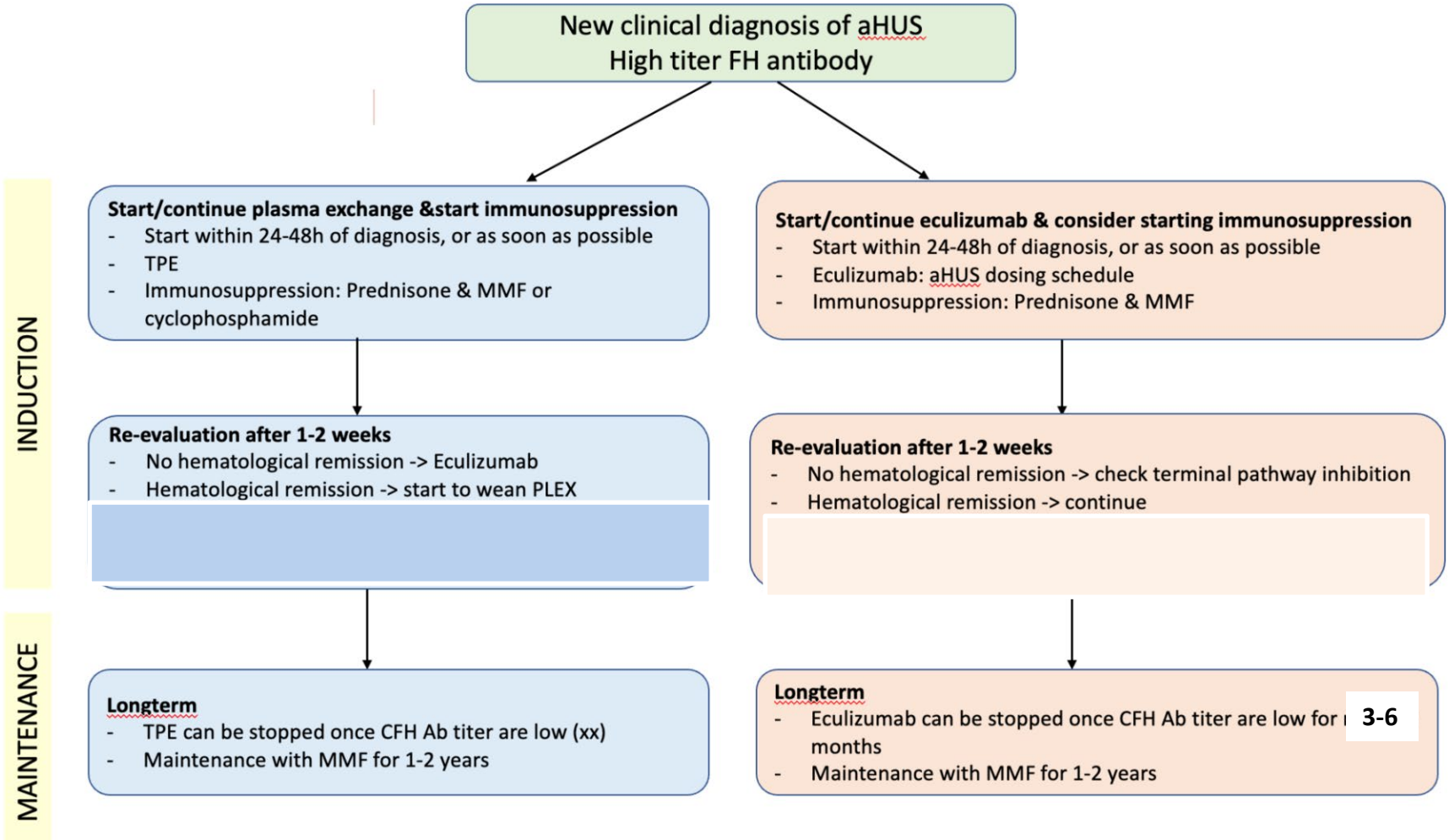
MMF *or* Azathioprine

Treat hypertension

Monitor antibody levels

P1-097: Abbreviated PEX in anti-FH associated aHUS

Anti-FH associated HUS, *relapse*



Summary, Credits

Common cause of atypical HUS in the sub-continent

Severe illness; diagnosis by ELISA

Prompt plasma exchanges & immunosuppression (IS)

Continue mIS for 1-2 yr to prevent (early) relapses

Eculizumab: Severe illness; issues with PEX; mutations

Outcome: Antibody level; prompt management

Department of Biotechnology, India: BT/PR14651/MED/30/566/2010
Indian Council of Medical Research: 5/7/1090/2013-RHN
Indo-French Centre for Promotion of Advanced Research: IFC/A/4703-1/2015/1562
Department of Science and Technology, India: EMR/2016/002781
Indian Council of Medical Research: 2021-RHN

Rapidly Progressive Glomerulonephritis

Anil Vasudevan

Professor and Head
Department of Pediatric Nephrology
St. John's Medical College Hospital
Bengaluru

Professor
Division of Molecular Medicine
St. John's Research Institute

2nd ANNUAL PEDIATRIC KIDNEY MEET, AIIMS Jodhpur
28-29, January 2023

Learning Objectives

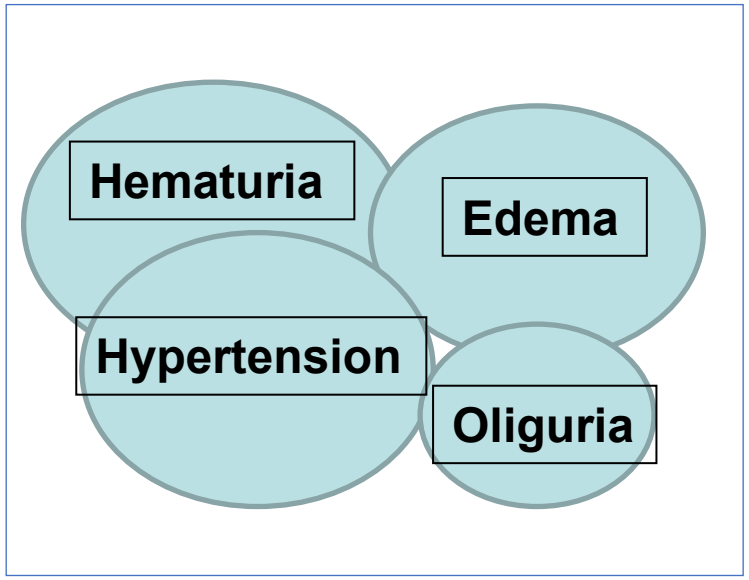
- **Review the definition and epidemiology of RPGN**
- **Identify the differential diagnosis and evaluation of RPGN**
- **To know the approach to treatment**
- **Describe the outcomes**
- **Possible therapies in future**

Case

- 12-year old girl presented with sudden onset of **vomiting and oliguria**. H/o fever, malaise and fatigue (x 1 month). No significant medical problems in the past.
- BP @ 95th centile; mild periorbital and pedal edema
- Routine urine analysis shows 2+ albumin and plenty of RBC's with occasional RBC casts
- Serum creatinine is 1.2 mg/dl

Clinical syndrome:?

What is Rapidly Progressive Glomerulonephritis (RPGN) ?



rapid loss of renal function

Days/weeks or months

usually, > 50% decline in eGFR within 3 months

Histologically characterized by glomerular crescent formation involving 50% or more glomeruli

RPGN ⟷ **crescentic glomerulonephritis**

Heptinstall RH: Rapidly progressive glomerulonephritis, in Pathology of the Kidney. London, J & A Churchill Ltd, 1966, pp 275-286

Couser WG Am J Kid Dis 11:449–464 1988

Confusing terminology and Differential Diagnosis

- ***Rapidly Progressive Renal Failure (RPRF):*** progressive kidney impairment over a period of few weeks that includes causes other than crescentic glomerulonephritis
  (**eg:** HUS, Acute interstitial nephritis, Acute Kidney Injury)

- **Acute Glomerulonephritis (AGN) with acute kidney injury (AKI):** kidney impairment over days that plateaus; quick recovery; no crescents on biopsy; may have additional causes for AKI

RPGN is a RENAL EMERGENCY

Epidemiology of RPGN

- Incidence of RPGN in children is not known (10.6 per 100,000 for systemic vasculitis including ANCA assoc. vasculitis)
- RPGN comprises 3- 5 % of unselected renal biopsies in children
- Crescentic GN contributes to 1.8% of all transplanted children – may be an underestimate

Covic et al Nephrol Dial Transplant 21: 419-24;2006
NAPRTCS 2006

Causes of RPGN

Immune complex Glomerulonephritis

Post Infectious – Post streptococcal nephritis, infective endocarditis, shunt nephritis, other bacterial infections, human immunodeficiency virus, hepatitis B and C

Systemic disease- Systemic lupus erythematosus, Henoch-Schönlein purpura

Primary GN - IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy

Panci-Immune Glomerulonephritis

Systemic vasculitis

Microscopic polyangiitis (MPA)

Granulomatosis with polyangiitis (Wegener's granulomatosis)

Eosinophilic granulomatosis with polyangiitis (Chugh Strauss)

Idiopathic/Renal Limited vasculitis

Medications - Penicillamine, hydralazine, Propylthiouracil

Anti GBM Glomerulonephritis

Good pasture's syndrome

Study	No of children (age range)	Pauci-immune (%)	Immune complex (%)	Anti GBM (%)	Others (%)
Niaudet et al (**1983**)	41	15.6	75.3	7.3	1.4
SWPNG (**1985**)	50 (1.7-17.2years)	14	74	6	6
Jardim et al (**1992**)	30 (3.7 -15.7 years)	16.6	63.3	6.6	13.3
Srivastava et al [1992]	43 (3.5 -14 years]	-	40	-	-
Jennette JC et (**2003**)	73 (1-20 years)	42	45	12	-
Dewan et al [2008]	22 [4-18 years]	1	86	9	-
Alsaad et al (**2011**)	37 (13.2± 5.2 years)	8.1	83.8	-	8.1
Sinha et al (**2012**)	36 (8-11.5years)	52.7	47.2	-	-
Piyaphanee et al (**2016**)	67 (2.5 -14.9 years)	7.5	88	1.5	3
Özlü et al [2016]	45 [5-16 years]	6.6	73	-	20

What are crescents?

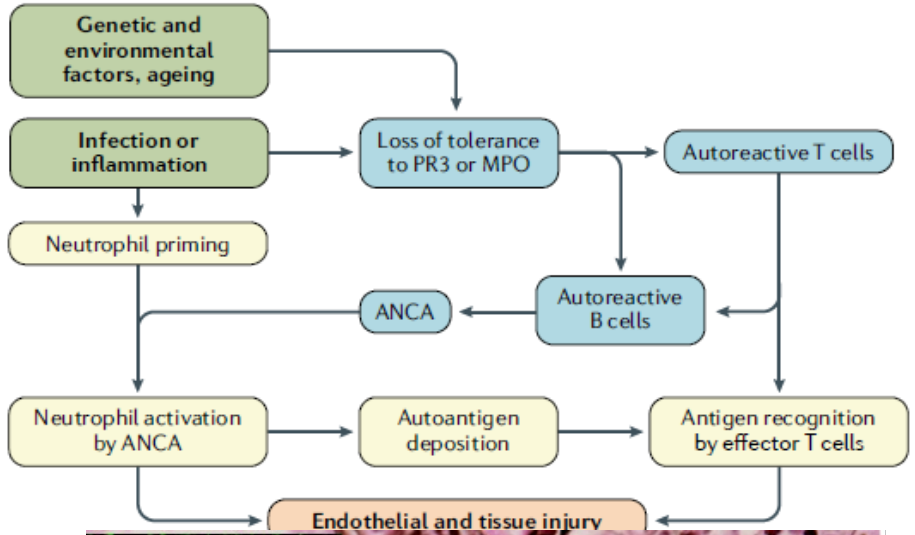
- Cellular crescents are defined as two or more layers of proliferating cells in Bowman’s space affecting 10%or more of the glomerular circumference
- Hallmark of inflammatory active glomerulonephritis and histologic marker of severe glomerular injury

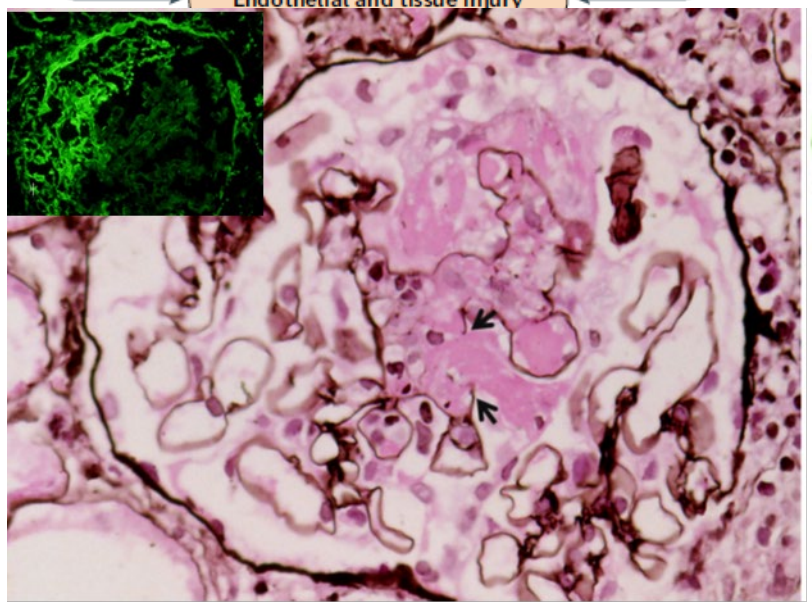
Pathogenesis of crescent formation in different glomerulopathies – three step process

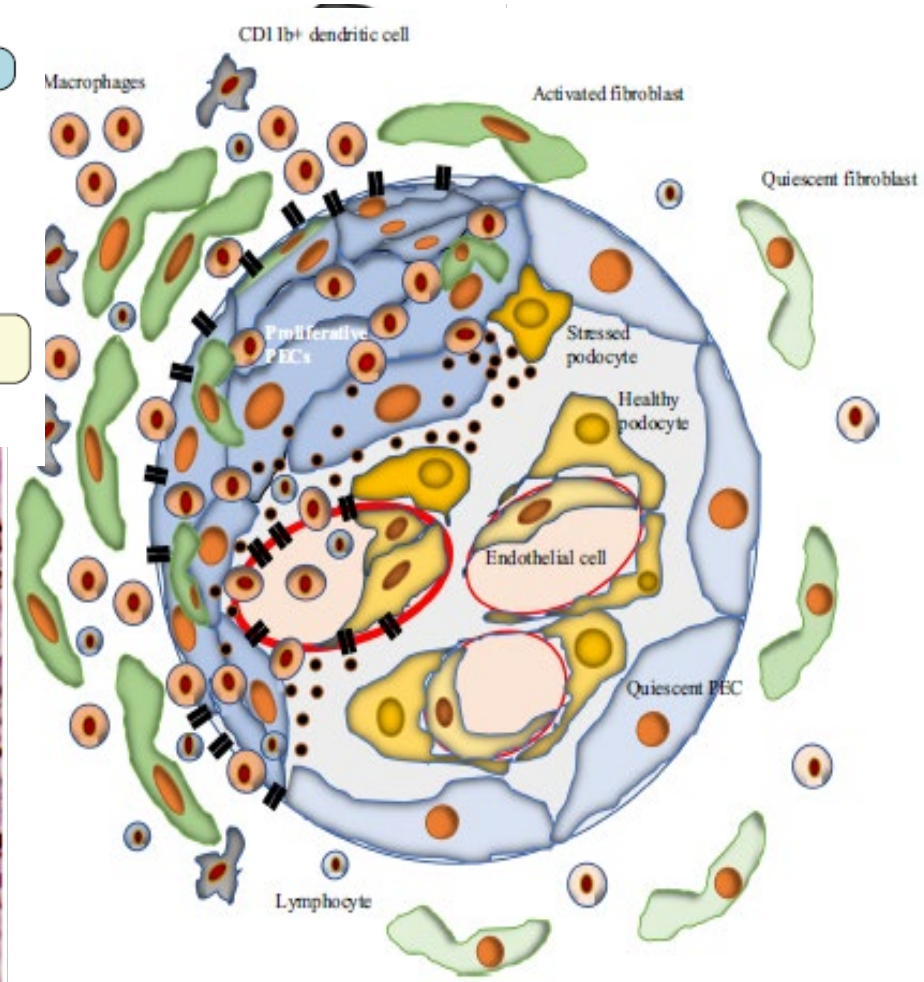
Damage of endothelial side of the glomerular filtration barrier

Vascular injury causing ruptures in the GBM

Formation of crescent





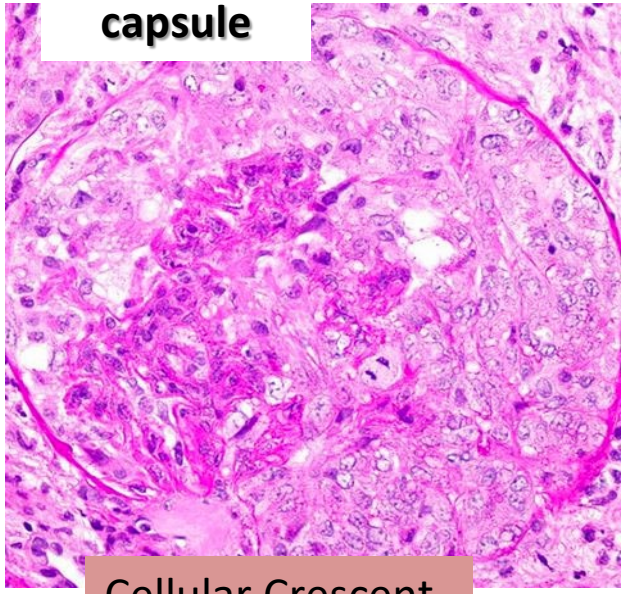


The fate of crescent

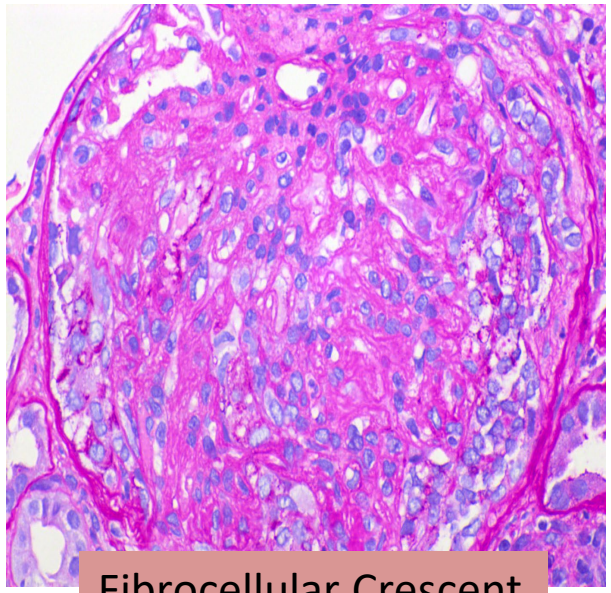
- Crescents progress or resolve may depend upon the integrity of Bowman's capsule and the cellular composition of the crescent

Intact Bowman's capsule

> 75% cells and fibrin

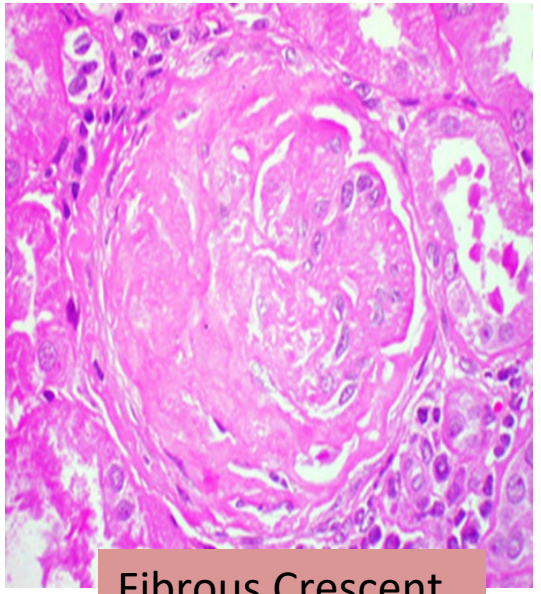


Cellular Crescent



Fibrocellular Crescent

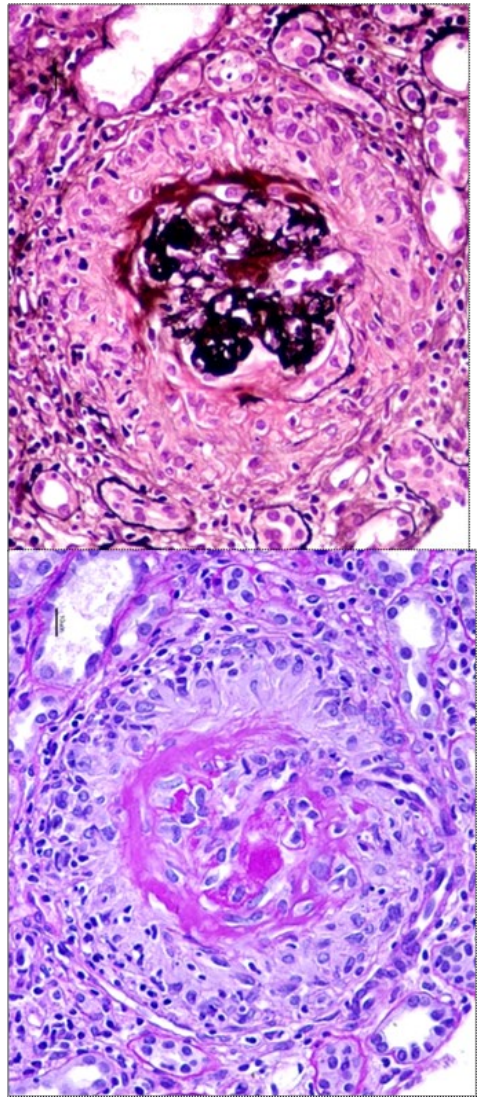
> more than 75% fibrous matrix



Fibrous Crescent

Ageing of Crescents [1 -2 weeks]

No Bowman's capsule

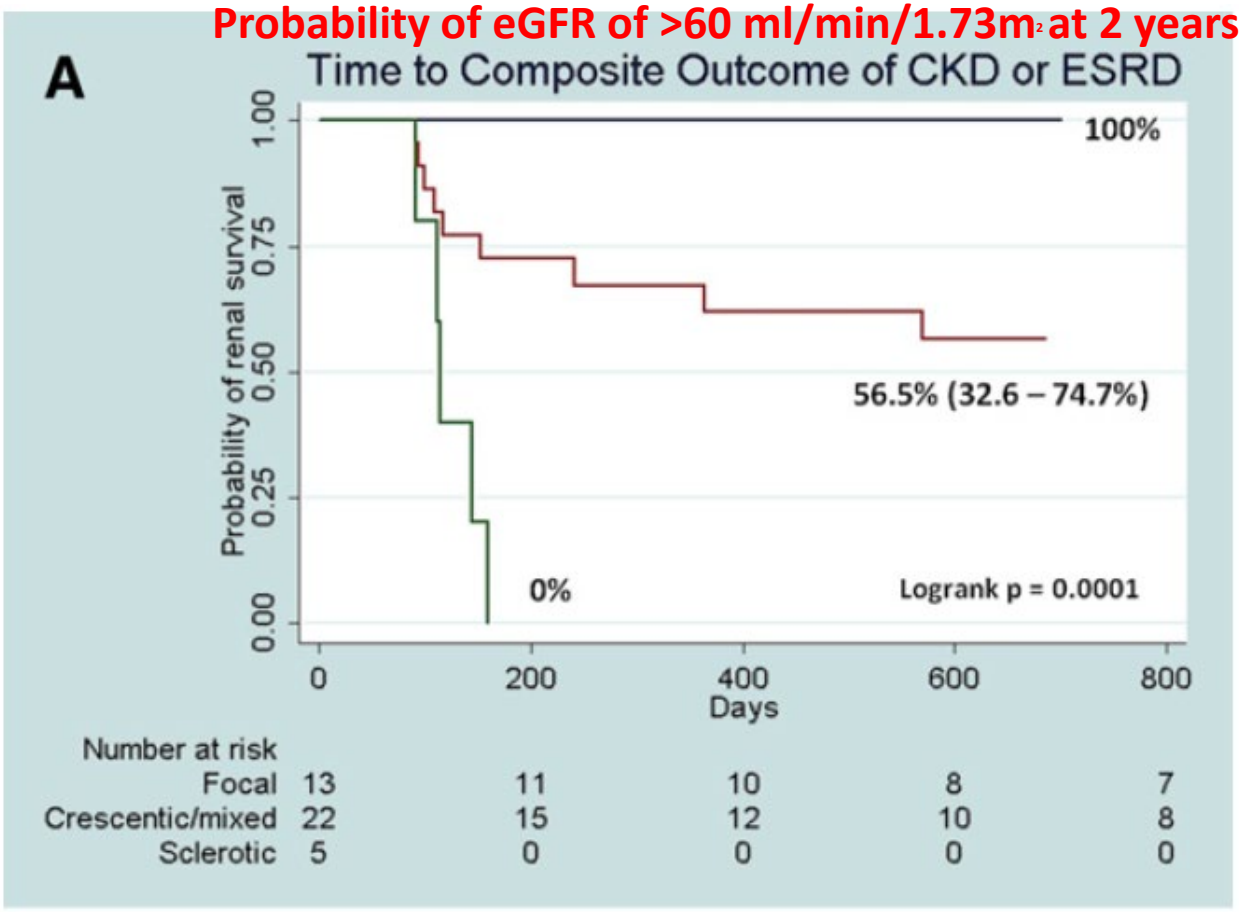


The New Histopathologic Classification of ANCA-Associated GN and Its Association with Renal Outcomes in Childhood

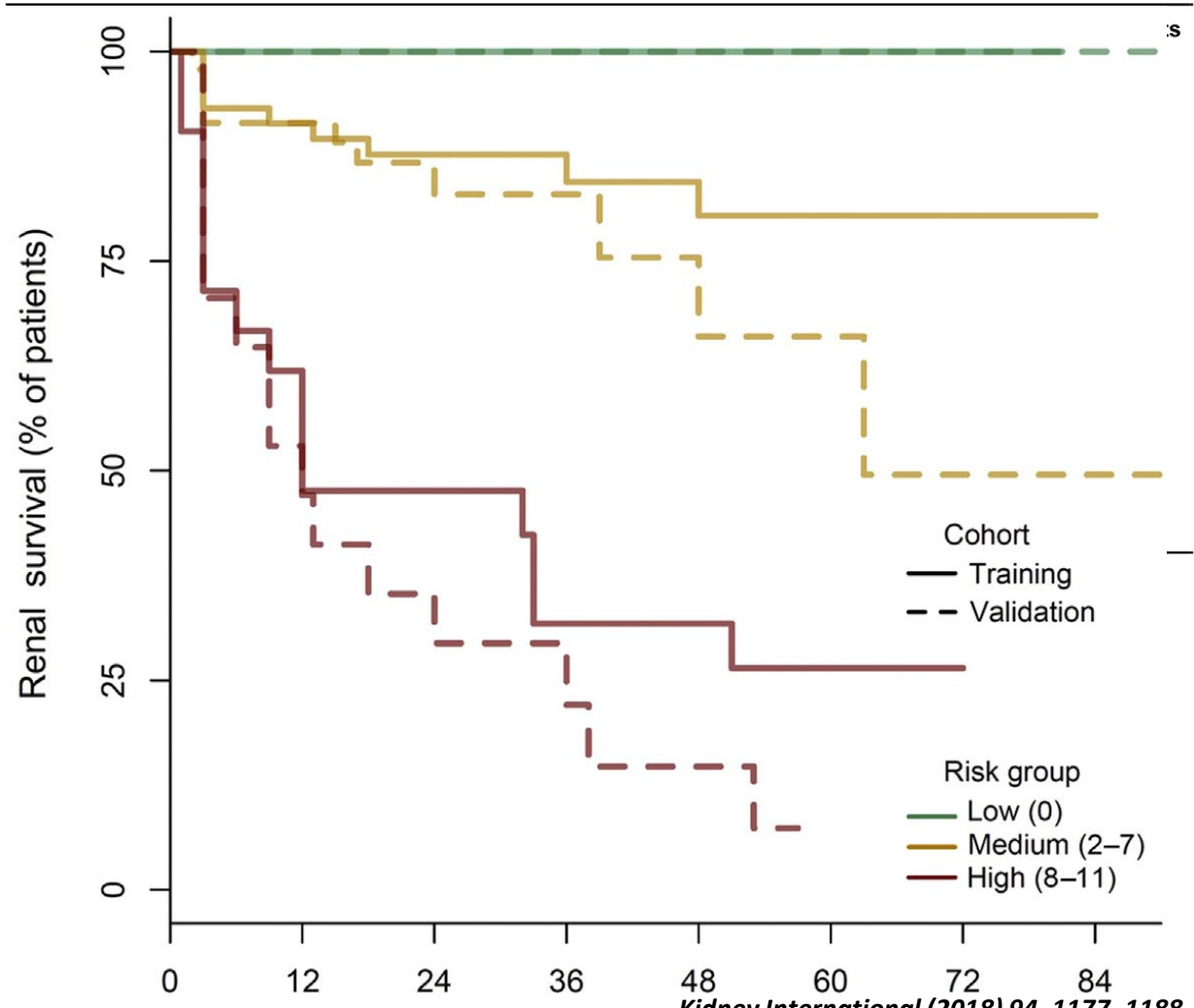
Damien G. Noone, Marinka Twilt,† Wesley N. Hayes,* Paul S. Thorner,‡§‖ Susanne Benseler,†§,¶ Ronald M Laxer,†¶ Rulan S. Parekh,*§¶** and Diane Hebert*¶*

40 children (70%female), followed for a median of 2.4 years

Probability of eGFR of >60 ml/min/1.73m^2 at 2 years



Risk group	Points
Low	0
Medium	2–7
High	8–11



Kidney International (2018) 94, 1177–1188

Case

- 12-year old girl presented with sudden onset of **vomiting and oliguria**. H/o fever, malaise and fatigue (x 1 month). No significant medical problems in the past.
- BP @ 95th centile; mild periorbital and pedal edema
- Routine urine analysis shows 2+ albumin and plenty of RBC's with occasional RBC casts
- Serum creatinine is 1.2 mg/dl at onset and was 2.6 mg/dl 7 days later

Clinical syndrome: RPGN

What additional history, physical examination investigations needs to be done ?

Diagnostic evaluation of children with RPGN

All children with RPGN
Complete blood counts, Peripheral smear, retic count
Blood urea, creatinine, electrolytes, calcium, phosphorus
Complement level (C3, C4)
ASLO, Hepatitis B antibodies, Anti-HCV antibodies, Blood culture
ANA, anti-ds DNA
ANCA
Renal Biopsy
In specific situation
Anti GBM IgG antibodies
Hepatitis serology, Bllod level of cryoglobulin
Imaging- Chest X ray, CT chest and sinuses

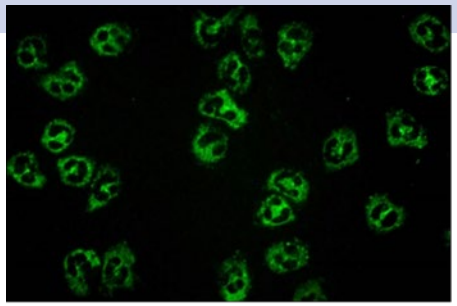
Clinical Relevance of ANCA Testing

When used together, **positive IIFA** with **positive ELISA** has a sensitivity of approximately 81% and a specificity of approximately 96% for pauci-immune crescentic GN

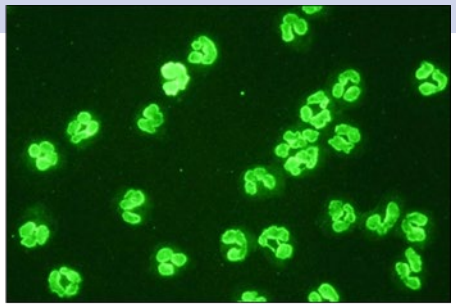
Use antigen-specific assays for PR3-ANCA and MPO-ANCA as the initial screening method when AAV is suspected, with IIF only performed if these assays are negative

An increase in ANCA titre during follow-up of patients with AAV, in the absence of signs of relapse, should prompt intensification of monitoring by measures such as urinalysis

Proportion of ANCA positivity in pauci-immune GN in children varies from 30 – 60 %



cANCA : PR3



pANCA : MPO

Tomasson G et al Rheumatology 51;2012: 100-109
Sinclair D et al J Clin Path 57: 2004; 131-134
Nat. Rev. Rheumatol. 13, 683–692 (2017).

Results in the case

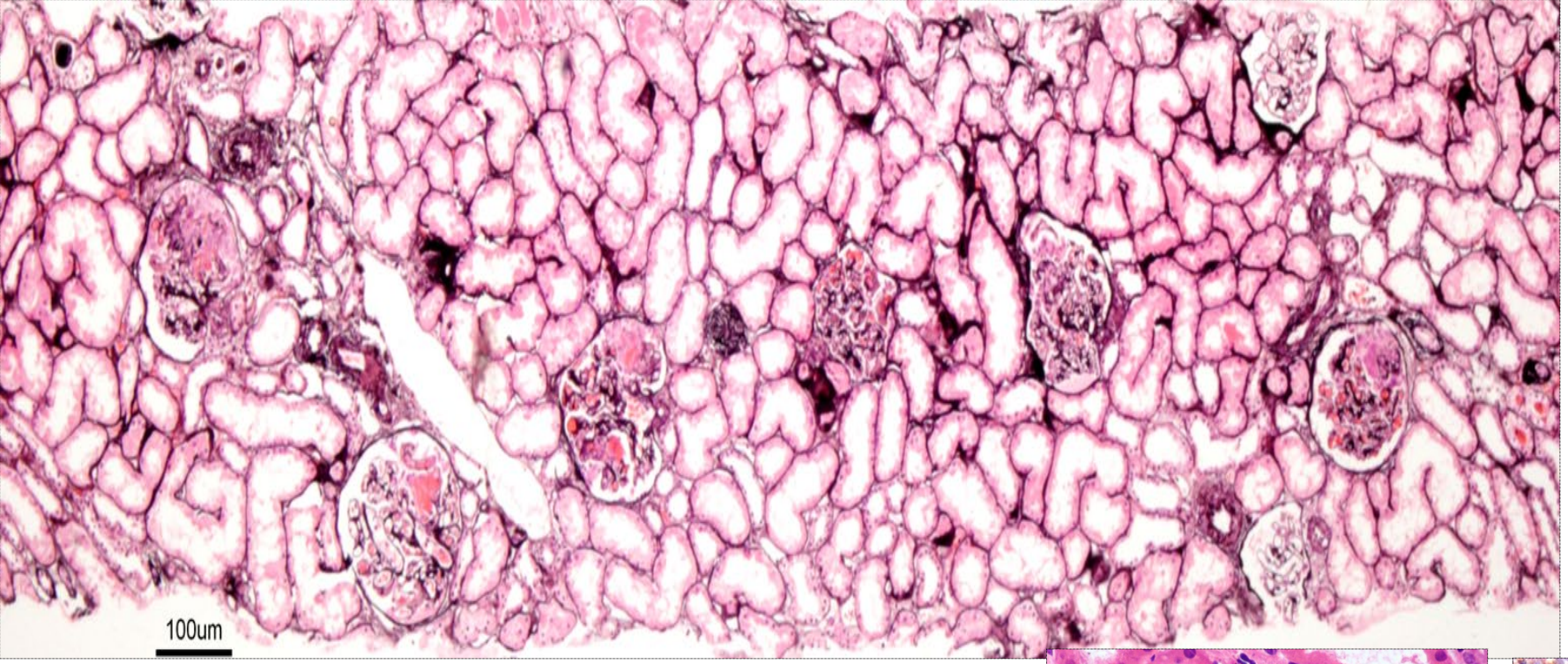
C3 is normal

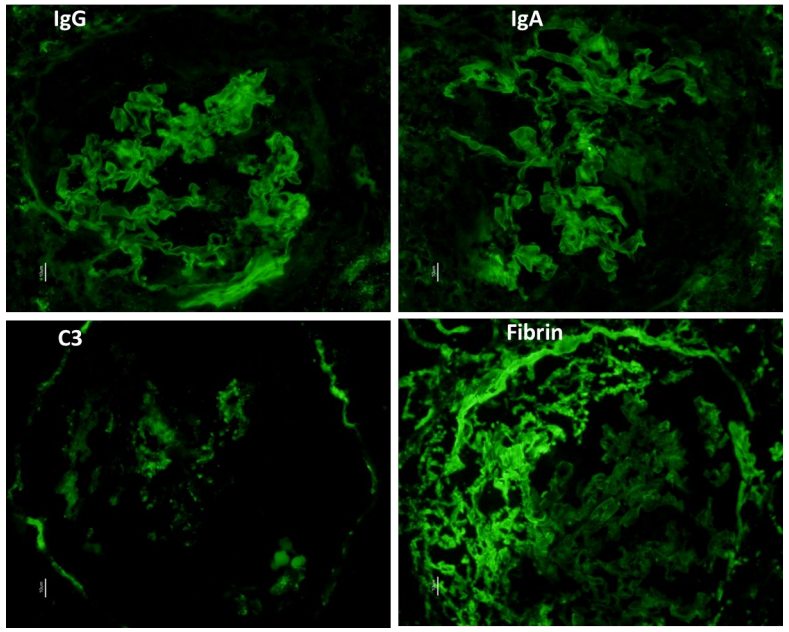
Serological studies show negative results for ANA, Anti-dsDNA

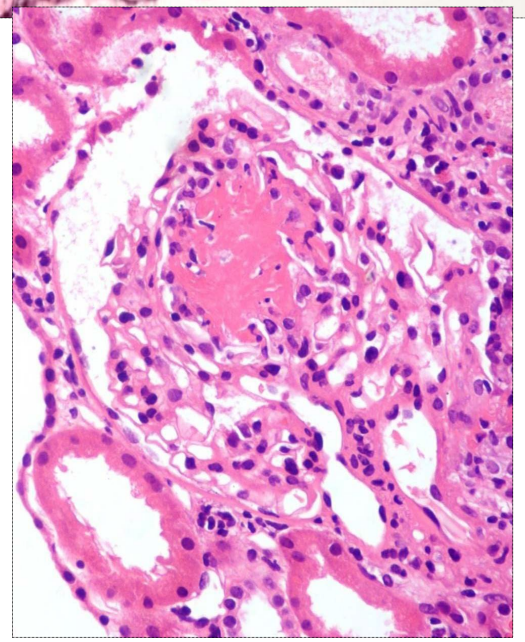
ANCA profile is positive for cANCA

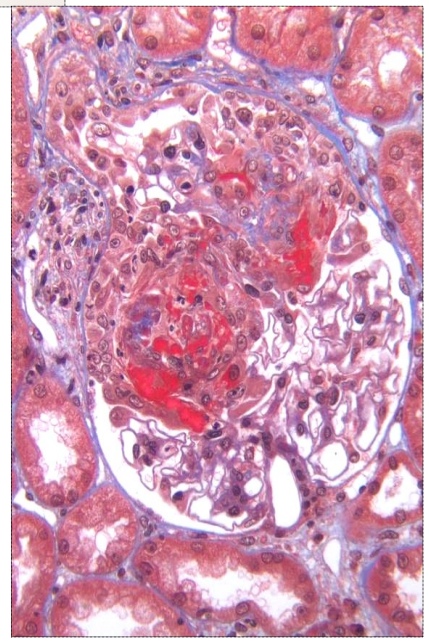
CXR normal, ENT evaluation normal

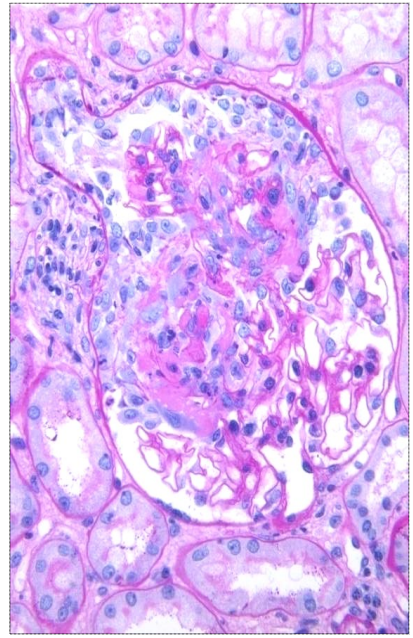
WHAT NEXT?


100um

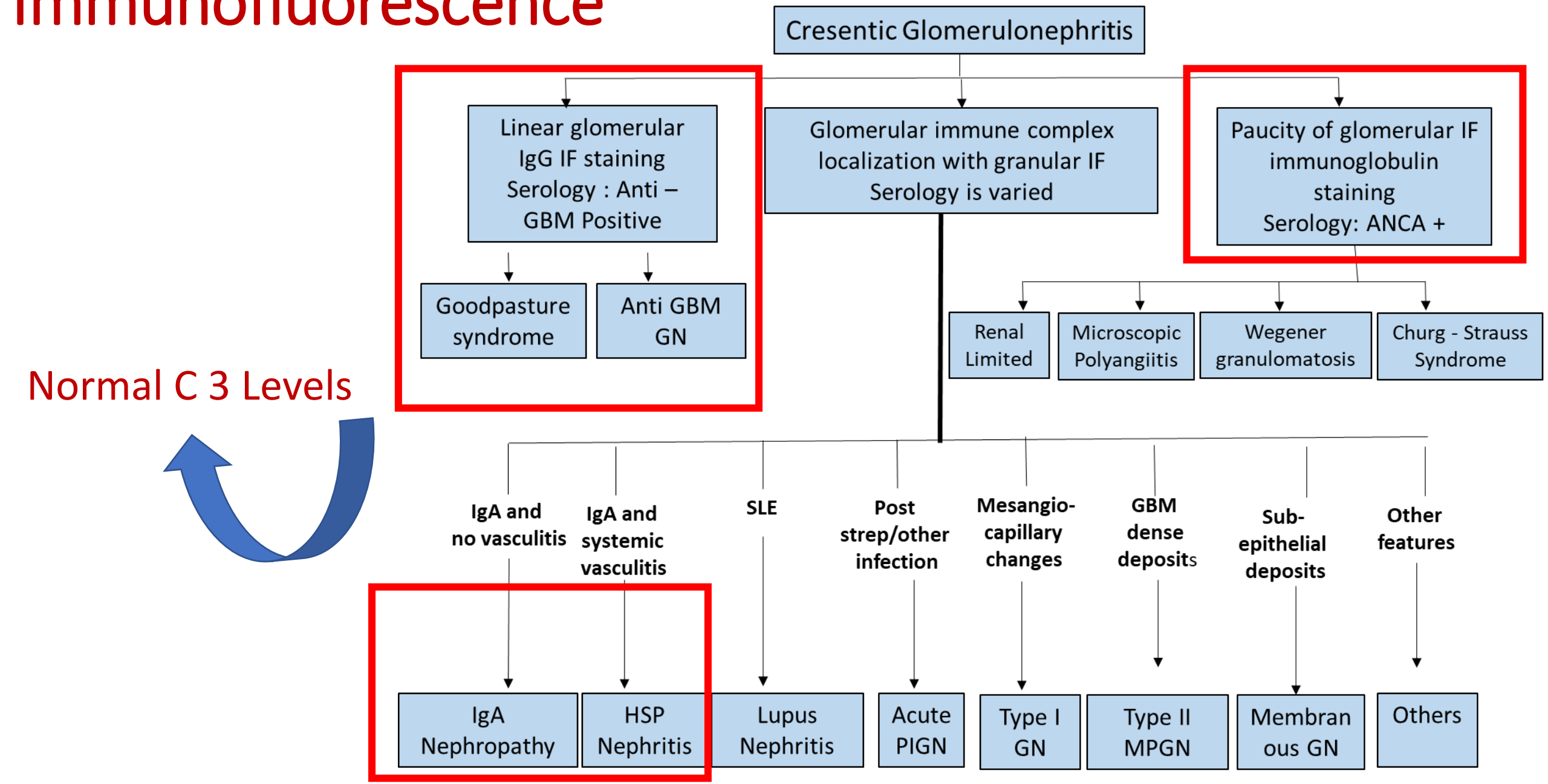

IgG
IgA
C3
Fibrin







Immunofluorescence



Types of crescentic or extra-capillary glomerulonephritis

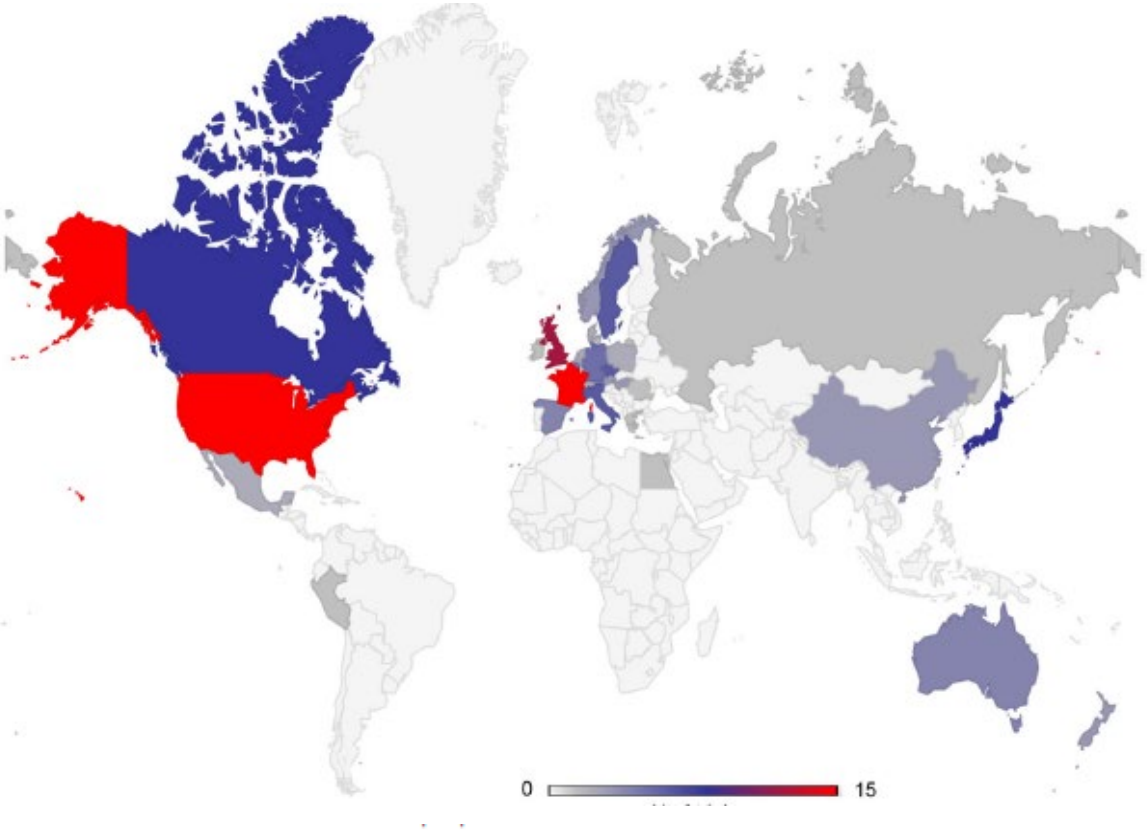
	Pauci immune GN	Anti-GBM	Immune GN
Glomeruli			
Crescents < 50%/>50 %	50/50	15/85	75/25
Ageing of crescents	Pleomorphic	Monomormphic / Pleomorphic	Monomorphic
Necrotizing lesion	+++	++	+
Rupture of GBM /Bow Capsule	++	++	- / + (rarely)
Periglomeurlar granuloma	++	++	-
Endocapillary proliferation	- / +	- / +	+++
Double contoured BM	-	-	++
Tubules			
Acute tubular injury	Severe, RBC casts +++	Severe, RBC casts +++	Severe, RBC casts ++
Interstitium			
Interstitial granuloma	++	- / +	-
Interstitial Inflammation	Severe / Lymphoplasmacytic	Severe / lymphocytic + PMN	Severe / lymphocytic + PMN
Vasculitis / Necrotizing arteritis	+	-	+HSP/Cryoglobulins
Immunofluorescence	- / (< 2+ C3 dep)	Linear IgG / (< 2+ C3 dep)	Granular Igs positive
EM	-	-	Deposits in Mes, SubEndo, SubEpi

Case : Diagnosis

- Diagnostic Categorization of “RPGN” based on clinical findings , serology and histopathology
- ANCA-associated vasculitis (AAV) or “Type 3 CGN”

ANCA associated Vasculitis - Renal limited?
MPA or GPA or Unclassified?

Evidence based treatment of RPGN



Population	*N* = 40
Age	
Adults and seniors (adults > 65 years)	33 (82.5)
Adults (18 to 65 years)	2 (5)
All ages	4 (10)
Children	1 (2.5)

Treatment generally categorized into two phases: induction and maintenance

Recommendations extrapolated from RCTs in ANCA associated vasculitis and trials chiefly in adults

Most trials not included severe kidney injury

Differences between guidelines (KDIGO and ACR)

Induction remission trials in ANCA associated vasculitis

Trial	Compared	Renal	Results	Rates of remission
CYCAZAREM (2003)	CYP vs CYP/AZA	Excluded those with S. Cr < 5.7 mg/dl	Equal remission	93%
CYCLOPS (2009)	IV vs oral CYP	Excluded those with S. Cr > 5.7 mg/dl	Equal remission	88.1% vs 87.7%
RAVE (2010)	RTX vs CYP Steroids for only 6 months	Excluded. S. creatinine ≥4.0 mg/dL	Equal remission: better response in relapsers and PR3-with RTX	64 % vs 53 % (off steroids by 6 months) 72% vs 42% in relapsers
RITUXIVAS (2010)	RTX/CYP vs CYP/AZA	All renal; Severe AKI included	Equal remission	76 vs 82%
MYCYC (2019) Included Children >6 yrs	MMF vs CYP	Excluded if GFR < 15 ml/min/1,73m2	Equal remission @ 6 months; More relapses with MPA	67% vs 61% 33% vs 19%
AVOCATE (2020) **Age ≥12 years**	AVOCOPAN vs Prednisolone with cyclophosphamide (oral or IV) followed by azathioprine or b) rituximab (four IV infusions).	Excluded if GFR < 15 ml/min/1.73m2	More remission with Avocopan @ 12 months	65.7 % vs 54.9% significant reduction in glucocorticoid-related toxicity and improvement in eGFR
PEXIVAS (2020) **Age ≥15 years**	plasma exchange as compared with no plasma exchange (with either cyclophosphamide or rituximab) Also low dose prednisolone vs standard dose	Excluded if GFR > 50 ml/min/1,73m2	Death or ESKD similar @12 months Low dose prednisolone non inferior to standard dose	28.4 % vs 31 %
PePRS (2022) **Age 6-17 years**	RTX (375 mg/m^2 body surface area) and glucocorticoids once per week for 4 weeks and maintenance Rituximab at clinicians discretion	No exclusion mentioned	Remission at 18 months	56%, 92%, and 100% of patients by months 6, 12, and 18

Role of Plasma exchange

MEPEX	GPA or MPA with biopsy-proven glomerulonephritis, SCr >500 µmol/l, ANCA$^+$ or ANCA$^-$	PLEX versus IV methylprednisolone as add-on to CYC and GCs	PLEX superior in rates of dialysis independence at 3 months and renal survival at 12 months	Long-term outcomes similar
PEXIVAS	GPA or MPA newly diagnosed or relapsing with renal involvement (eGFR <50 ml/min/1.73 m^2) or pulmonary haemorrhage, ANCA$^+$	1) PLEX as add-on to CYC or RTX and GCs 2) Low-dose GCs versus high-dose GCs, plus RTX or CYC	1) PLEX not superior 2) Low-dose GCs non-inferior, with fewer serious infections	Effects similar across subgroups

- No RCT addressing use of plasma exchange in children with RPGN

- The largest cohort described: n= 32 (over 10 years)

  ANCA associated ; PAN; HSP; Unclassified

  11 with renal involvement – GFR improved from 29 ml /min/1.73 to 69 ml/min/1.73

  Success also reported for HSP with Cresentic GN

Wright etal Eur J Pediatr 2006

Comparison of guideline recommendations

Disease Severity	ACR 2021	EULAR/ERA-EDTA 2016	KDIGO 2021	SHARE 2019
New onset of organ or life-threatening disease	RTX over IV CYP + Steroids@ IV CYP in children	IV CYP or RTX + steroids	IV RTX + steroids IV CYP if S.Cr > 4.0 mg/dl	IV CYP + steroids
Relapse of organ or life-threatening disease	Based on first line IV RTX or IV CYP+ steroids	Based on first line IV RTX or IV CYP+ steroids	-	Based on first line IV RTX or IV CYP+ steroids Also MPA an option
New onset or relapsing with serum high serum creatinine	Plasma exchange as adjuvant if risk if ESKD high Anti-GBM disease	S.Creatinine > 5.4 mg/dl	ANCA associated vasculitis with anti GBM disease	-
Maintenance regime	RTX over MTX/AZA; AZA over MPA + low dose steroids	AZA or RTX or MTX over MPA + low dose steroids	RTX or AZA + low dose steroids	AZA or MPA or RTX + low dose steroids
Refractory disease**	Switch IV RTX to IV CYP or vice-versa ± IV Ig	Switch IV RTX to IV CYP or vice-versa	-	Switch IV RTX to IV CYP or vice-versa
Duration of treatment	> 18 months (potentially longer)	24 months	18 months	12 months of sustained remission + 6 months of taper

INDUCTION

- **IV methylprednisolone 30mg/kg (max 1g)** once daily prednisolone (as above)
- IV cyclophosphamide 0.5-1g/m2 monthly (with mesna to prevent cystitis) for 6 months. Alternative is oral cyclophosphamide dosing (2-3mg/kg once daily for 2-3 months) **OR**
- Rituximab: 350mg/m^2/dose IV (max 1000mg)-for 4 doses weekly or 1 gm/m^2 2 doses

MAINTENANCE

Azathioprine (0.5-2.5 mg/kg once daily PO for 1 year or more) with **steroid tapering (low dose regime*) for at least 18 months**

Rituximab @ 6 , 12, 18, months

MPA in Immune complex associated RPGN

* 1 mg/kg (60 mg max; taper by 01-0.2 mg/kg to reach 10-15 mg by 6 mo; 7.5 by 12 m ; 5 mg by 18 mo)

Severe/ Refractory*

- **Switch Cyclophosphamide or Rituximab**
- **Plasma exchange:** 5 or 10-day course of 2-volume PEX with 5% Human albumin solution
- **IVIg: 2g/kg**

Relapse

Repeat Induction therapy

Switch to Rituximab if received CYP

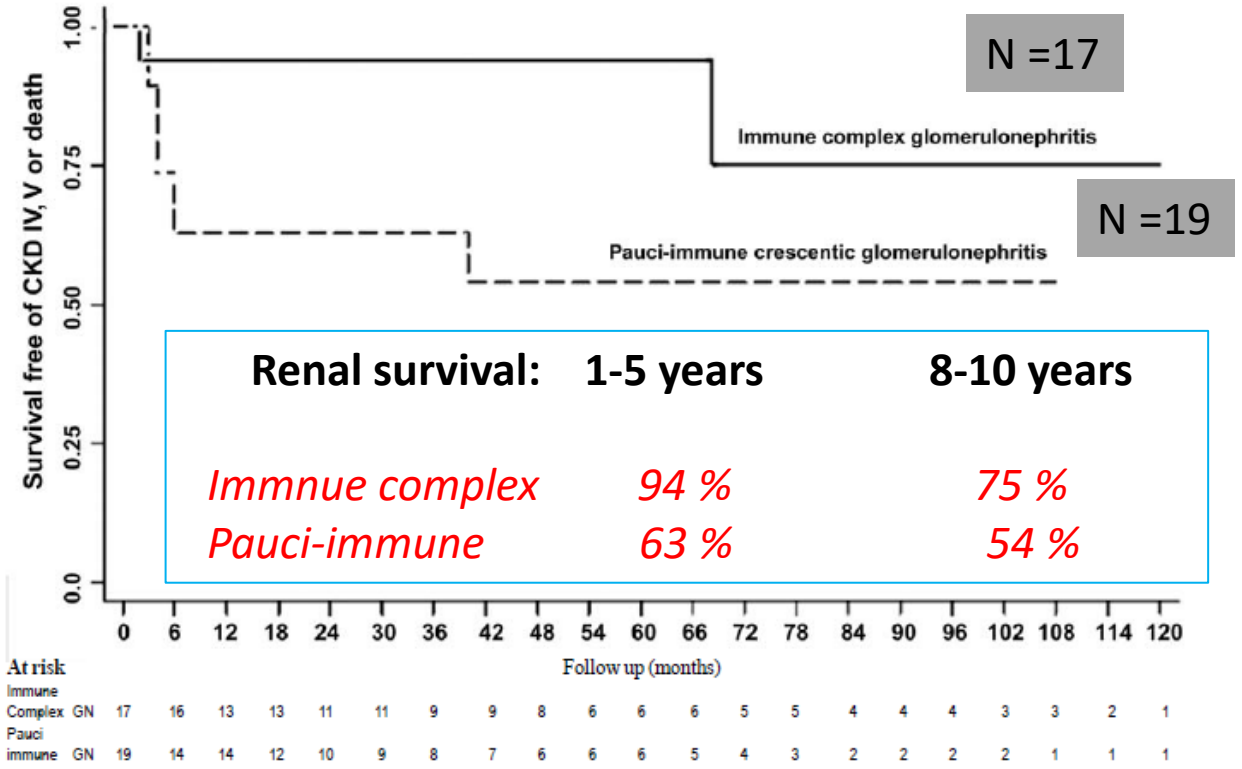
Newer therapies

- **Discontinue cyclophosphamide therapy after 3 months in patients who remain dialysis-dependent**
- **Use of Immunosuppression in PIGN needs more research**

Outcomes in RPGN

Cohort/Country (Year)	Number/Etiology	Median Follow up duration (months)	Kidney Outcome (%)	Study Duration
SWPNG/USA (1985)	50; SLE, PIGN, IgA/HSP Pauci-immune (20%) Anti-GBM 6%	24 (0.1 – 110)	CKD 1-4 - 12 ESKD - 48	-
Sinha et al/India (2012)	36; SLE, PIGN Pauci immune (53 %)	34 (19 -72)	CKD-4 and ESKD 30.6%	2001-2010
Piyaphanee et al/Thailand (2016)	67/ PIGN Pauci immune 7.5 % Anti-GBM 1.5 %	12 (0.1 -120)	CKD 41.8 ESKD 35.8	1997-2014
Rianthavorn et al/Thailand (2017)	72/SLE,IgA/HSP,PIGN Pauci-immune 11 % Anti-GBM 2 %	100 (IQR 42–224)	ESKD 25 1-year kidney survival rate 81.0% (95% CI 69.6–88.5).	1998 -2015
Maliakkal et al/USA (2020)	***305/***SLE, IgA/HSP, PIGN Pauci-immune 13% Anti-GBM 3%	36 (12-132)	ESKD 12% @ 1 yr; 16% at last follow up	2004-2019
Mayer et al/Germany (2020)	60/ IgA, SLE, HSP, PIGN Pauci-immune 17 % Anti-GBM 2%	10 (8 -14)	CKD (I-IV) 58 ; ESKD 8	1999-2015
Takahashi-Kobayashi et al /Japan (2020)	82/IgA/HSP, SLE Pauci immune 30% Anti-GBM 3 %	24	ESKD 23	1989 - 2007
Kaykı et al /Turkey (2022)	88/IgA/HSP, SLE Pauci immune 4 % Anti-GBM	38 $\pm$ 36 (mean;SD)	CKD 14 ESKD 17	2000-2016

Outcomes: Immune complex vs Pauci-immune



Renal survival:	1-5 years	8-10 years
Immnue complex	*94 %*	*75 %*
Pauci-immune	*63 %*	*54 %*

Prognostic factors: Serum creatinine at presentation; Percentage of normal glomeruli ; > 80 % Crescents; chronic lesions; Ratio of fibro-cellular to cellular crescents; Time lag between onset and diagnosis

Sinha et al Ind Pediatr 2013

Transplant in RPGN

13.8.1: We recommend delaying transplantation until patients are in complete extrarenal remission for 12 months. (*1C*)

13.8.2: We recommend not delaying transplantation for patients who are in complete remission but are still ANCA-positive. (*1C*)

- Renal function post-transplantation is also comparable to control subjects, with similar patient and graft survival rates seen at 1, 5 and 10 years of follow up
- Pooled analysis from 1999 described a recurrence rate of 17% among 127 patients; time to relapse -31 months (5 days to 13 years)
- ANCA positivity (MPO or proteinase 3) at time of KT did not affect (post-KT) recurrence rates

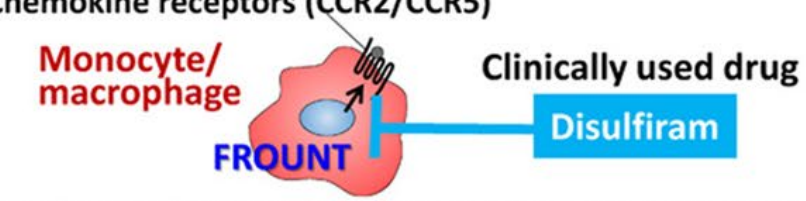
Future Studies

Inhibition of the chemokine signal regulator FROUNT by disulfiram ameliorates crescentic glomerulonephritis.

kidney INTERNATIONAL

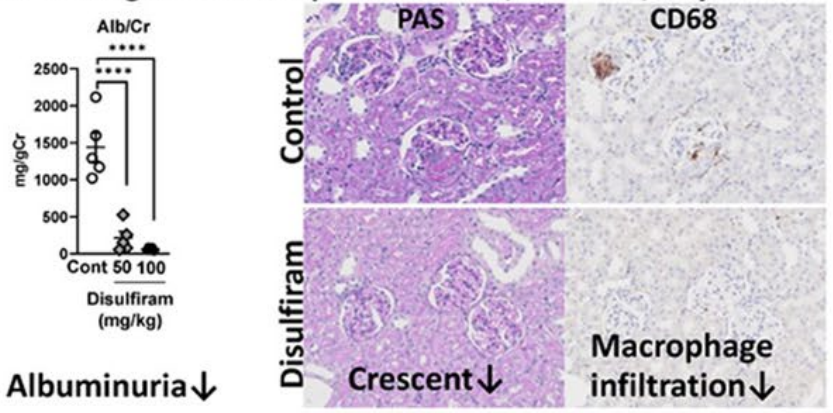
ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Chemokine receptors (CCR2/CCR5)



Disulfiram inhibits FROUNT-mediated chemotaxis signal and macrophage activation

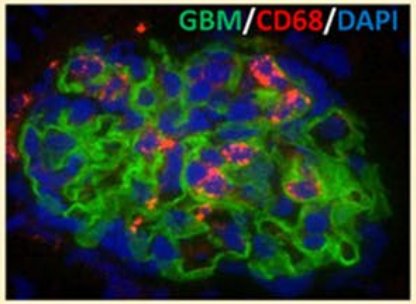
Anti-GBM glomerulonephritis model, WKY rat, day 7



Albuminuria↓

Monocytes/macrophages in anti-GBM glomerulonephritis

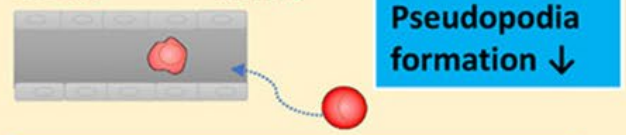
Recruitment/
Pseudopodia
formation



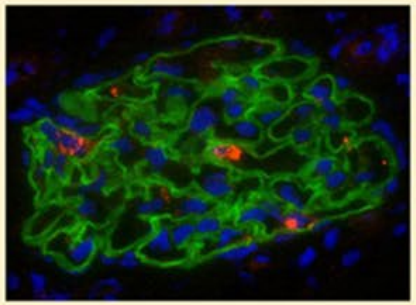
Activation and cytokine expression

→Glomerular damage and crescent

With disulfiram treatment



Recruitment↓
Pseudopodia
formation ↓



Activation ↓ Cytokine expression ↓

→ Ameliorated crescentic glomerulonephritis

Toda & Sawada et al, 2022

CONCLUSION

DSF is an effective and safe drug for treating glomerulonephritis that acts by modulating chemotactic responses and activation of monocytes/macrophages in the glomerulus.

Nat Rev Dis Primers **6**, 71 (2020)

Conclusions

- RPGN is rapid clinical progression of GN with pathologic finding of glomerular crescents and is a **renal emergency**
- Most common cause childhood RPGN is immune complex mediated GN
- The treatment strategy extrapolated from adult experience
- RPGN is associated with significant risk of ESKD and needs long term follow up


THANK YOU

Plasma Exchange

Therapeutic Apheresis: What's in a name?

A procedure to pass patient's blood through an extracorporeal medical device to separate its components in order to treat a disease

Therapeutic plasma exchange (TPE)	Patient's plasma is removed and replaced with a colloid (e.g., 4.5-5% albumin or plasma) +/- crystalloid solution
Plasmapheresis	Less than 15% of total plasma volume is removed without replacement with a colloid. Used to collect plasma for blood or plasma components
LDL apheresis	The selective removal of low-density lipoproteins (LDL) from the blood while returning the remainder. Is based on charge (dextran sulfate and polyacrylate), size (double-membrane filtration), or immunoadsorption (with anti-Apo B-100 antibodies). May use double filtration plasmapheresis (DFPP)
Immunoadsorption	Patient's plasma is separated and passed through a device that removes immunoglobulins by binding them to an active component. May use DFPP

Ideal target molecule for removal by TPE?

Identified etiologic agent or toxic substance

High molecular mass (≥15,000 D)

Slow rate of formation

Low turnover

Low volume of distribution (intravascular location)

Sieving coefficient
The ratio of solute concentrations between filtrate and blood sides of the membrane (calculated for large molecules)

SV ~=1: Molecular mass between albumin (66 D) to β-lipoprotein (2,400,000 D), up to cryoglobulins (900,000 D

SV low: For platelets (1–2 μm), very high molecular mass proteins (3,000,000 D) , e.g., vitamin B12, vitamin B_{12}

Effectiveness of extracorporeal therapies in relationship to the size of target substances

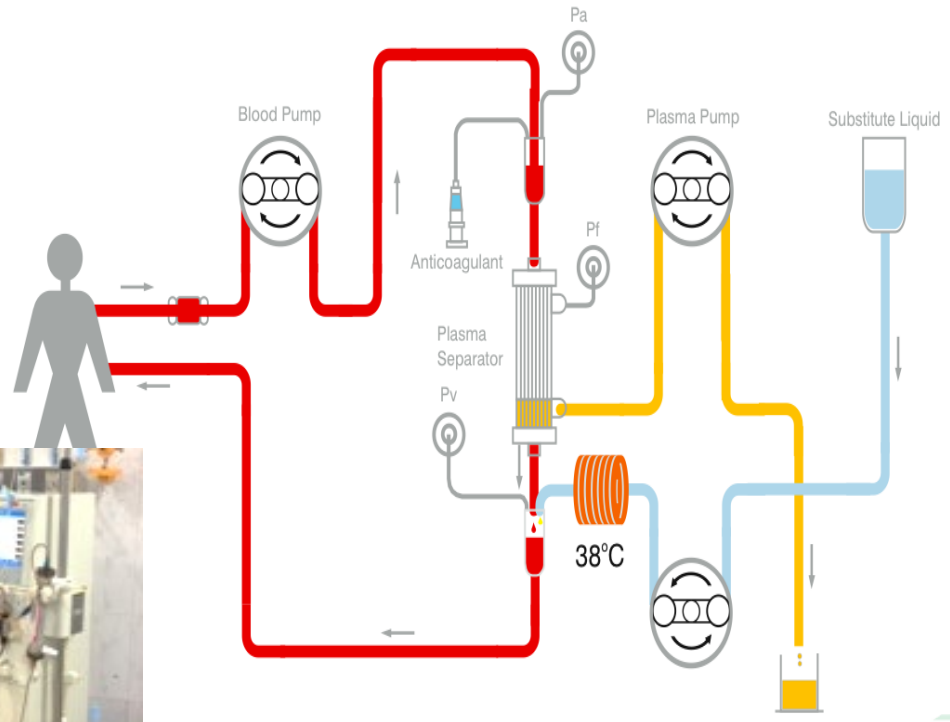
Examples of pathogenic target molecules for TPE in kidney disease (Category I, ASFA 2019)

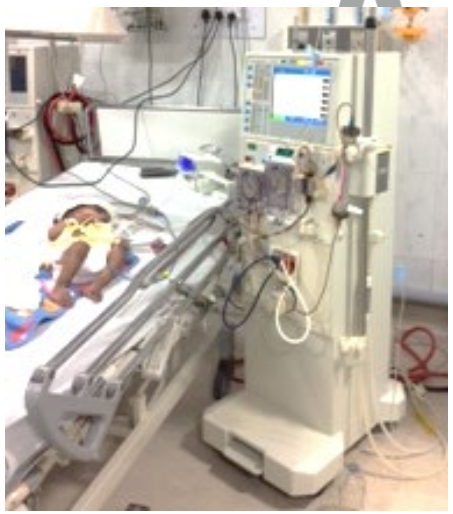
Kidney Disease	Target Molecule
Anti-GBM disease	Autoantibody reactive with type IV collagen; rapid decline in anti-GBM antibodies with TPE
Thrombotic thrombocytopenic purpura	Acquired autoantibody reactive with ADAMTS13 enzyme
Pauci-immune rapidly progressive GN	Autoantibodies against components of the cytoplasm of neutrophils-sequential ANCA levels have not been performed
Multiple myeloma	Free κ and λ light chains
Cryoglobulinemia	IgM anti-IgG antibody, immune complexes
Recurrent FSGS	Circulating glomerular permeability factor
Atypical HUS	Complement regulatory components or autoantibodies; not specifically shown
Kidney transplantation	Alloantibodies reactive with HLA antigens; donor specific antibodies

Membrane based therapeutic plasma exchange (mTPE)

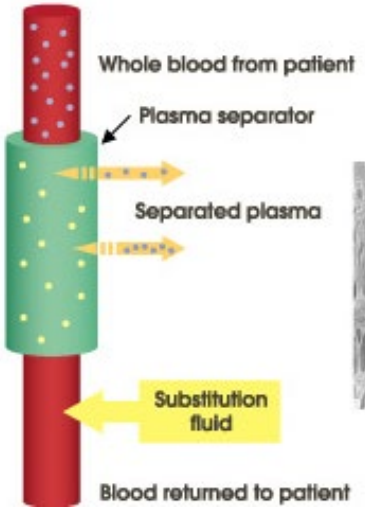
Membrane plasma separation (MPS)

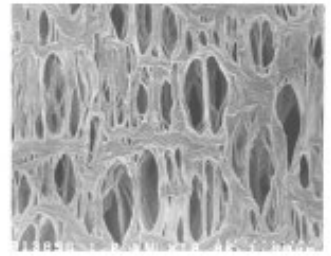
Circuit

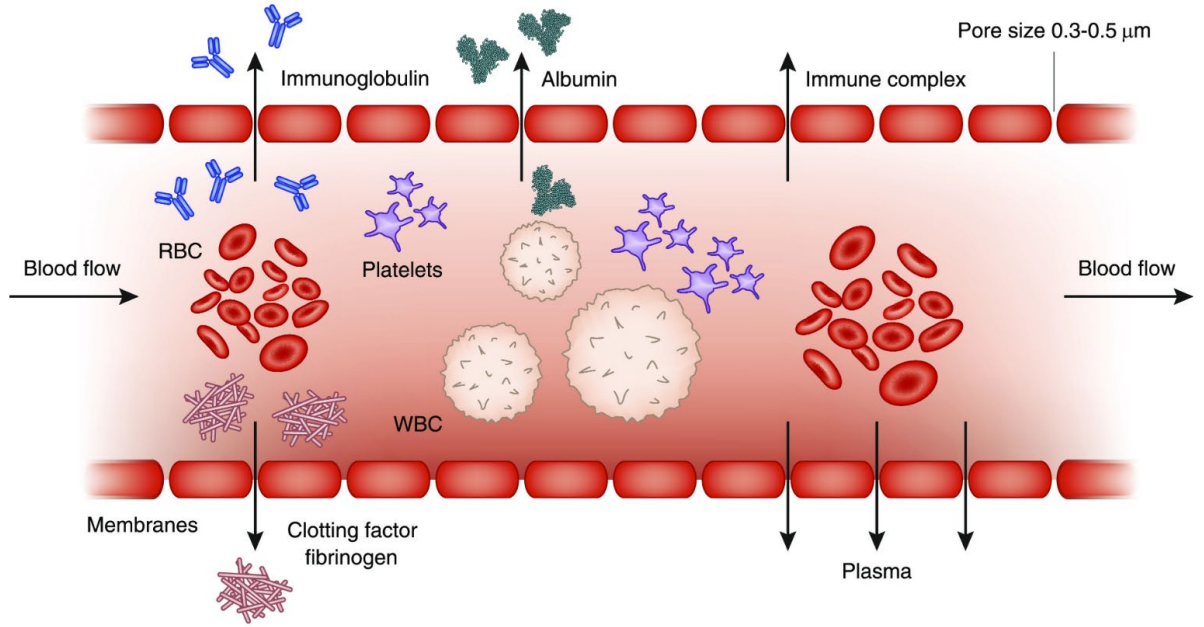




Hollow fibre plasma filter







Membrane based therapeutic plasma exchange (mTPE)

Vascular Access

Temporary central venous catheter

Weight	Line	Arterial	Venous
<7 kg	6.5F, 10 cm	0.75 ml	0.78 ml
7-30 kg	8F, 12.5 cm	0.88 ml	0.9 ml
>30 kg	11F, 12.5 cm	1.2 ml	1.26 ml

Tunnelled/cuffed central venous catheter (split-cath or double lumen)

Weight	Line
<20 kg	8-12.5 F; 19 cm or 23 cm
>30 kg	14 F; 24cm

Blood Flow Rate

Based on weight, about 3-5 ml/kg/min:

- <25 kg: 60-70 ml/min
- 25-50 kg: 100 ml/min
- >50 kg: 150 ml/min

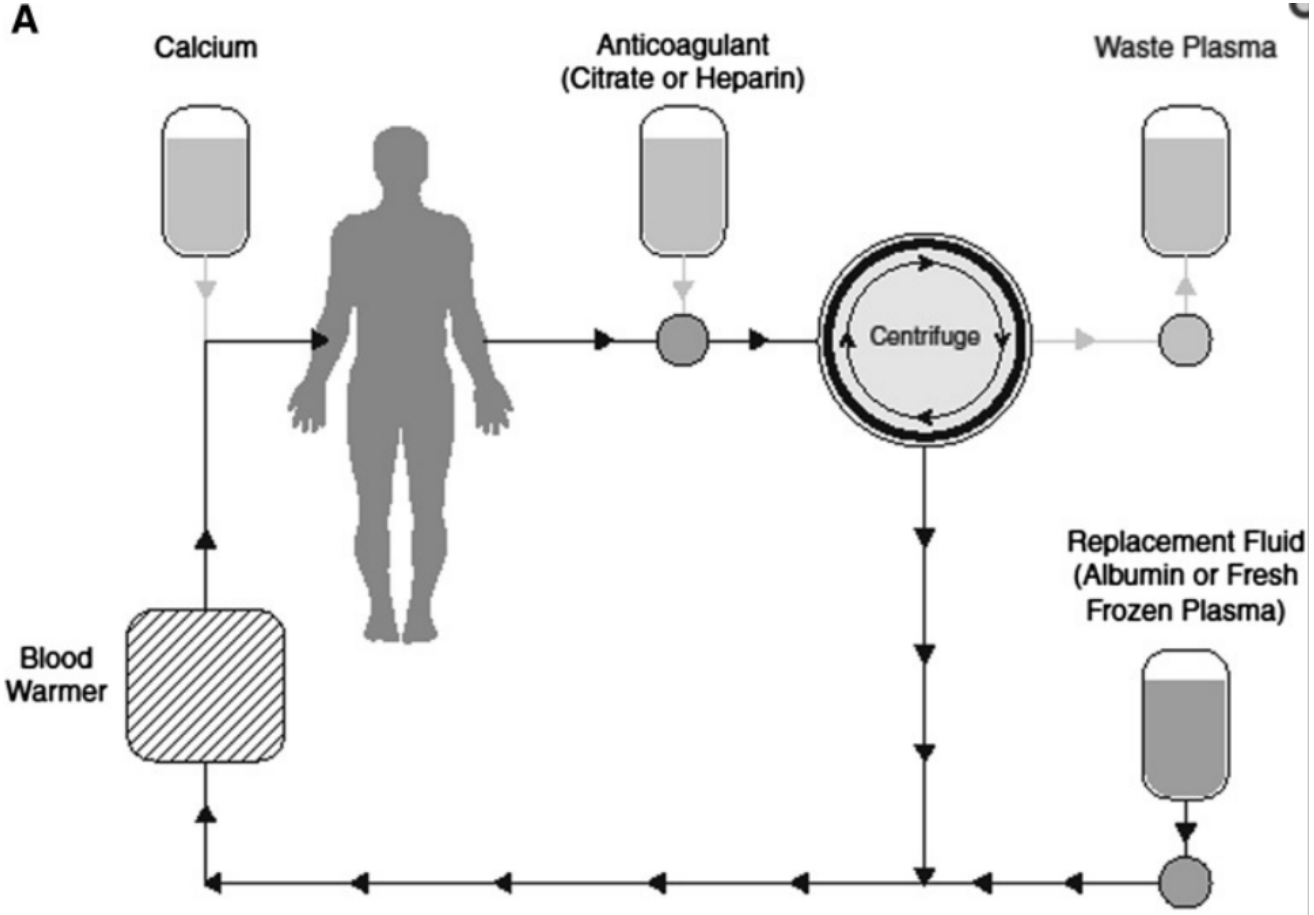
Run the blood pump for 4-8 minutes before the exchange starts

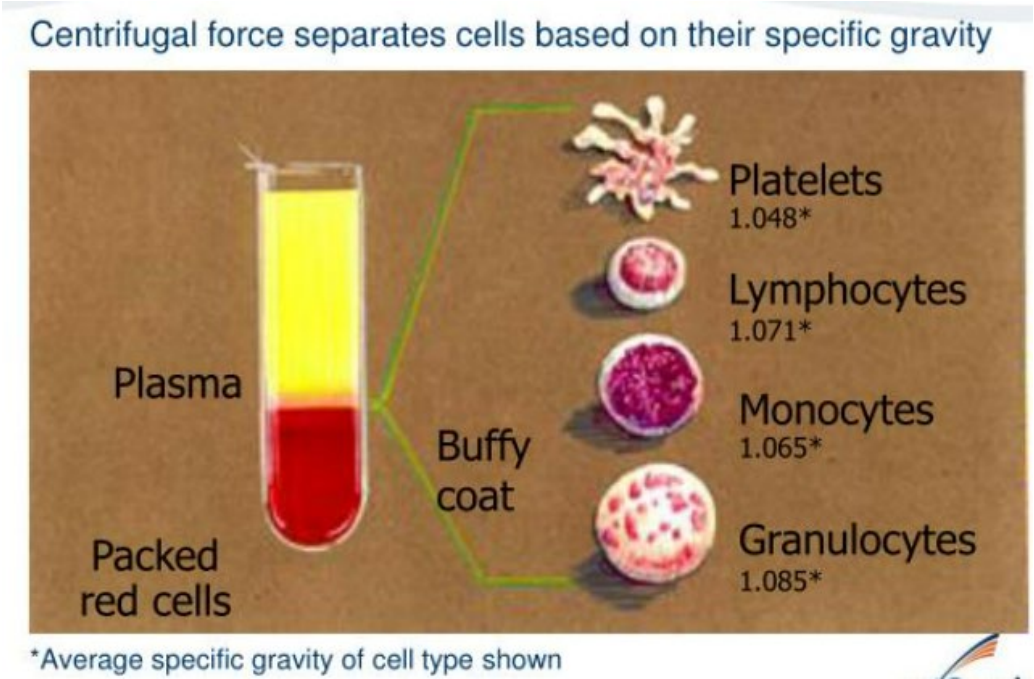
Filters for mTPE *versus* hemodialysis

Specification	TPE 2000 Filter	Asahi Plasmaflo Filter	F200NR Dialyzer
Indication for use	Plasma exchange	Plasma exchange	Hemodialysis
Molecular mass cutoff, D	3 million	Estimated ~ 3 million	Estimated 15,000
Pore size, µm	0.5	0.3	NA
Fiber material	Polypropylene	Polyethylene	Polysulfone
Hollow fibers	Yes	Yes	Yes
Surface area, m^2	0.35	0.5	2
Blood volume in filter, ml	55	41	113
TMP, mm Hg	120–193	100	600 (maximum)
Anticoagulation	Heparin (citrate rare)	Heparin (citrate rare)	Heparin
Blood flow rate, ml/min	100–250	Up to 200	Up to 600
Sieving coefficient			
Albumin	0.97	0.99	0
IgG	1	1	0
IgA	1	1	0
IgM	0.92	1	0
Sterilization	Ethylene oxide	γ-Ray	Ethylene oxide

Clin J Am Soc Nephrol 2020; 15: 1364-1370

Centrifugation based procedure





Membrane versus centrifugal TPE

Characteristic	Centrifugal TPE	Membrane TPE
Mechanism	Centrifugal force Particle density	Capillary membrane filter Molecular size
Blood flow (ml/min)	10–150	30-150
Plasma extraction (%)	80	30
Plasma removal (ml/min)	Variable	30
Anticoagulation	Citrate	Heparin
Separation	Specific gravity	Size
Blood volume in circuit (ml)	Approximately 180	125
Molecular weight cutoff (D)	N/A	3 million
Sterilization	γ Irradiation or ethylene oxide	Ethylene oxide
Fluid replacement	Albumin, fresh frozen plasma	Albumin, fresh frozen plasma

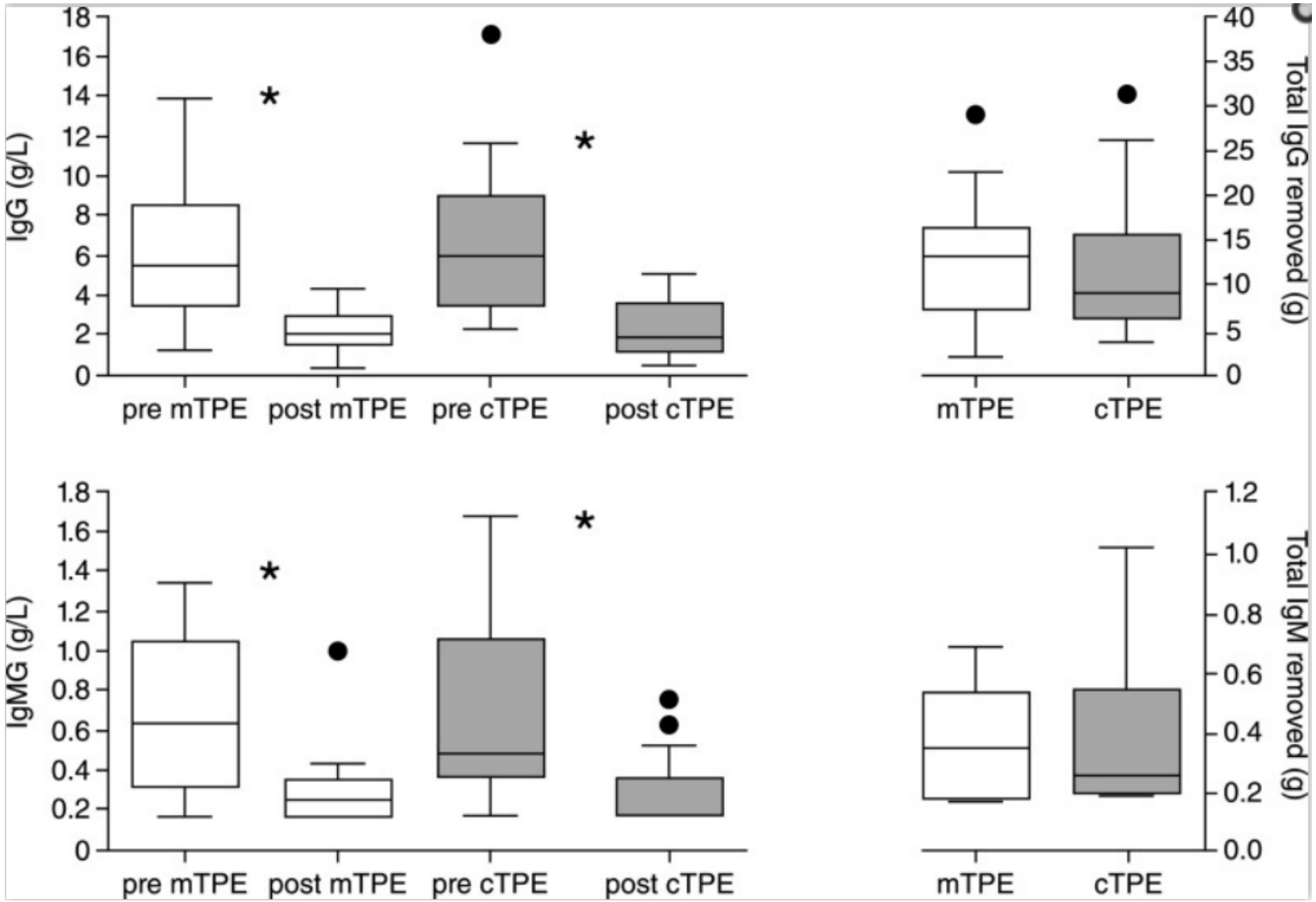
Transfusion medicine

North America

Nephrologists

Asia (Japan)
Europe (Germany)

Membrane versus centrifugal: No real difference



Blood constituents removed during TPE

Protein	Concentration , mg/ml	Mol weight × 10^3 D	% Intravascular
IgG (except IgG3)	12	150	45
IgG3	0.7	150	64
IgMa	0.9	950	78
IgA	2.5	160	42
IgD	0.02	175	75
IgE	0.0001	190	45
Albumin	45	66	44
C3	1.4	240	67
C4	0.5	200	66
Fibrinogen	3–4	340	81
Factor VIII	0.1	100–340	71
Antithrombin III	0.2	56–58	45
Lipoprotein cholesterol	1.5–2.0	1300	>90

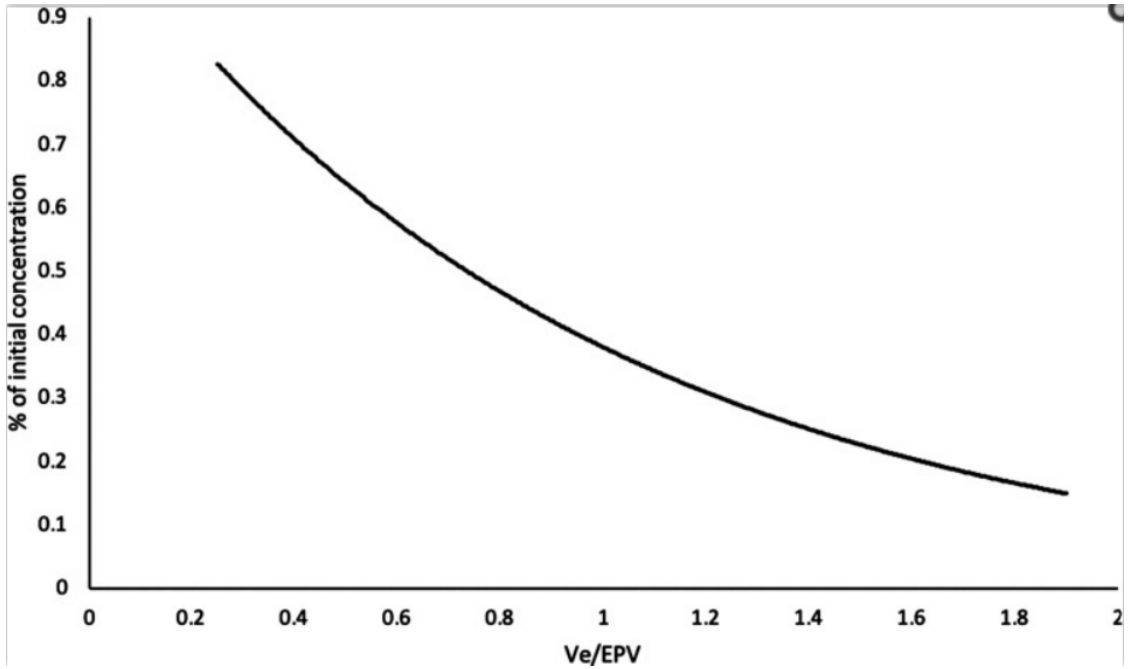
Removal, after one plasma volume exchange

Constituent	*Decrease*	*Recovery-48hrs*
Clotting factors	25 – 50%	80 – 100%
Fibrinogen	63%	65%
Immunoglobulins	**63%**	**45%**
Paraproteins	20 – 30%	Variable %
Liver Enzymes	55 – 60%	100%
Bilirubin	45%	100%
C3	63%	60 – 100%
Platelets	25 – 30%*	75 – 100%

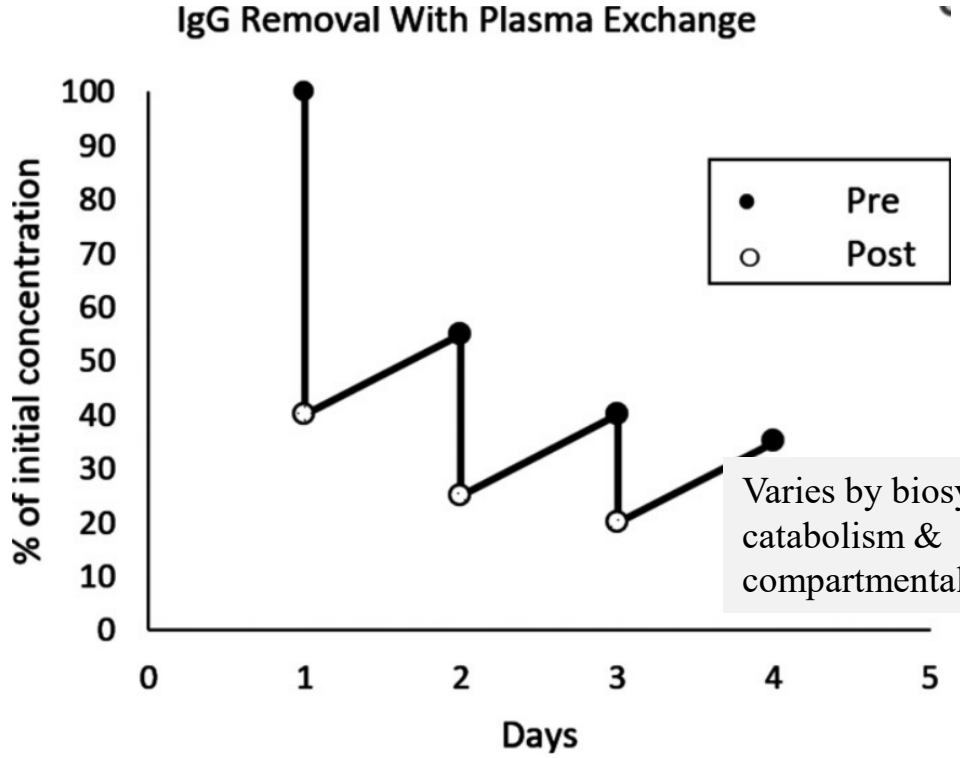
* Apheresis instrument dependent

Volumes of plasma exchanged and its frequency determines % removal

Plasma volume exchanged (V_e), estimated plasma volume (EPV), in relation to % reduction in initial concentration



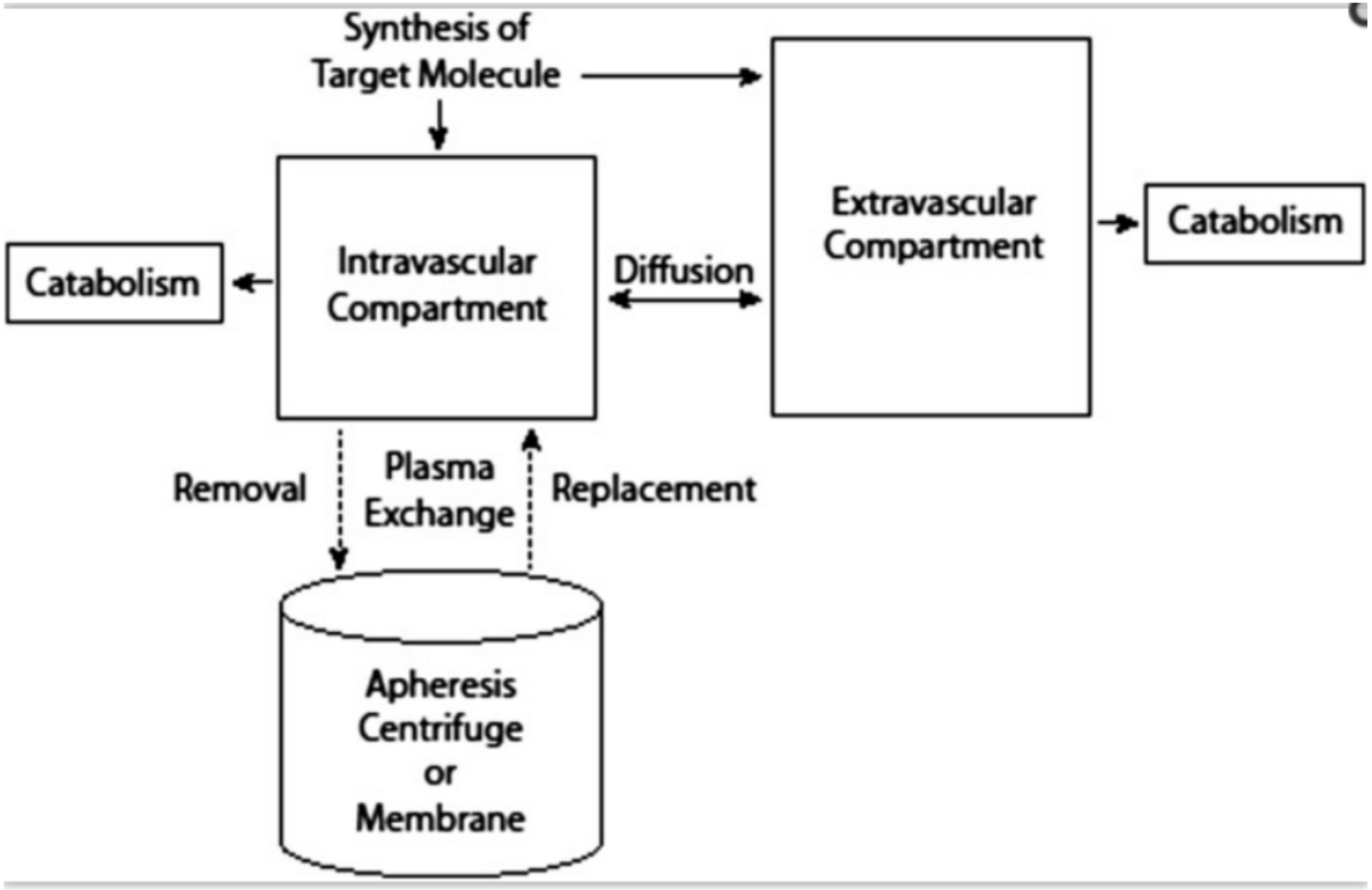
Changes in concentration while on daily therapeutic plasma exchange in relation to initial concentration



Varies by biosynthesis, catabolism & compartmental equilibration

One plasma volume exchanged (V_e/EPV=1) removes 63% of the pretreatment concentration
1.5 plasma volume exchanged (V_e/EPV=1.5) removes 80% of the substance

Relationships between internal compartmental & external distribution of target molecules during TPE



Indications of TPE

American Society for Apheresis (ASFA)

Category definitions for therapeutic apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviation: IRB, institutional review board.

Grading recommendations, strength, and quality of evidence

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Evidence Based Guidance: ASFA 2019

Disease	Indication	Apheresis modality	Category	Recommendation grade	Technical notes
FSGS	Recurrent in KT	PE/IAS	I	Grade 1B	Volume treated: TPE, LA, or IA with single use adsorbers: 1.0–1.5 TPV; IA with regenerative adsorbers: 2–3 TPV Frequency: Daily or every other day at initiation of treatment. Subsequent frequency and duration based on patient response.
	Recurrent in KT/Steroid resistant in native kidney	LDL-A	II	Grade 2C	
	Steroid resistant in native kidney	PE	III	Grade 2C	
Anti-GBM GN	DAH	PE	I	Grade 1C	Volume treated: 1–1.5 TPV Frequency: daily or every other day for 14 days or until anti-GBM undetectable
	Dialysis-independence	PE	I	Grade 1B	
	Dialysis-dependence (Cr > 5.7mg/dl)	PE	III	Grade 2B	
ANCA-associated disease	MPA/GPA/RLV				Volume treated: 1–1.5 TPV Frequency: daily in DAH, typically every other day in absence of DAH
	RPGN, Cr ≥ 5.7mg/dl	PE	**II***	**Grade 1B***	
	RPGN, Cr < 5.7 mg/dl	PE	IIII	Grade 2C	
	DAH	PE	I	Grade 1C	
	EGPA	PE	III	Grade 2C	
SLE	Severe complications	PE	II	Grade 2C	Volume treated: 1–1.5 TPV Frequency: LN or DAH: daily or every other day; Other severe complications: 1–3 times per week. Typically course of 3–6 PE is enough to see response

*ASFA 2020 update, after PEXIVAS was published

Evidence Based Guidance: ASFA 2019

Disease	Indication	Apheresis modality	Category	Recommendation grade	Technical notes
Thrombotic microangiopathy	TTP	PE	I	Grade 1A	Volume treated: 1–1.5 TPV Frequency: daily until platelets >150K and LDH near normal for 2–3 consecutive days, taper vs abrupt discontinuation practices vary
	STEC-HUS	PE/IAS	III	Grade 2C	Volume treated: 1–1.5 TPV Frequency: daily until improvement, no standardized approach exists
	Atypical HUS				Volume treated: 1–1.5 TPV Frequency: daily until clinical response (complement mediated), daily or every other day for coagulation mediated TMA
	Factor H autoantibody	PE	I	Grade 2C	
	CF gene mutations	PE	III	Grade 2C	
Kidney Transplant					
ABO incompatible	Desensitization	PE/IAS	I	Grade 1B	Volume treated: 1 - 1.5 TPV Frequency: daily or every other day, till antibody titer is less than critical threshold prior to KT
	AMR	PE/IAS	II	Grade 1B	
ABO compatible	Desensitization	PE/IAS	I	Grade 1B	Volume treated: 1–1.5 TPV Frequency: usually 5 or 6, daily or every other day
	AMR	PE/IAS	I	Grade 1B	

Non-renal indications: ASFA 2019

AIDP; Guillain-Barre syndrome	TPE TPE	Primary Treatment After IVIG	I III	1A 2C	1-1.5 1-1.5	EOD EOD	Albumin Albumin	5-6 10-14 5-6 10-14
AIHA; warm AIHA; cold agglutinin disease	TPE TPE	Severe warm AIHA Severe cold agglutinin disease	III II	2C 2C	1-1.5 1-1.5	D or EOD D or EOD	Albumin Albumin (at 37°C)	Titrate to response Titrate to response
Cardiac transplantation	TPE TPE	Desensitization Antibody mediated rejection	II III	1C 2C	1-1.5 1-1.5	D or EOD D or EOD	Albumin, plasma Albumin, plasma	Titrate to response
Catastrophic APL syndrome	TPE		II	2C	1-1.5	D or EOD	Plasma+/- albumin	1-3 weeks or longer; titrate
CIDP	TPE		I	1B	1-1.5	2-3/week	Albumin	Taper to 1/week - 1/month
Familial hypercholesterolemia	LDL apheresis LDL apheresis TPE	Homozygotes Heterozygotes Homozygotes & small blood volume	I II II	1A 1A 1C	1-1.5 1-1.5 1-1.5	Once/1-2 weeks Once/1-2 weeks Once/1-2 weeks	Not applicable Not applicable Albumin	Indefinitely; adjusted to reduce time averaged LDL cholesterol by ≥60%
Hemophagocytic lymphohistiocytosis; MAS	TPE		III	2C	1-1.5	D, titrated to response	Albumin, plasma	Uncertain; titrate to response
Immune thrombocytopenia	TPE IA	Refractory Refractory	III III	2C 2C	Unclear 2-4	Unclear Once/2-7 days	Not available Not applicable	Non-response to 6 sessions or platelets >50000/mm^3

Non-renal indications: ASFA 2019

Liver transplantation	TPE TPE TPE	Desensitization, ABOi LD Desensitization, ABOi DD AMR (ABOi & HLA)	I III III	1C 2C 2C	1-1.5 1-1.5 1-1.5	D or EOD D or EOD D or EOD	Plasma +/- albumin Plasma +/- albumin Plasma +/- albumin	Titrated to titre (to below critical threshold) Titrated to response	
NMDA-R antibody encephalitis	TPE		I	1C	1-1.5	EOD	Albumin	5-6	10-14
Poisoning	TPE	Drug overdose/poisoning	III	2C	1-2	D	Albumin, plasma	Till response; removal	
PANDAS	TPE	PANDAS exacerbation	II	1B	1-1.5	D or EOD	Albumin	3-6	7-14
TTP	TPE		1	1A	1-1.5	D	Plasma	D till remission; tapered	
Vasculitis	TPE TPE TPE TPE	HBV-PAN Idiopathic PAN EGPA Behcet's disease	II IV III III	2C 1B 1B 2C	1 1 1 1	2-3/week Unclear Unclear 1/week	Albumin Albumin Albumin Albumin	9-12 Unclear Unclear 5 sessions	
Wilson disease	TPE	Fulminant	I	1C	1-1.5	D or EOD	Plasma, albumin	1-11 sessions; titrate to response	

Calculating plasma volume

	Neonates	Children	Adolescents
Total blood volume, ml/kg	100	80	60
Extracorporeal volume (10%), ml/kg	10	8	6
Plasma volume (=2/3 blood volume), ml/kg	67	54	40
1.5 plasma volumes, ml/kg	100	80	60

Usually 1-1.5 plasma volumes are replaced in TPE and DFPP

The extracorporeal volume, i.e., the total blood circuit, should not exceed 10% of blood volume

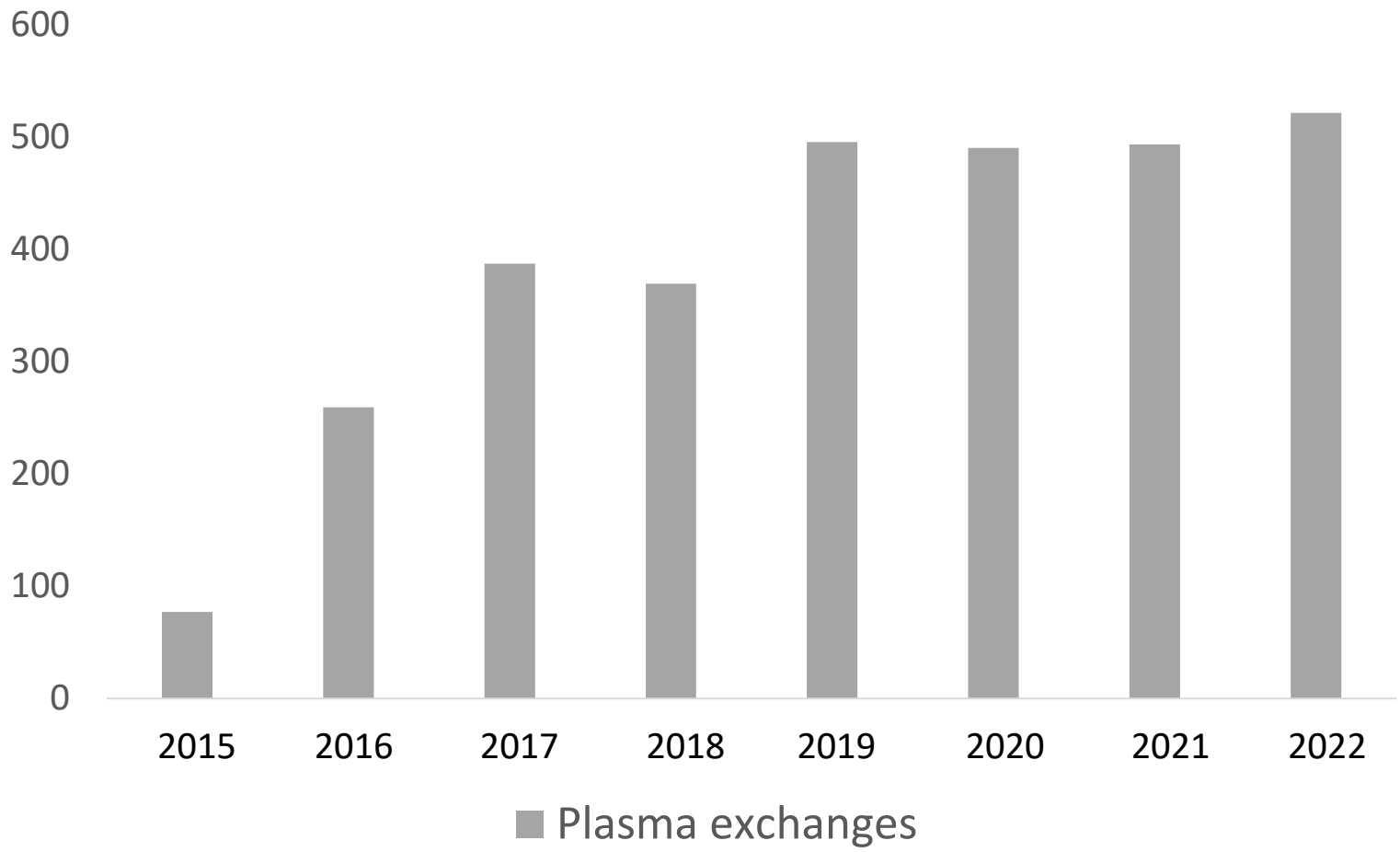
Where ECV is exceeded,one should consider additional priming with 4.5% HAS or blood

The size of the filter is approximately 75-100% of the child's body surface area

Increased use of PEX in last 5-10 years

Diverse indications

Atypical HUS
Crescentic GN
Refractory lupus
Recurrent FSGS; MPGN
Allograft rejection
NMDA encephalitis; GBS
Wilson disease



Adverse events with PEX for Atypical HUS: 2013-18

Adverse events	PEX sessions (n=2024)
None	**1779 (87.9)**
Mild (self-limiting)	**185 (9.1)**
Chills	112 (5.5)
Vomiting	51 (2.5)
Urticarial rash	26 (1.3)
Abdominal pain	17 (0.8)
Moderate (required intervention)	**30 (1.5)**
Hypotension requiring bolus or with vomiting; tachycardia with vomiting	20 (0.9); 3 (0.1)
Hypocalcemic tetany/ cramps	3 (0.1)
Urticarial rash with tachycardia or wheeze	3 (0.15)
Pericatheter leak	1 (0.05)
Severe (life-threatening)	**22 (1.1)**
Hypotension with desaturation/bradycardia	8 (0.4)
Hypotension requiring >1 fluid bolus, vasopressor or procedure cessation	6 (0.3)
Seizures	5 (0.25)
Significant bleed (intrabdominal, intracranial)	3 (0.1)

Filter-related (clotting or leak)	8 (0.4)
Catheter related bloodstream infection	1.45/1000 catheter-days

J Clin Apher. 2019;1–8.

Efficacy of PEX for Atypical HUS: 2013-18

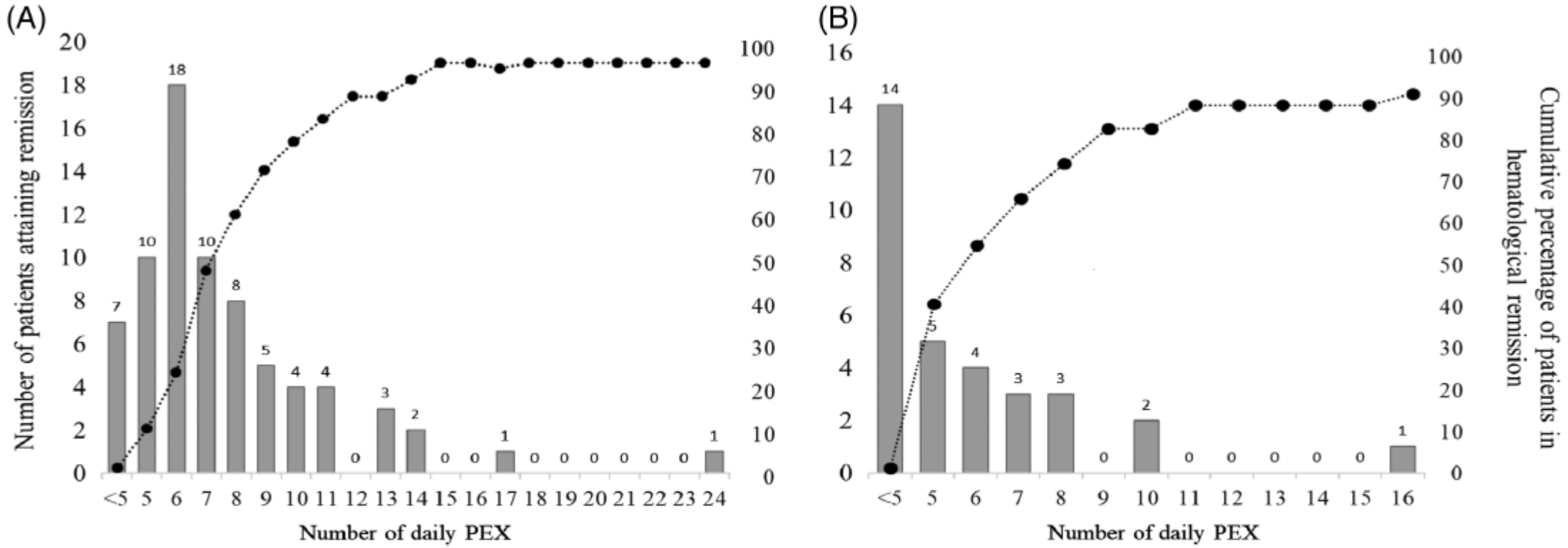


FIGURE 1 Chart indicating duration of daily plasma exchange (PEX) required to reach hematological remission for patients with atypical hemolytic uremic syndrome with (A) or without (B) anti-factor H (FH) antibodies. Bars depict frequency of patients achieving remission corresponding to days of daily PEX. Of 109 patients, the cumulative proportion of patients with and without anti-FH antibodies achieving hematological remission were 60.8% and 74.3% (by day 7) and 97.2% and 88.6% (by day 14), respectively (dashed lines)

J Clin Apher. 2019;1–8.

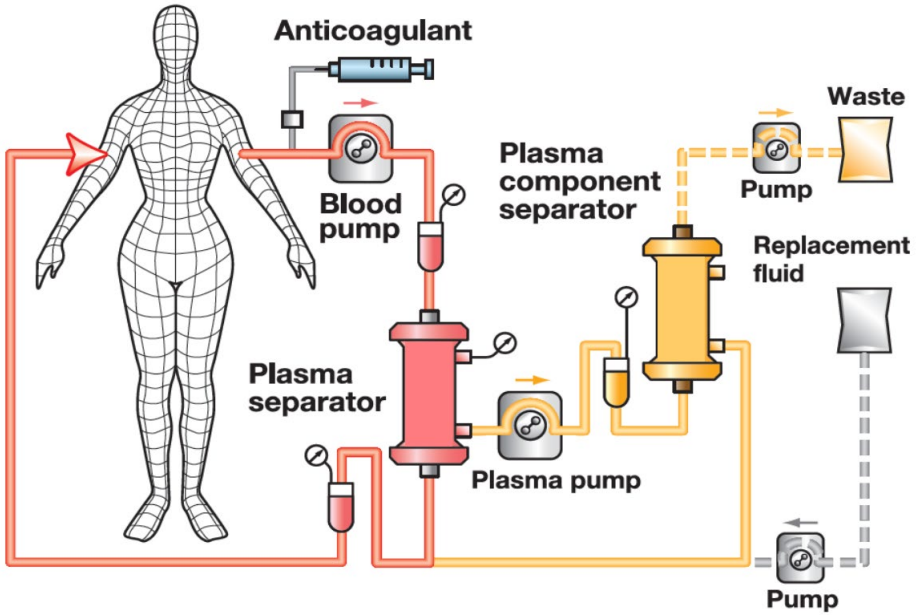
Audit of PEX for Atypical HUS: 2013-2018

Outcomes	N=109
Duration of PEX, days	38 (29-45)
Number of sessions	17 (14-20.5)
Duration of dialysis, days	15 (2.5-31)
Dialysis independence by 1-month	88 (80.7)
Hematological remission	105 (96.3)
Days to remission from starting PEX	8 (5-11)
Number of PEX for remission	6 (5-8)
Refractoriness to PEX	34 (31.2)
Days for subsequent response	3 (1-4.5)
Outcome at 3-months	
Stage 2 HTN or proteinuria ≥2+	56 (51.4)
CKD stages 2-3	17 (15.6)
Adverse outcome CKD stage 4-5; death	12 (11)
Relapse	18 (16.5)

J Clin Apher. 2019;1–8.

Double filtration plasmapheresis

Semi-selective blood purification modality



Filter 2 (plasma component separator)
Large molecular weight components discarded
Small molecular weight components returned to plasma
Pore size determines substance removed (e.g., IgG vs. LDL)

More selective compared to TPE
Lower volume of replacement fluid
Fewer adverse events (allergy, infections)

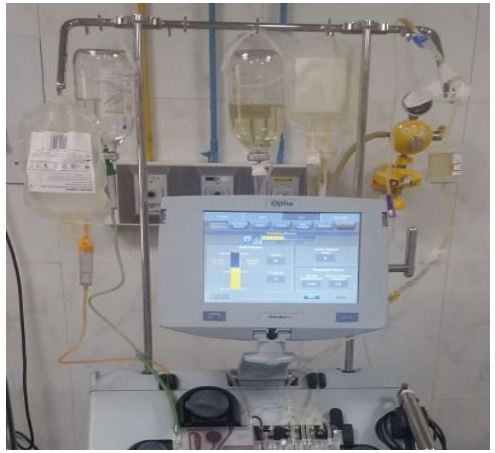
1 session ~ 1.5 plasma volume
0-20% plasma replaced with NS or 5-12% albumin

Cascadeflo EC
Evaflux

4 pore sizes each

Metabolic Disorders	Familial hypercholesterolemia
Kidney Disease	Anti-GBM antibody mediated rapidly progressive GN ANCA mediated rapidly progressive GN Focal segmental glomerulosclerosis
Organ Transplantations	ABO/HLA incompatible kidney transplant ABO/HLA incompatible liver transplant
Neurological Disorders	Myasthenia gravis Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy Multiple sclerosis
Rheumatic Disorders	Systemic lupus erythematosus Malignant rheumatoid arthritis Kawasaki disease
Hematological Disorders	Thrombotic thrombocytopenic purpura Hemolytic uremic syndrome Multiple myeloma Macroglobulinemia Hemophilia with inhibitor
Liver Disease	Chronic hepatitis C Acute hepatic failure Postoperative hepatic failure
Dermatologic Disorders	Pemphigus vulgaris Pemphigoid Toxic epidermal necrolysis Stevens-Johnson syndrome
Others	Arteriosclerosis obliterans Severe blood-type incompatible pregnancy

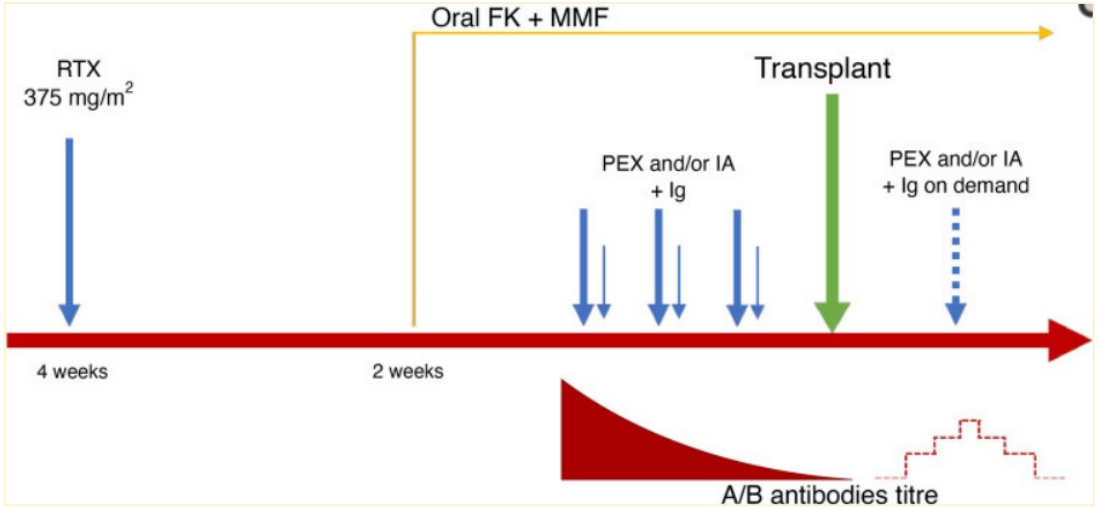
Ther Apher Dial 2021; 25: 145-151



Immunoadsorption

Indication	Pathogenic factor
Systemic lupus erythematosus	Anti-ds-DNA or anti-nuclear antibodies, immune complexes
Focal segmental glomerulosclerosis	Circulating humoral factor
ANCA-associated small vessel vasculitis	ANCA
Goodpasture's disease	Anti-GBM antibodies
TTP	ADAMTS-13 antibodies
Cryoglobulinaemia	Immune complexes
Highly sensitized kidney transplant recipient	HLA and non-HLA alloantibodies
Antibody-mediated allograft rejection	HLA and non-HLA alloantibodies
ABO-incompatible transplantation	Blood group isoagglutinins

Combination with immunosuppression in ABO-incompatible transplantation



Lipoprotein Apheresis

Extracorporeal selective elimination of apolipoprotein (apo)-B containing lipoproteins

FDA approved indications

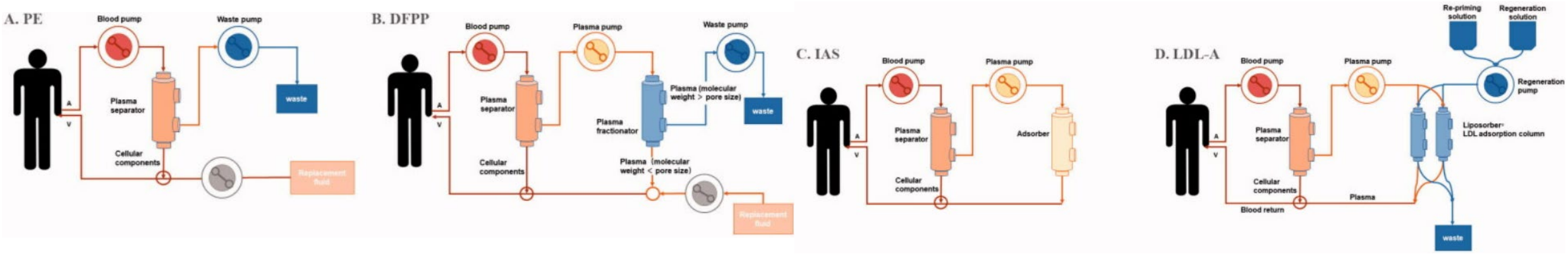
Homozygous familial hypercholesterolemia

Refractory FSGS (Liposorber® LA15, Kaneka Pharma, Japan)

						Selective removal from whole blood	
	Plasmapheresis	**Double or Cascade filtration plasmapheresis**	**Immunoadsorption**	**Dextran sulphate immunoadsorption**	**HELP**	**DALI**	**Whole blood adsorption with polyacrylate lipocollect**
Main method	Plasma exchange	LDL is cleaned from the plasma passing through the filtration columns by considering the particle size	Circulating LDL, VLDL, and Lp (a) are cleared using polyclonal sheep anti-apoB antibodies	ApoB containing lipoproteins are electrostatically bound to dextran sulfate and removed from the circulation	With the help of heparin, LDL particles in the plasma are precipitated	Treatment with whole blood without separating plasma	Treatment with whole blood without separating plasma
Lipoproteins and fibrinogen mean reduction in percent of original concentration (%)							
LDL	72	65	65	73–80	69	67	61
HDL	65	40	22	10	14	11	22
Apolipoprotein B	69	59	56	62	53	55	51
Apolipoprotein A1	68	45	20	16	12	25	25
Lipoprotein (a)	68	52	53	72	50	50	61
Fibrinogen	58	36	23	16	44	25	39

Comparison of techniques

	TPE	DFPP	IA	LDL-A
Selectivity	Non-selective	Semi-selective	Semi-selective	Semi-selective
Plasma processing volume	1–1.5 times (very limited)	1–2 times (limited)	2–3 times (unlimited theoretically)	2–3 times (unlimited theoretically)
Substitution solution	Crystalloid/colloid (HSA or FFP)	Little HSA or saline	No substitution solution	No substitution solution
Removal of protein	Remove all plasma components	Remove macromolecules	Remove pathogenic factors selectively (predominantly Ig)	Remove LDL and other lipoproteins



Acute Kidney Injury

Jitendra Meena, MD, DM
Assistant Professor
AIIMS, New Delhi

Overview

- Definition
- Epidemiology
- Diagnosis & Risk-stratification Models
- Evaluation for Etiology
- Complications
- Non-dialysis management
- Outcome

Definition

"Acute kidney injury is characterized by the rapid decline in kidney function with an accumulation of nitrogenous waste and inability of the kidney to maintain fluid and electrolyte homeostasis"

Acute Kidney Injury has replaced "acute renal failure" to emphasize the disease continuum as even modest reductions in kidney function are associated with worse outcomes

Moore et al, Am J Kidney Dis. 2018; 72(1):136-148
Ronco et al, Lancet 2019; 394: 1949–64
Kellum et al, Nature reviews, Disease primers, 2021,7:52

Global Epidemiology of AKI

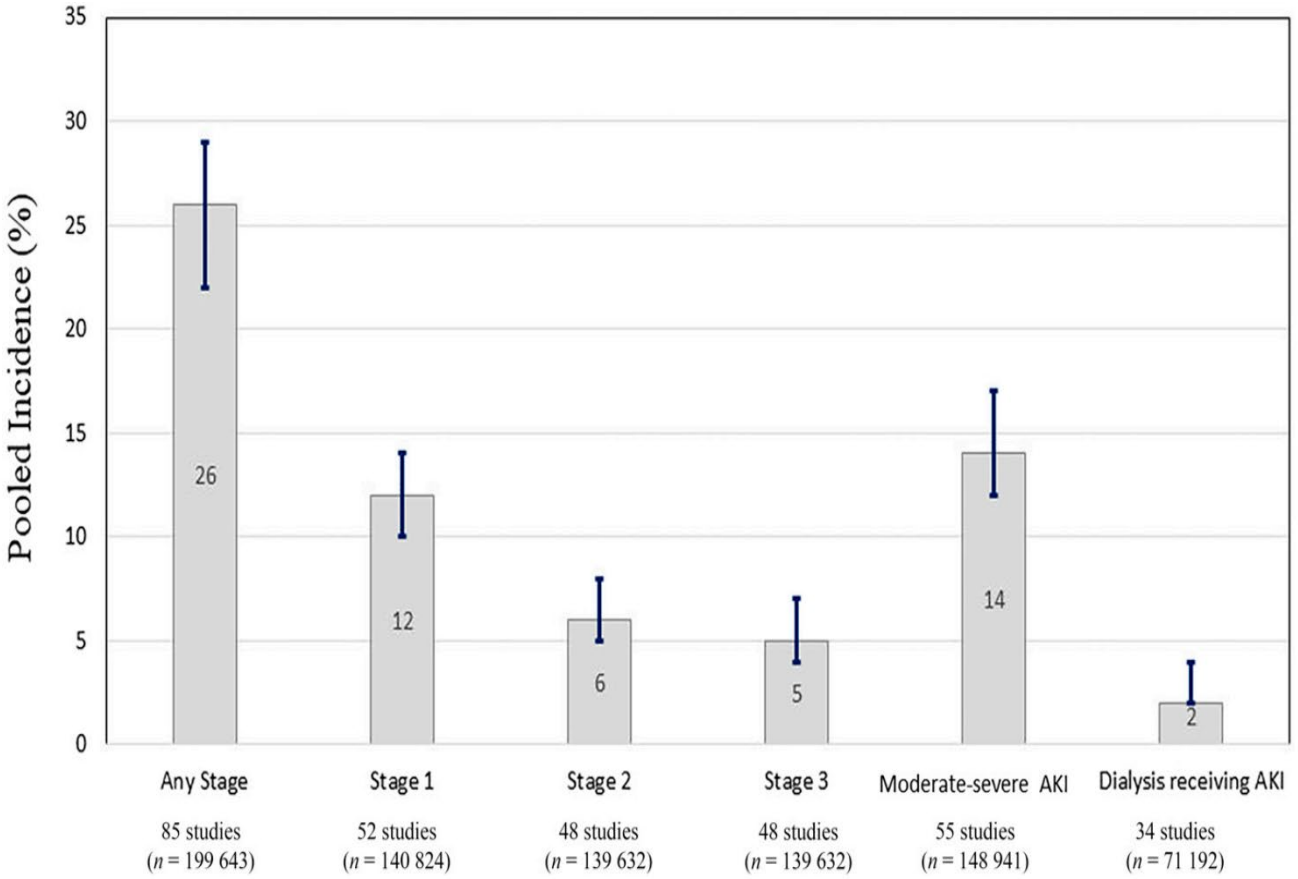
~One-quarter of hospitalized children develop AKI

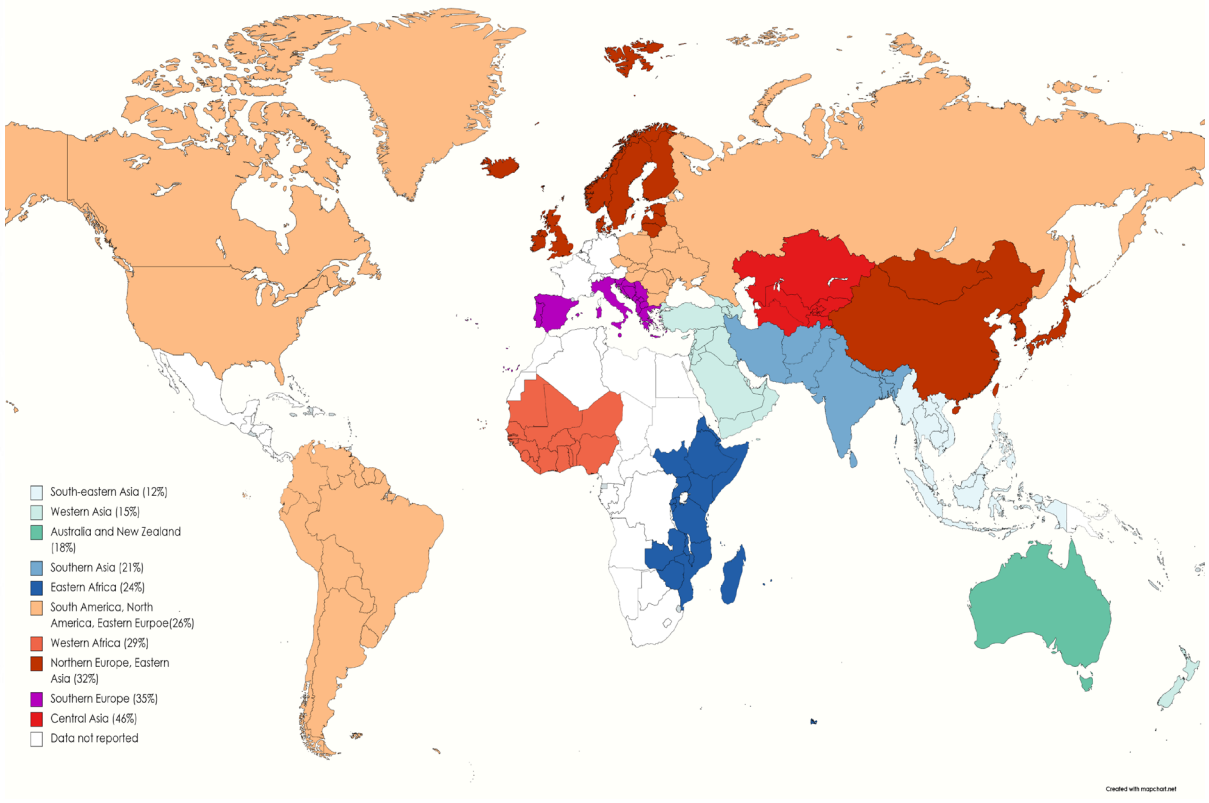
94 large cohort studies;
KDIGO criteria
202694 children

> Pediatrics. 2023 Jan 17;e2022058823. doi: 10.1542/peds.2022-058823. Online ahead of print.

Incidence of Acute Kidney Injury in Hospitalized Children: A Meta-analysis

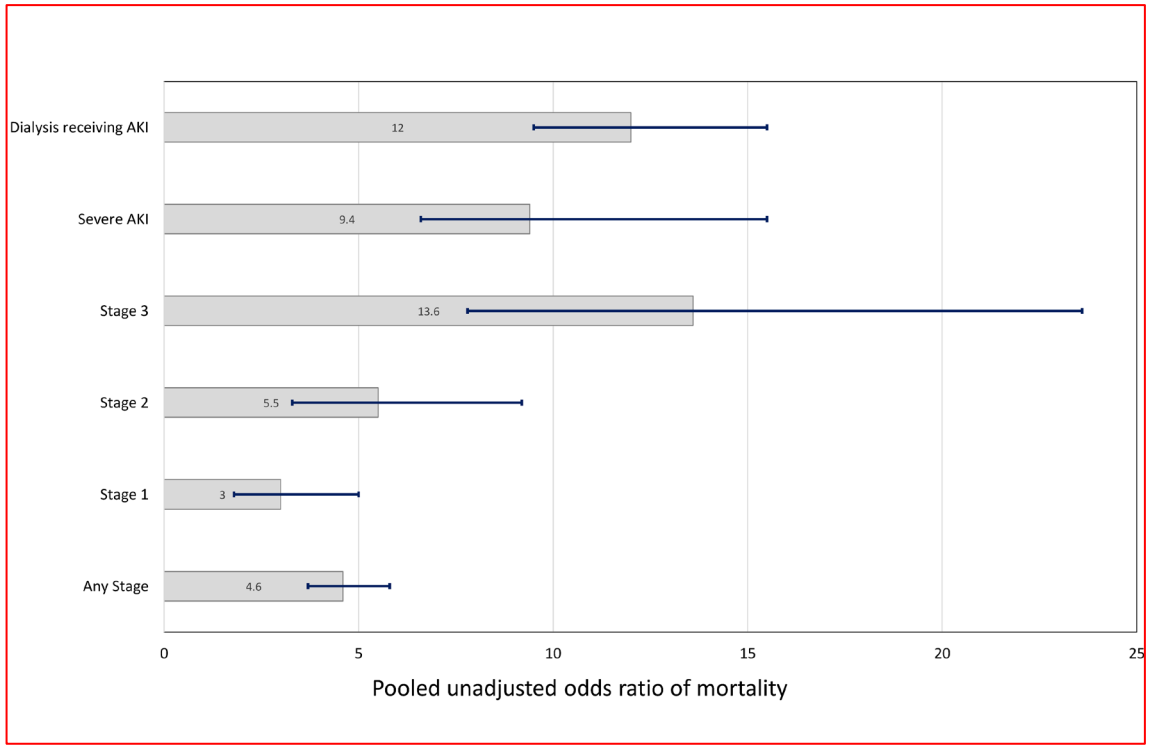
Jitendra Meena [1], Georgie Mathew [2], Jogender Kumar [3], Rahul Chanchlani [4]

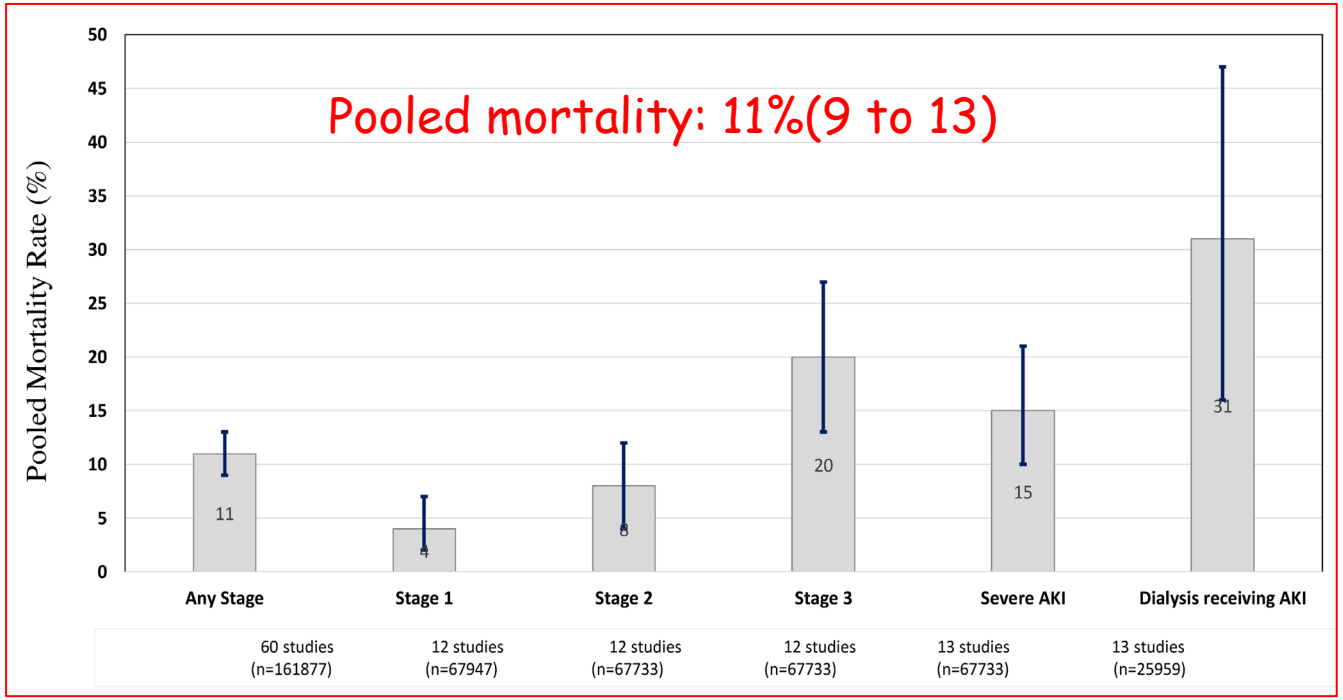




AKI associated Mortality in Children: Worldwide trend

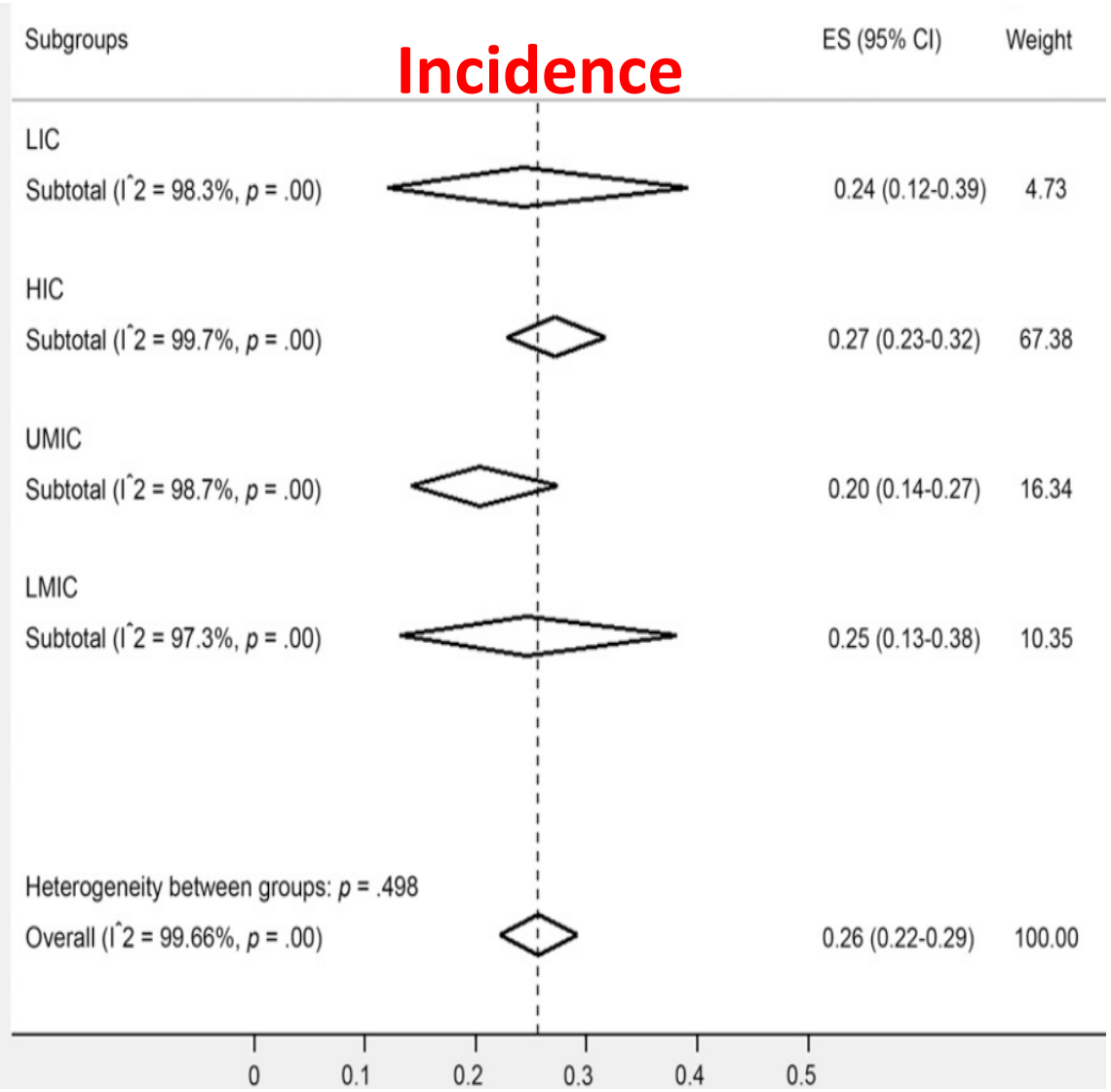
AKI vs non-AKI mortality OR: 4.6 (3.7 to 5.8)

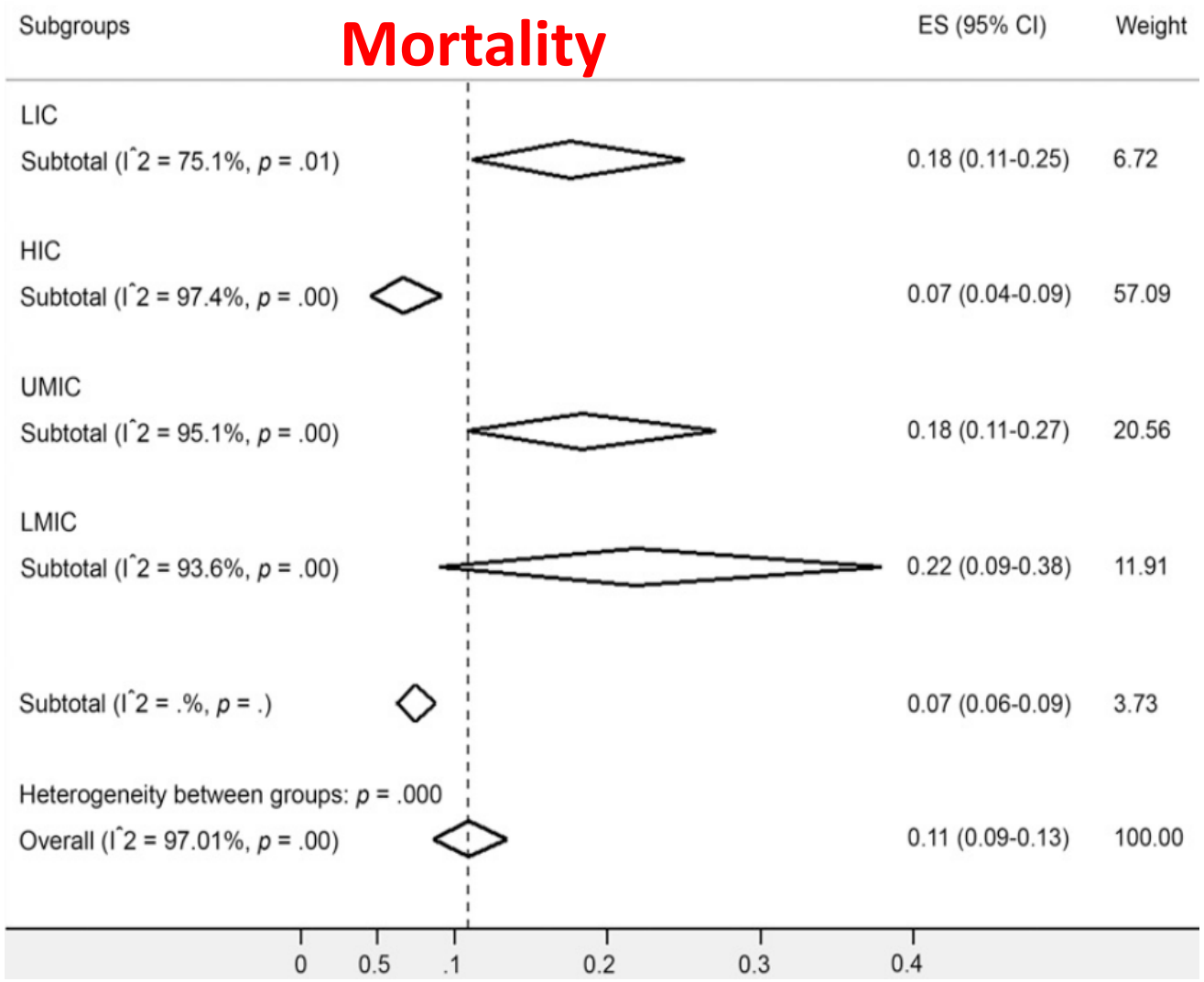




Meena J et al Pediatrics. 2023 Jan 17;e2022058823.

AKI associated mortality is higher in LIC & LMIC compared to HIC despite a similar AKI burden





Meena J et al Pediatrics. 2023 Jan 17;e2022058823

Diagnosis & Staging Criteria

pRIFLE criteria

Stage	↓eCCL	UO
R	by 25%	<0.5 ml/kg/h for 8 h
I	by 50%	<0.5 ml/kg/h for 16 h
F	by 75%	<0.3 ml/kg/h for 24 h or anuric for 12 h

AKIN criteria

Stage	↑SCR from baseline	UO
1	≥ 0.3 mg/dl or 1.5- to 2-fold	<0.5 ml/kg/h for >6h
2	> 2- to 3-fold	<0.5 ml/kg/h for ≥12 h
3	> 3-fold	<0.3 ml/kg/h for ≥24 h or Anuria ≥12 h

2004 **2007** **2012**

RIFLE criteria

Stage	Rise in Scr /eCCL	UO
R	1.5x/ >25%	<0.5 ml/kg/h for 6 h
I	2x/ >50%	<0.5 ml/kg/h for 12 h
F	3X/ >75%	<0.3 ml/kg/h for 24 h or anuric for 12 h
L= loss of kidney function >4 weeks E= loss of kidney function >3 month		

KDIGO criteria

Stage	↑SCr	UO
1	0.3 mg/dl in 48 h or 1.5-1.9 within 7d	<0.5 ml/kg/h for 6–12 h
2	2-2.9 times	<0.5 ml/kg/h for ≥12 h
3	≥3 times baseline or ≥4 mg/dl or Dialysis	<0.3 ml/kg/h for ≥24 h or Anuria ≥12 h

Shortcomings of Current Criteria

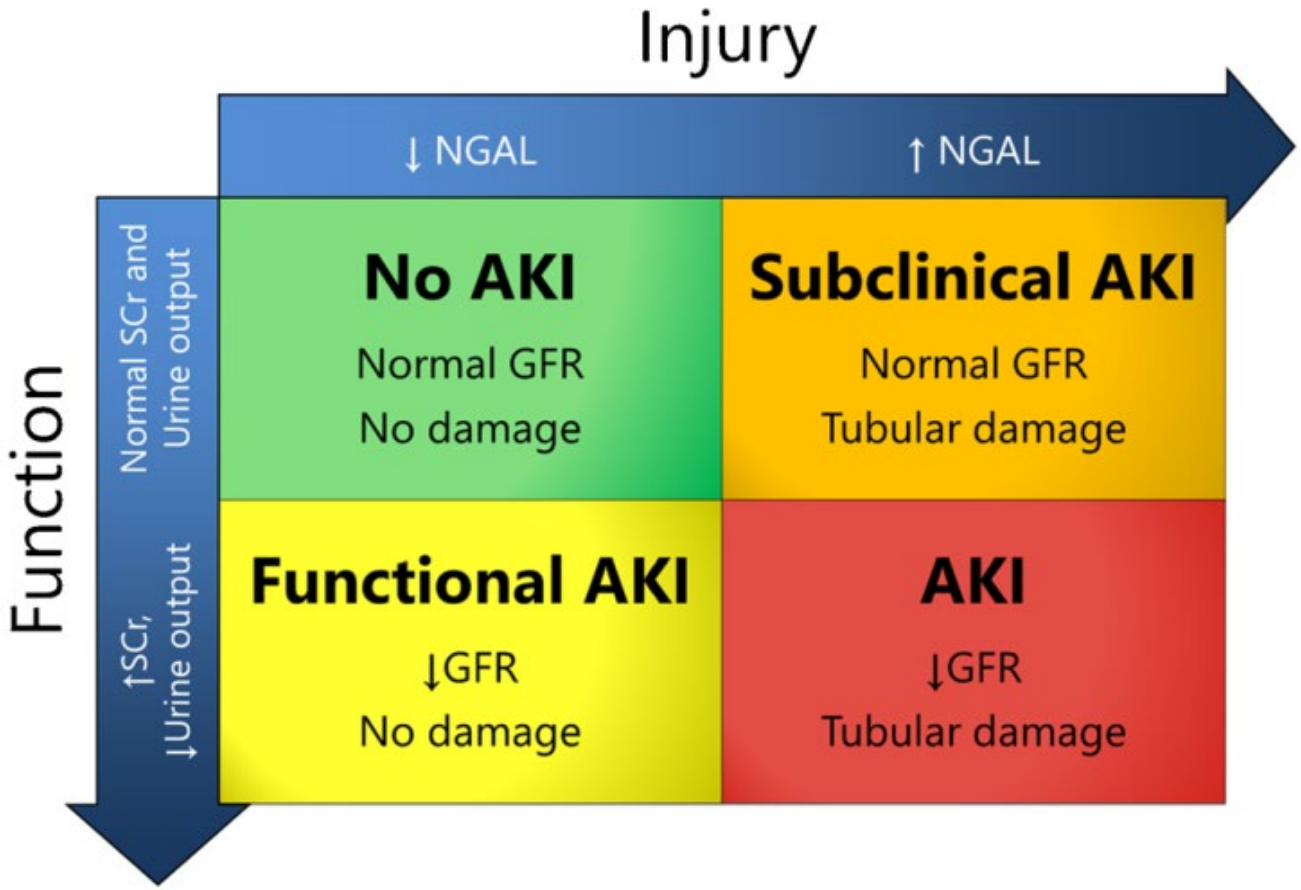
Serum Creatinine

- ❖ Non-availability of baseline creatinine
- ❖ Alteration by nonrenal determinants
- ❖ Delayed rise following injury
- ❖ Variation in lab measurement; IDMS

Urine output

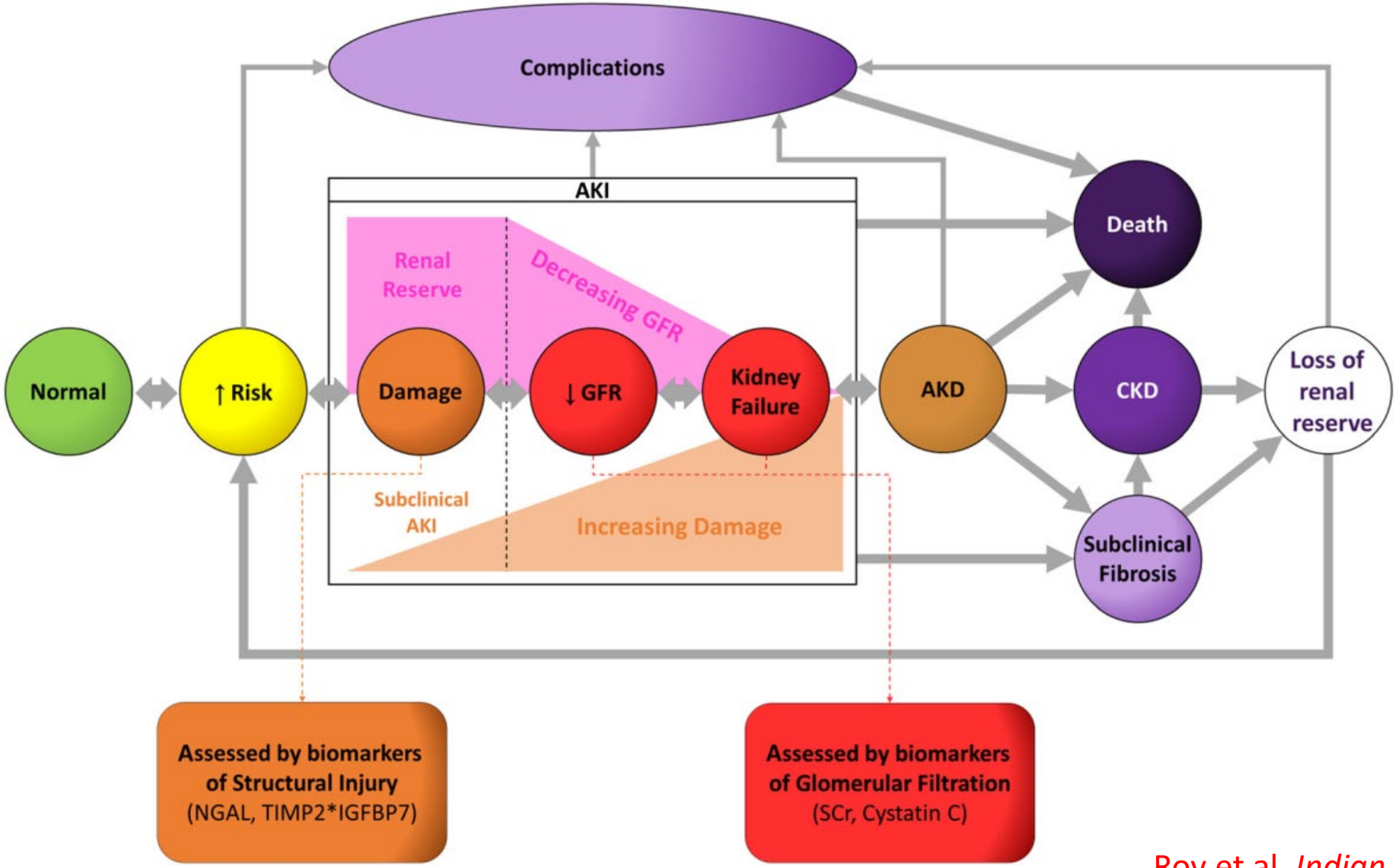
- ❖ Cumbersome, may not be accurate

Pre-renal AKI = Functional AKI



Roy et al. *Indian J Pediatr* **87,** 600–607 (2020)

AKI to CKD continuum



Roy et al. *Indian J Pediatr* **87,** 600–607 (2020)

Proposed New Definition of AKI

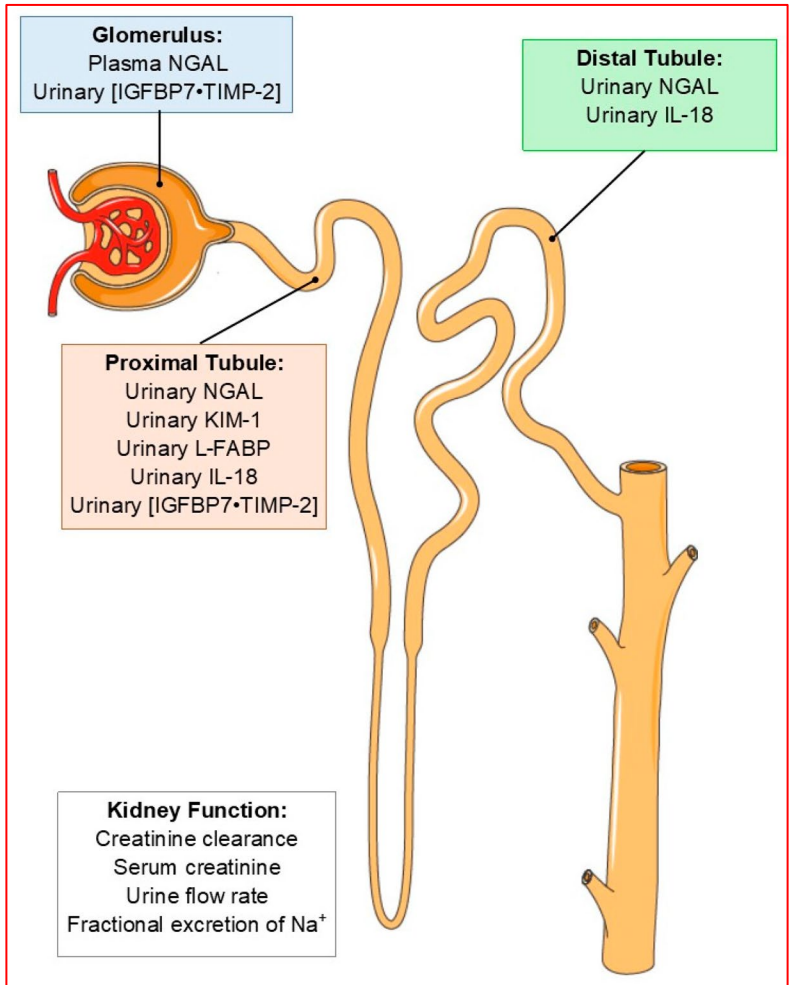
Functional criteria	Stage	Damage criteria
No change or sCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of sCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of sCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of sCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

A combination of damage and functional biomarkers + clinical information:

- Improve the diagnostic accuracy
- Assess the severity
- Recognition of pathophysiology

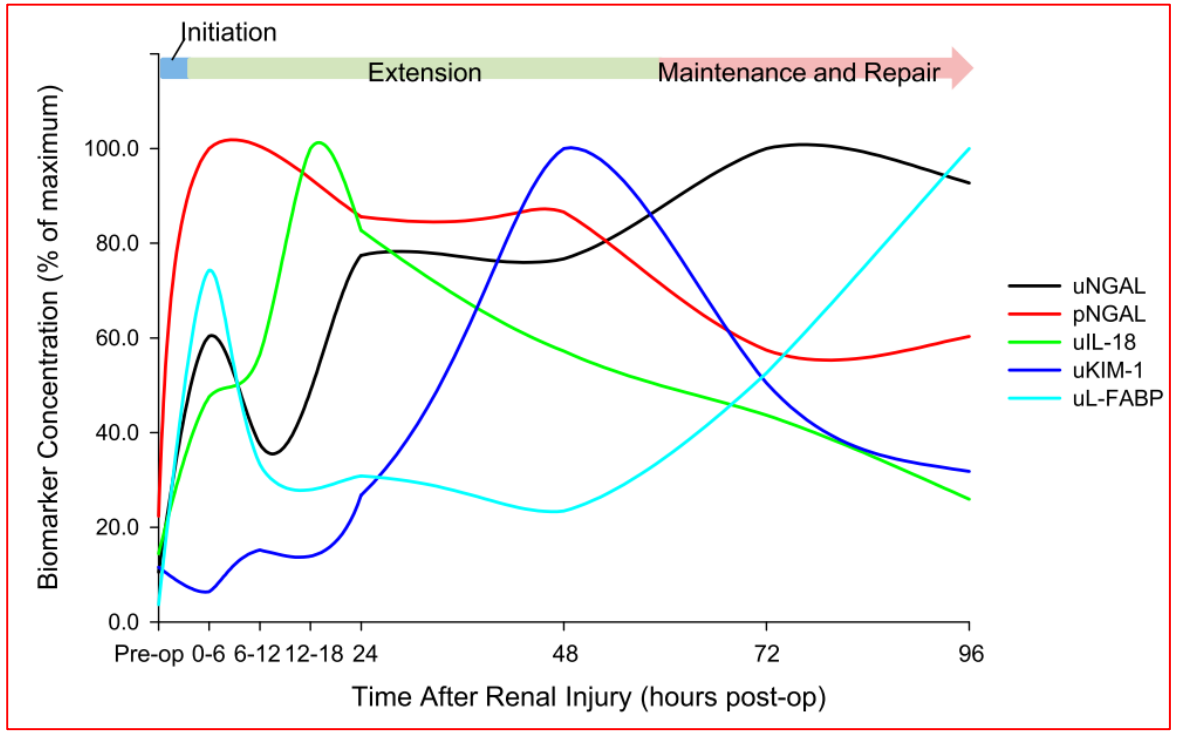
Ostermann et al JAMA Network Open. 2020;3(10):e2019209

Biomarker in AKI



Biomarker	Potential etiology
Plasma NGAL	Ischemia
Urinary NGAL	Nonspecific
Urinary KIM-1	Nonspecific
Urinary L-FABP	Hypoxemia & oxidative stress
Urinary IL-18	Inflammation
Urinary [IGFBP7•TIMP-2]	Nonspecific

Biomarker	Mechanism of action upon injury
NGAL	Chelates iron from damaged tubules preventing free-radical formation
KIM-1	Promotes apoptotic and necrotic cell clearance
LFABP	Upregulated, binds lipid hydroperoxides and other ROS
IL-18	Upon injury, caspase-1 cleaves pro-Il-18 inactive form
TIMP-2 X IGFBP7	G1 cell cycle arrest



Biomarkers for prediction of Acute Kidney Injury in pediatric patients: a systematic review and meta-analysis of diagnostic test accuracy studies

HYPOTHESIS: Biomarkers of kidney injury may aid in early detection of AKI in children

DESIGN & OUTCOMES:

Database search
Embase, PubMed, Web of Science, Cochrane Library (n = 1952)

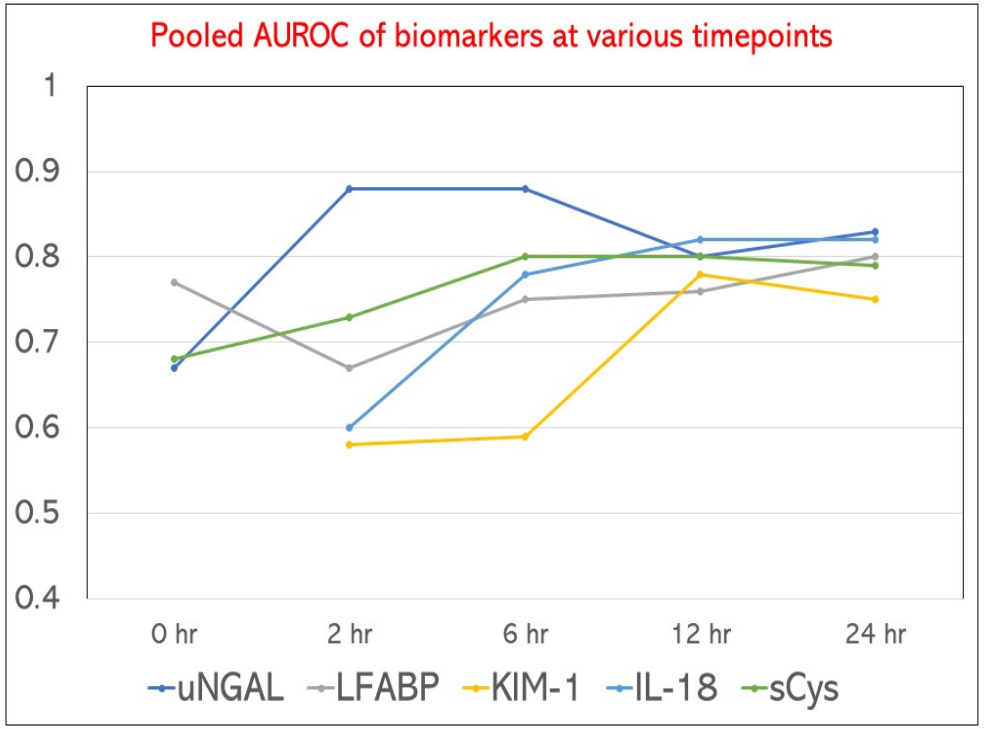
Screening

92 Studies

13,097 Participants

Diagnostic Performance

Biomarker	Pooled AUROC (95% CI)
uNGAL	0.82 (0.77-0.88)
sNGAL	0.74 (0.64-0.84)
sCystatin C	0.80 (0.76-0.85)
uTIMP-2*IGFBP7	0.79 (0.72-0.85)
uKIM-1	0.70 (0.63-0.75)
uLFABP	0.80 (0.73-0.88)
uIL-18	0.69 (0.62-0.76)



CONCLUSION: **NGAL, L-FABP, TIMP-2*IGFBP7 in urine, and cystatin C in serum, showed satisfactory diagnostic accuracy in early recognition of AKI.**

Meena J et al. 2023

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association

Utility of biomarkers in clinical practice is limited

- Only moderate accuracy
- Lack of uniform well defined cut-off
- Lack of standard analysis method
- Not readily available
- Cost-effectiveness

Biomarkers and Renal Angina Index in AKI

Angina Pectoris

Cardiovascular risk factors

Symptoms of MI: Chest pain, ECG abnormalities

\+ Troponin

Renal Angina

Risk factors for kidney injury

Symptoms of kidney injury: rise in SCr, fluid overload

\+ AKI Biomarkers

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
>1×–1·49×	5–10	2
1·5×–1·99×	11–15	4
≥2×	>15	8

Risk × injury
Scores: 1–40

Renal angina fulfilled with renal angina index score ≥8

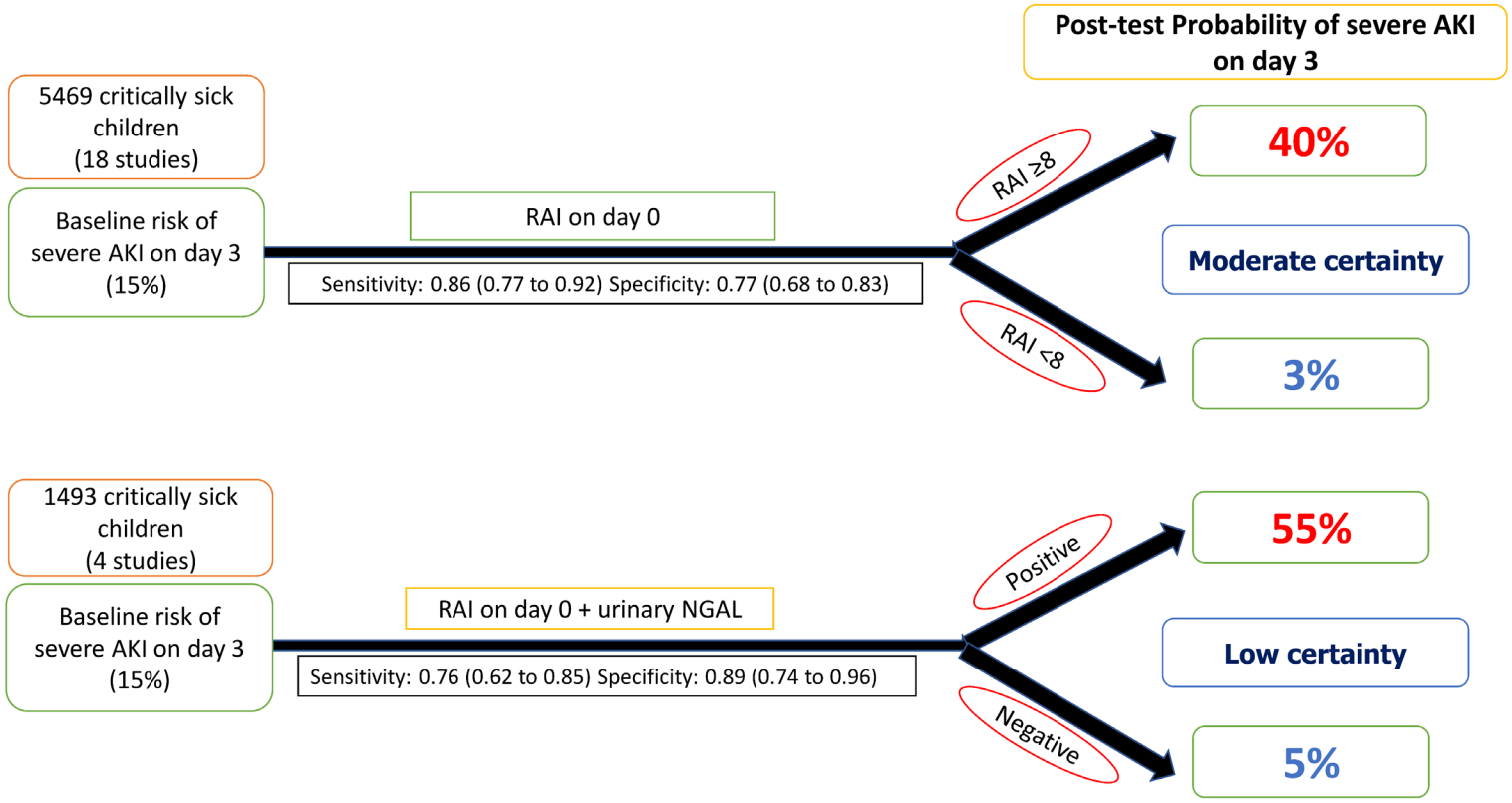
Sensitivity-86%
Specificity-77%

Basu et al, Lancet Child Adolesc Health 2017
Meena J et al, Pediatr Nephrol. 2022

Positive RAI (≥8) has a good predicting ability to recognize children at risk of severe AKI on day 3 and receipt of dialysis

Meta-analysis
22 studies (14001 participants)

Outcome/ parameters	Sensitivity [95% CI]	Specificity [95%CI]	DOR [95%CI]
Severe AKI on day 3	0.86 [0.77 - 0.92]	0.77 [0.68 - 0.83]	21 [12 -37]
Any AKI on day 3	0.79 [0.62 - 0.90]	0.81 [0.64 - 0.91]	16 [5 -51]
Severe AKI on day 3 in sepsis	0.91 [0.80 - 0.97]	0.61 [0.47 - 0.73]	17 [8 -36]
Requirement of KRT	0.82 [0.71 - 0.90]	0.74 [0.66 - 0.81]	14 [7 -26]



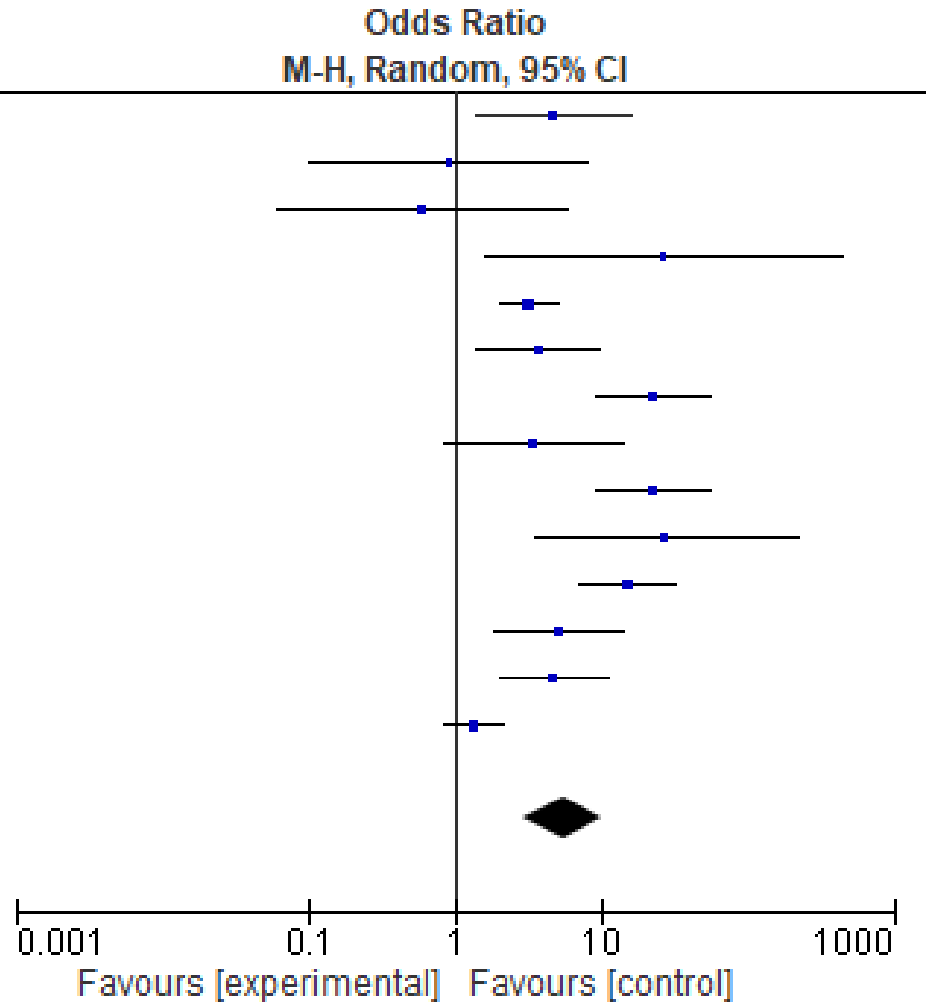
Meena J et al, Pediatr Nephrol. 2022

Comparison of mortality between patients with renal angina index positive (≥8) and negative (<8)

Study or Subgroup	RAI+ Events	RAI+ Total	RAI- Events	RAI- Total	Weight	Odds Ratio M-H, Random, 95% CI
Basu 2014 (cohort1)	9	51	4	93	7.2%	4.77 [1.39, 16.37]
Basu 2014 (cohort2)	1	18	6	100	4.4%	0.92 [0.10, 8.15]
Basu 2014 (cohort3)	1	38	3	70	4.2%	0.60 [0.06, 6.01]
Basu 2014 (cohort4)	23	145	0	69	3.2%	26.67 [1.59, 445.82]
Basu 2017	32	286	49	1304	9.7%	3.23 [2.03, 5.14]
Gawadia 2019	21	86	6	76	8.1%	3.77 [1.43, 9.92]
Huang 2020	22	69	7	344	8.4%	22.53 [9.13, 55.63]
Jakanattane 2017	7	57	3	76	6.7%	3.41 [0.84, 13.81]
Kaur 2018	22	69	7	344	8.4%	22.53 [9.13, 55.63]
Menon 2016	11	60	1	124	4.7%	27.61 [3.47, 219.64]
Perez 2018	54	95	10	127	8.8%	15.41 [7.19, 33.04]
Ribeiro-Mourão 2021	8	101	8	492	8.0%	5.20 [1.91, 14.21]
Stanski 2021	35	207	7	172	8.6%	4.80 [2.07, 11.10]
Sundarraraju 2019	59	141	50	144	9.6%	1.35 [0.84, 2.18]
Total (95% CI)		**1423**		**3535**	**100.0%**	**5.53 [3.01, 10.18]**
Total events	305		161			

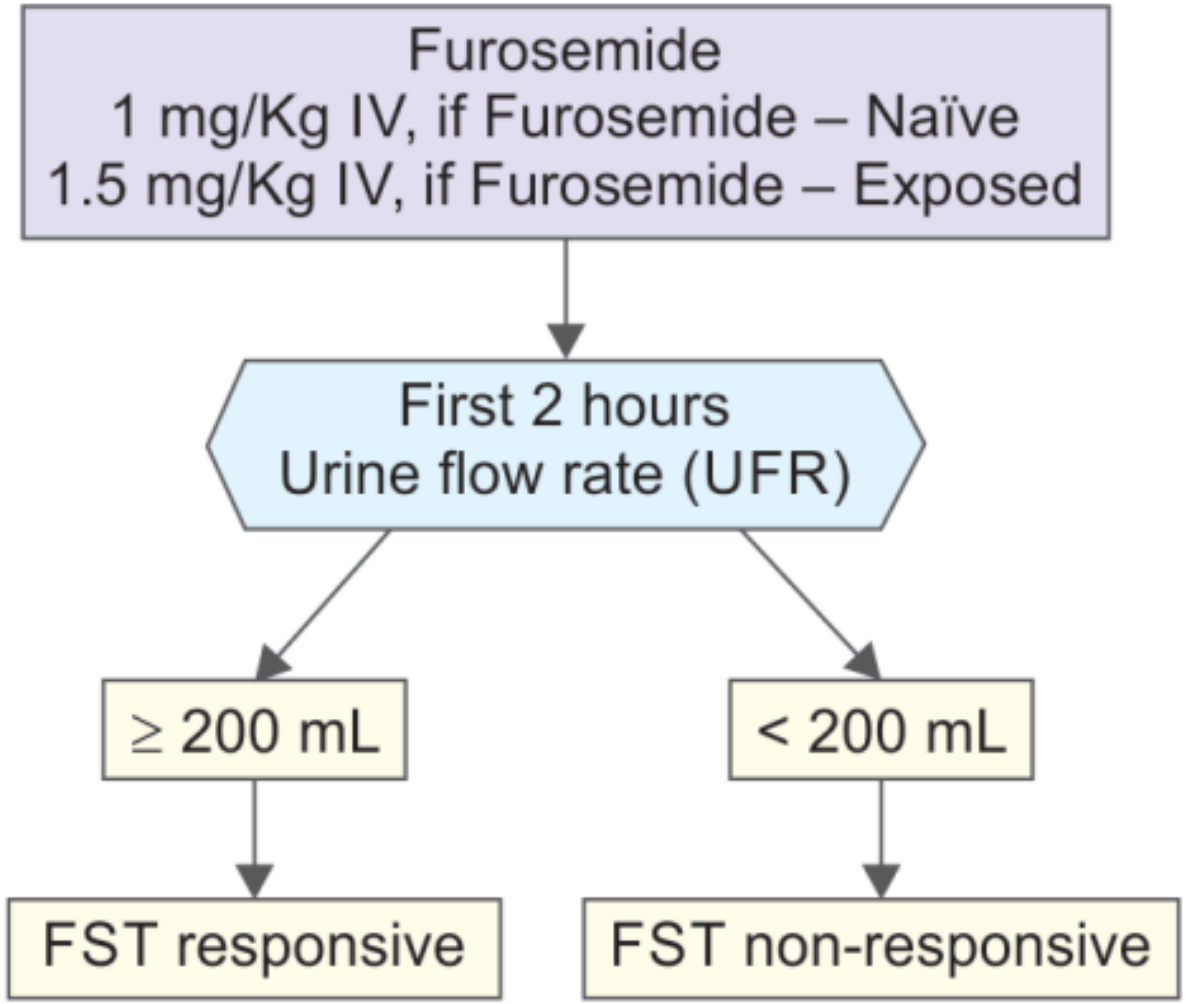
Heterogeneity: $Tau^2 = 0.95$; $Chi^2 = 70.32$, df = 13 ($P < 0.00001$); $I^2 = 82\%$

Test for overall effect: $Z = 5.50$ ($P < 0.00001$)



Meena J et al, Pediatr Nephrol. 2022

Furosemide Stress Test



Meta-analysis: 11 RCTs (1366 participants)

AKI progression **Sensitivity: 0.81 (0.74-0.87)**
Specificity: 0.88 (0.82-0.92)

Dialysis requirement **Sensitivity: 0.84 (0.72-0.91)**
Specificity: 0.77 (0.64-0.87)

Chawla et al, Crit Care. 2013 Sep 20;17(5):R207

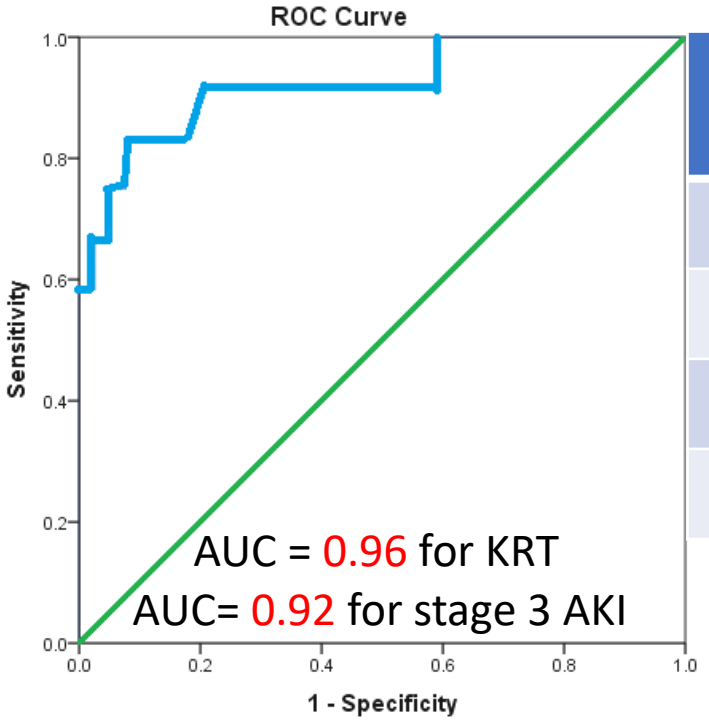
Chen et al, Crit Care. 2013 Sep 20;17(5):R207

Furosemide Stress Test in children

AIIMS, New Delhi

N = 51 (208)

Urine output >2 ml/kg within the first 2-h deemed furosemide responsive



FST 2ml/kg	Stage 3 AKI
Sensitivity	66.7%
Specificity	97.4%
PPV	88.9%
NPV	90.5%

Data courtesy: Dr. Sudarshan

AIIMS, Jodhpur

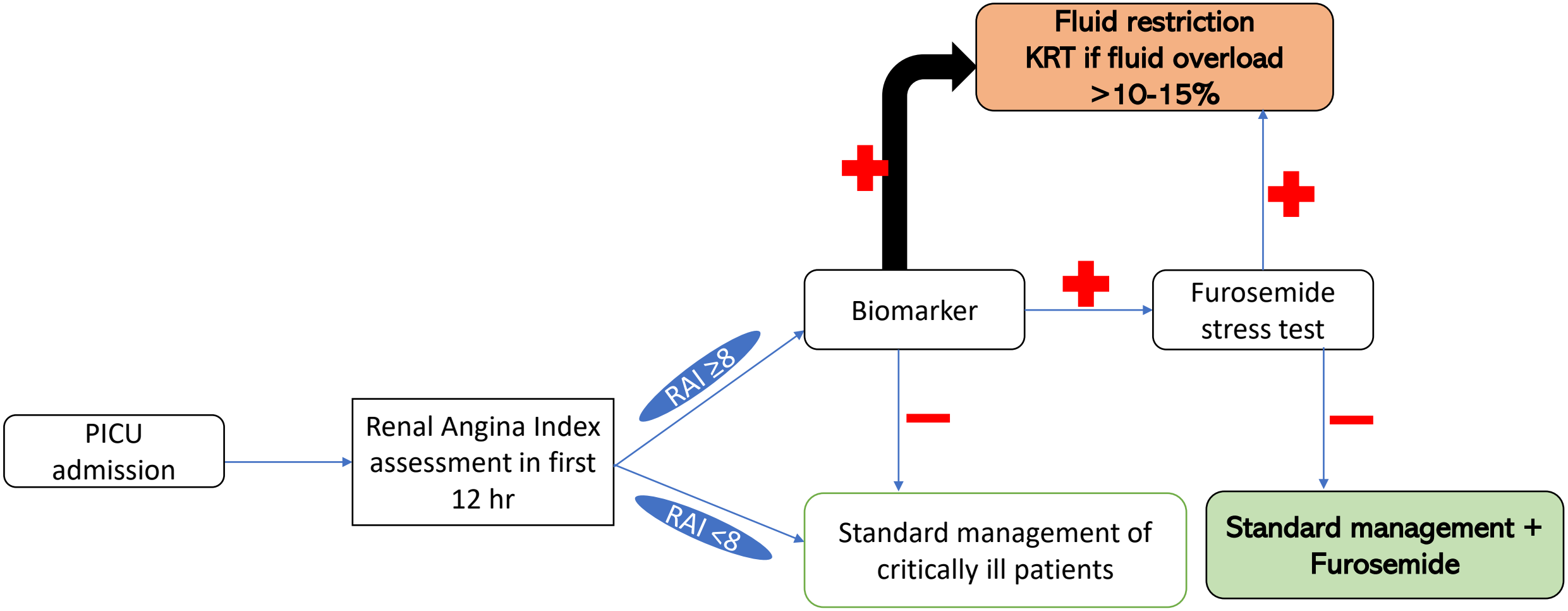
N = 41 (92)

Urine output >0.5 ml/kg within the first 2-h deemed furosemide responsive

AUROC for predicting severe AKI=0.84
Sensitivity = 57.14%
specificity = 100%

Data courtesy: Dr. Dyvik

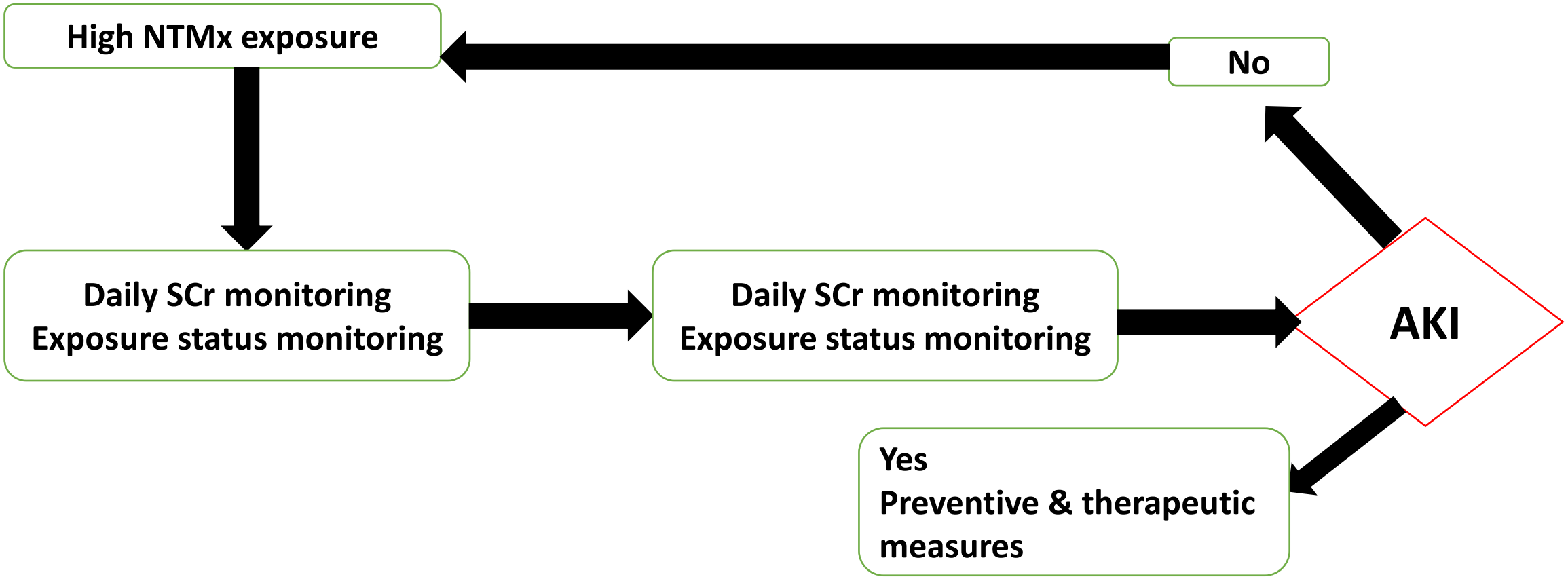
Risk Stratification Model in AKI



Goldstein et al, Kidney Int Rep (2018) 3, 516–518

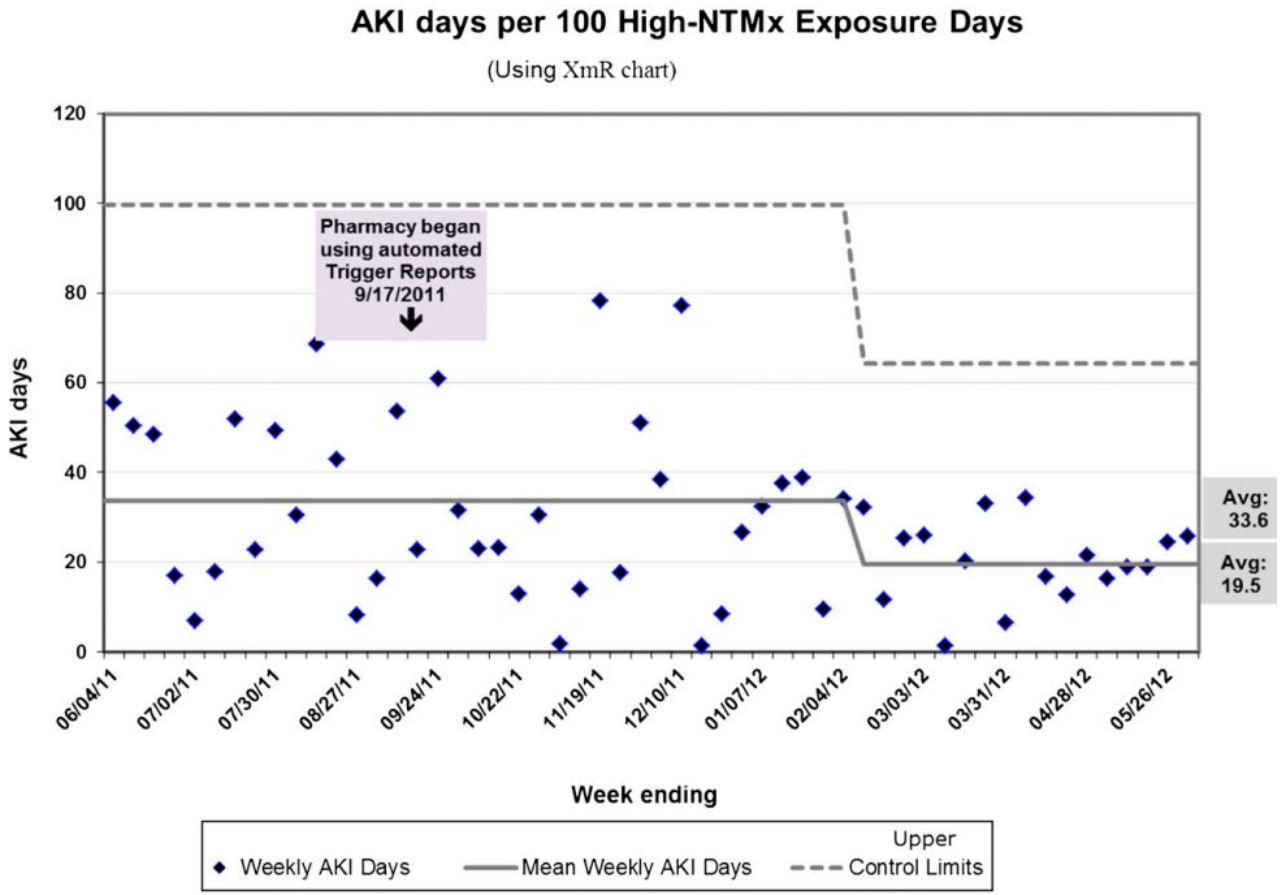
Nephrotoxic Injury Negated by Just-in-time Action (NINJA)

- Concomitant nephrotoxin exposure increases the risk of AKI
- Awareness of this risk has the capacity to modify care and outcomes

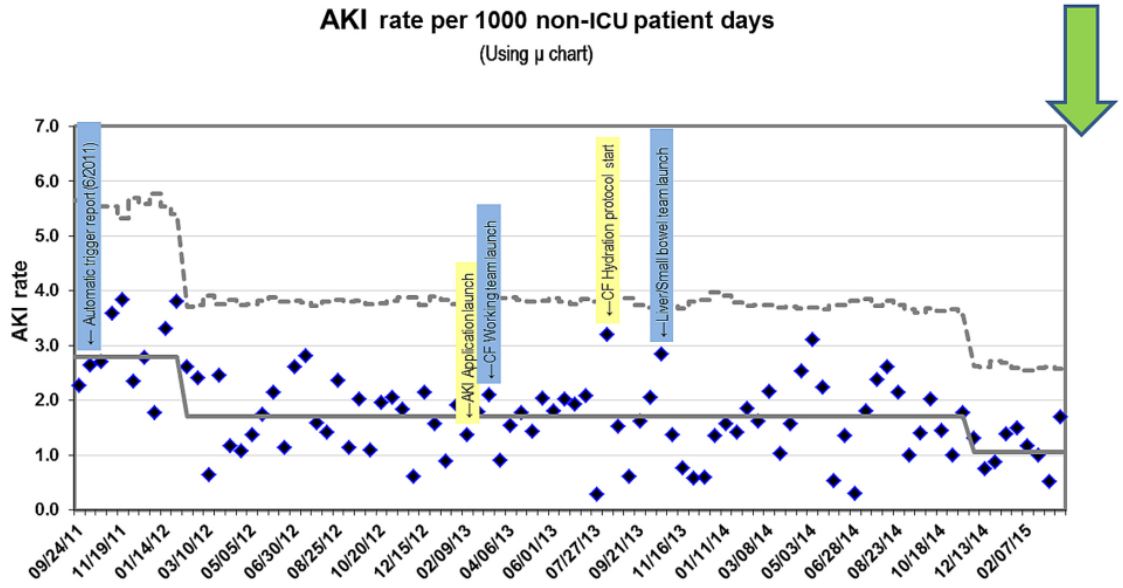


High NTMx: Aminoglycoside >3 days or ≥3 nephrotoxic medications

The mean AKI intensity rate decreased by 42%



AKI rate decreased by 64% (2.96–1.06 episodes/1000 patient days)



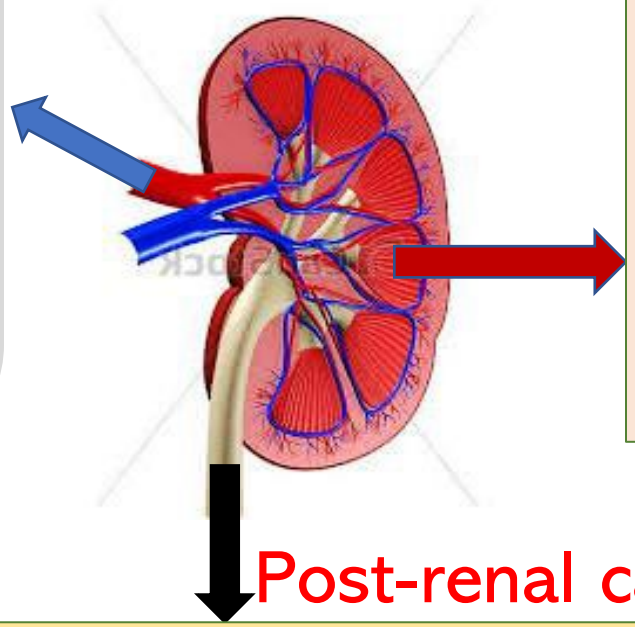
Goldstein et al, Pediatrics. 2013

Goldstein et al, Kidney international. 2016

Etiology

Decreased kidney perfusion

Hypotension/Low intravascular volume:
Bleeding/Haemorrhage, dehydration, sepsis
Reduced colloid pressure:
NS, liver failure, hypoalbuminemia, Sepsis/capillary leak, burns
Reduced cardiac output: CHF
Vascular insult: renal artery or vein thrombosis



Intrinsic causes

Glomerular: PIGN, RPGN, HSP, IgA

Vascular: HUS, TTP, hypertension

Tubular: Prolonged ischaemia, hypotension, nephrotoxins, hemolysis, rhabdomyolysis

Interstitial: Infections, Drugs, contrast media

Tumor lysis syndrome

Post-renal causes

PUV, uretheral stricture

Bilateral PUJO

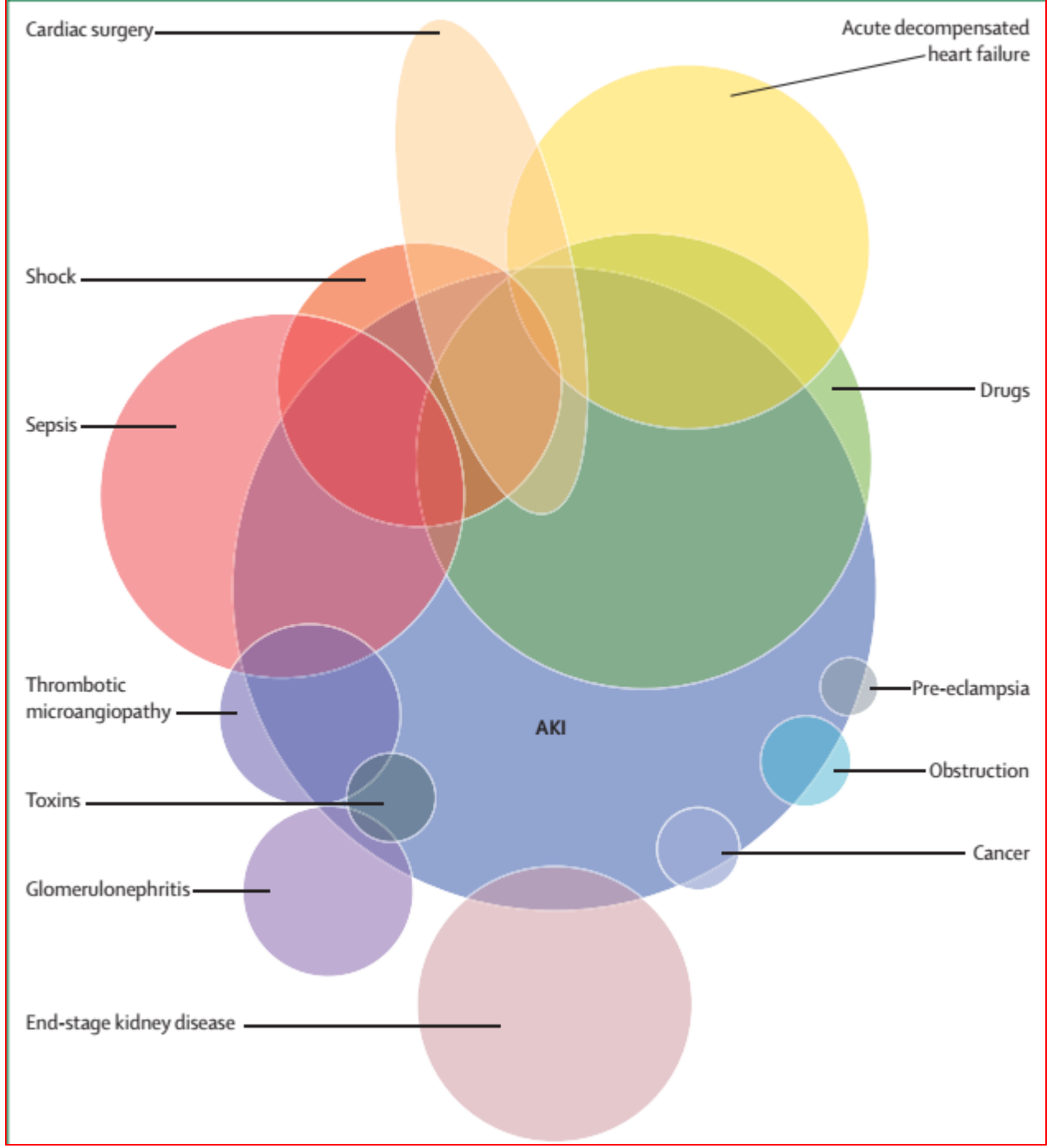
Ureteral obstruction: stenosis, stone

Neurogenic bladder

Etiology: Global Snapshot study

Etiology	All	HIC	UMIC	LLMIC	P-value
Dehydration	115 (32)	45 (26)	22 (30)	47 (43.5)	0.011
Hypotension, shock	113 (32)	46 (26)	31 (32)	43 (40)	0.043
Infection	104 (29)	33 (18.97)	23 (31.94)	48 (44.44)	<0.001
Nephrotoxic agents	71 (20)	23 (14)	14 (19)	33 (30)	0.3642
Primary kidney diseases	62(17)	14 (8.05)	19 (26.39)	29 (26.85)	<0.001
Post-surgical	56 (16)	47 (27.01)	3 (4.17)	6 (5.56)	0.0218
Systemic diseases	48 (14)	23 (13.22)	16 (22.22)	9 (8.33)	<0.001
Cardiac diseases	41 (12)	34(19.54)	2(2.78)	5(4.63)	0.1334

Macedo et al PLoS ONE 2018;13(5): e0196586



Ronco et al, Lancet 2019; 394: 1949–64

Approach to a child with suspected AKI

History

- Vomiting, diarrhea, blood loss, oral intake, fever
- Edema, hematuria, pallor, jaundice, skin rash, joint pain
- Dysuria, flank pain, voiding dysfunction, recurrent UTI, drug intake
- Seizures, altered sensorium, headache, resp. distress

Examination

- Vitals (BP), Pallor, icterus, edema, rash, fundus, GCS
- Fluid overload (S3 gallop, crepitations, edema)
- Organomegaly, bladder, kidneys

Investigation

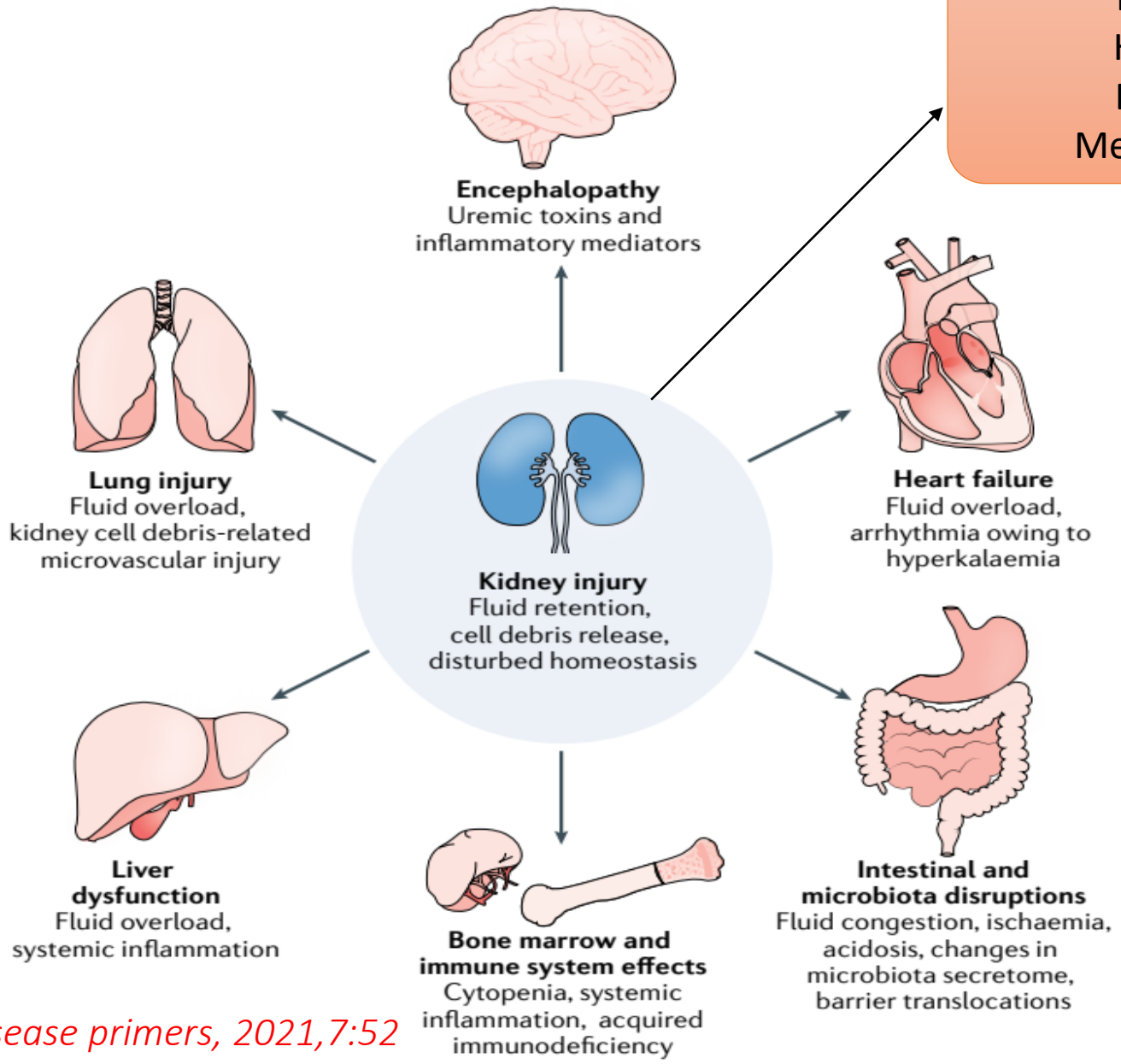
- Serum creatinine, urea, pH, Na/K, CBC
- Urinalysis: RBC/WBC, cast, protein
- Ultrasound KUB

Specific investigation

Condition	Investigations
Acute Glomerulonephritis	Serum C3/C4, ANA, ANCA, ASO/AntiDNAaseB Kidney Biopsy
Thrombotic microangiopathy (HUS/TTP)	Peripheral smear, serum LDH, Serum haptoglobin, Coagulation profile Serum C3, ANA Anti-CFH antibody, stool for shiga toxin, DCT, ADAMTS13 activity
Tropical infections	Smear for malaria parasite, dengue serology, scrub serology, leptospiral serology etc.
Suspected nephrotoxin exposure	Drug levels if available
Obstructive pathology	CT/MRI, MCU study, DTPA scan

Acute Complications

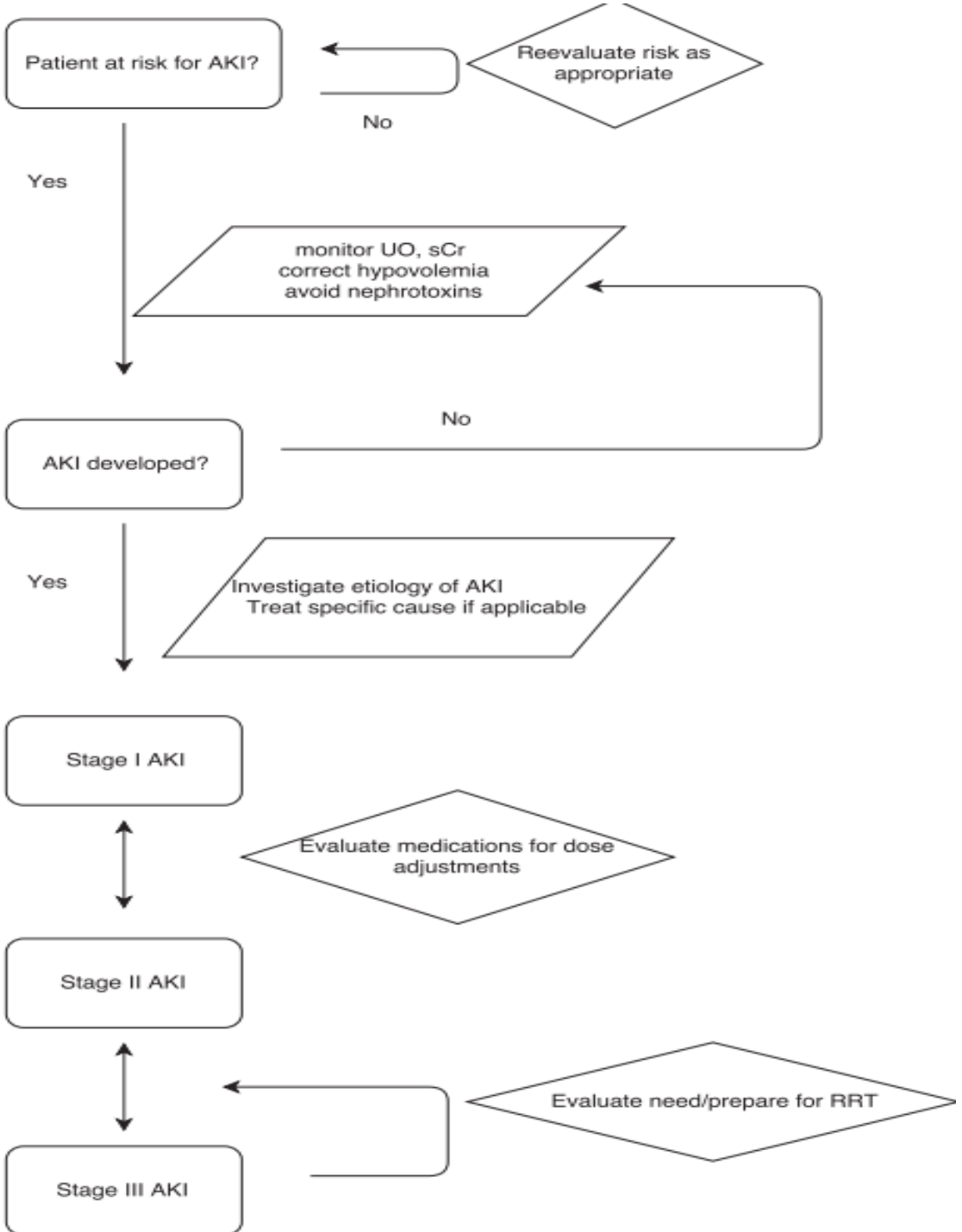
Hypertension
Hyperkalemia
Dysnatremias
Metabolic acidosis



Kellum et al, Nature reviews, Disease primers, 2021,7:52

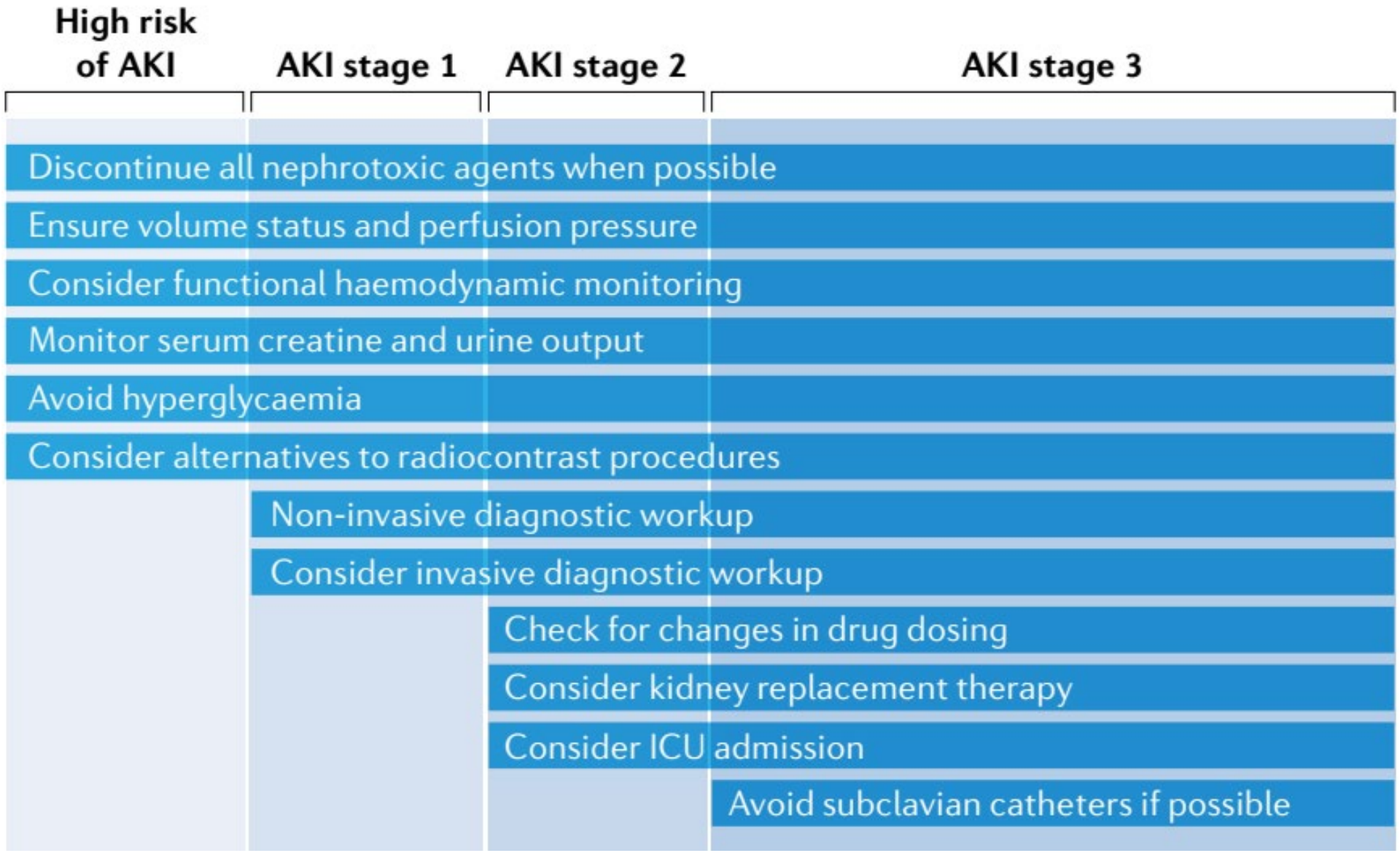
Management of Pediatric AKI

Conceptual model for the Management of AKI



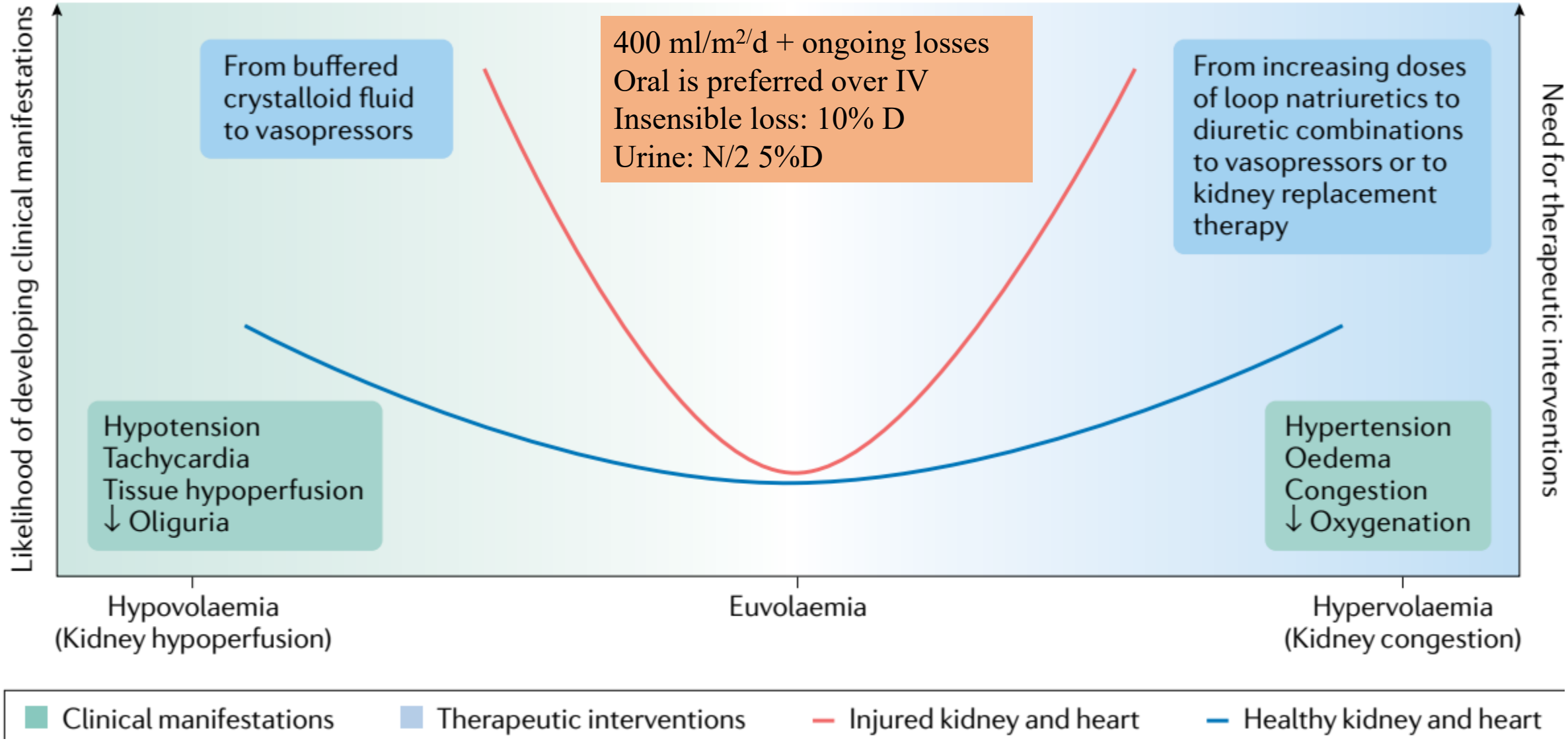
Moore et al, Am J Kidney Dis. 2018,72(1):136-148

Management: General Principles



KDIGO clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.* **2**, 1–138 (2012)

Fluid management in AKI: Guided by clinical assessment



Fluid management: Monitoring

- Strict input-output monitoring
- Daily weight
- Physical examination for fluid status: HR, RR, BP, edema, Crepts, S3 gallop
- Serum sodium, hematocrit

Judicious fluid administration with appropriate composition should allow 0.5-1% weight loss every day

Management of Complications

Complication	Management
Pulmonary edema	Oxygen, ventilation, fluid restriction, dialysis, IV furosemide 2-4 mg/kg (if delay in KRT)
Hypertensive emergency	Nitroprusside infusion 0.5-8 mcg/kg/min; Labetalol infusion 0.25-3 mg/kg/hr, furosemide if fluid overloaded, 25% of desired blood pressure reduction should be done with in 8h and remainder reduction over next 12 -24 h
Metabolic acidosis	Sodium bicarbonate oral or IV , if bicarbonate levels <18 mEq/L ; monitor for fluid overload and hypernatremia
Hyponatremia	Restrict fluid intake If altered sensorium, seizures: 3% saline 6-12 ml/kg over 30-90 minutes

Management of Hyperkalemia

Drug	Dose	Onset	Remarks
Calcium gluconate (10%)	1ml/kg IV over 3-5 min. may repeat after 10 min	5 min	Stabilizes cell membrane; prevent arrhythmias, administered given under cardiac monitoring
Salbutamol	5-10 mg through nebulization over 10 min	30 min	Shift potassium into cells
Insulin-dextrose	0.1 U/kg of insulin with 0.5 g/kg glucose IV over 30 min	20 min	Shifts potassium into cells , monitor for hypoglycemia
Sodium bicarbonate (7.5%)	1-2 ml/kg IV over 5-10 min	15-60 min	Shifts potassium into cells, do not give with calcium gluconate
Calcium or sodium resonium	1 g/kg/d orally or per rectally	2 h	Slow action with variable efficacy

Drug dose adjustment in AKI

Aim: To avoid kidney injury and toxic accumulation of the drugs

- Most drugs excreted by kidney will require dose modification @ eGFR < 50 ml/min/1.73 m^2
- If drug level measurement is available for a specific agent, it should be used to adjust its dosing during AKI
- Most medication do not require dose modification for first dose
- Avoid nephrotoxic drugs especially combination i.e. ACE+NSAIDs

  Vancomycin+ Zosyn, Colistin + Vancomycin

Pharmacotherapy for AKI

- Fenoldopam, ANP- not recommended currently

3.5.1: We recommend not using low-dose dopamine to prevent or treat AKI. (*1A*)

3.5.2: We suggest not using fenoldopam to prevent or treat AKI. (*2C*)

3.5.3: We suggest not using atrial natriuretic peptide (ANP) to prevent (*2C*) or treat (*2B*) AKI.

- Adenosine receptor antagonists- single dose of theophylline (5-8mg/kg) in neonates with severe perinatal asphyxia, at high risk of AKI

Vasopressors in AKI

There is no evidence that from a renal protection standpoint, there is a vasopressor agent of choice to improve kidney outcome

Nutrition in AKI: Can improve recovery rate

- Patients with AKI have increased metabolic requirement; usually catabolic
- Energy intake of 60-70 Calorie/kg
- Protein: 0.8-1.2 g/kg/day (increase to 1.0-1.5 g/kg/day if on PD)
- Supplement water soluble vitamins and other micronutrients if on hemodialysis

Enteral feeding should be preferred for all patients with AKI

Management of specific causes of AKI

Functional AKI	Crystalloids; Stop diuretics, NSAIDS, ACE inhibitors, Ionotropes
ATN	Supportive care, Withdraw drug or toxins, treat cause of circulatory failure
Glomerulonephritis	Supportive care, Immunosupression guided by specific etiology
HUS	Supportive Care, Plasma exchanges, Eculizimab, other immunosuppression (anti-CFH HUS)
Vasculitis	Immunosuppresion, Plasma exchange
Interstitial nephritis	Discontinue offending drug, Consider Steroids
Renal Artery/ Vein Occlusion	Anticoagulation, Thrombolysis or surgery
Intra-renal obstruction	Discontinue offending drug, alkaline diuresis for Rhabdomyolysis, hemoglobinuria or urate nephropathy
Urinary tract obstruction	Bladder catheter or nephrostomy, Correction of obstruction

Kidney replacement therapy

- Defining the intent and goals of kidney support therapy is crucial when deciding to commence KRT

Indications *When kidneys no longer have the capacity to meet the metabolic and fluid demand placed on them*

Urgent indications	Severe metabolic acidosis refractory to medical treatment
	Severe hyperkalemia refractory to medical treatment
	Pulmonary edema
	Uremic complications (pericarditis, encephalopathy, bleeding)
	Fluid overload coupled with organ dysfunction
	Concomitant intoxication with a dialysable drug or toxin
Relative indications	Progressive and/or persistent AKI (sCr >3 baseline and/or profound oliguria)
	Severe non-kidney organ dysfunction worsened by AKI
	Worsening trajectory of critical illness

Early versus Late KRT in AKI: Crux of the debate

Early vs Late criteria

Mortality

ELAIN trial (N=231)
Early: Stage 2 AKI (within 8 hr)+ NGAL >150 + ≥ 1 risk factor
Late: Stage 3 (within 12 hr), urgent indications, BUN >100 mg/dl

90 day 39% vs 64%

"Immediate initiation of KRT in the absence of a pressing AKI-related emergency does not lead to a meaningful improvement in clinical outcomes"

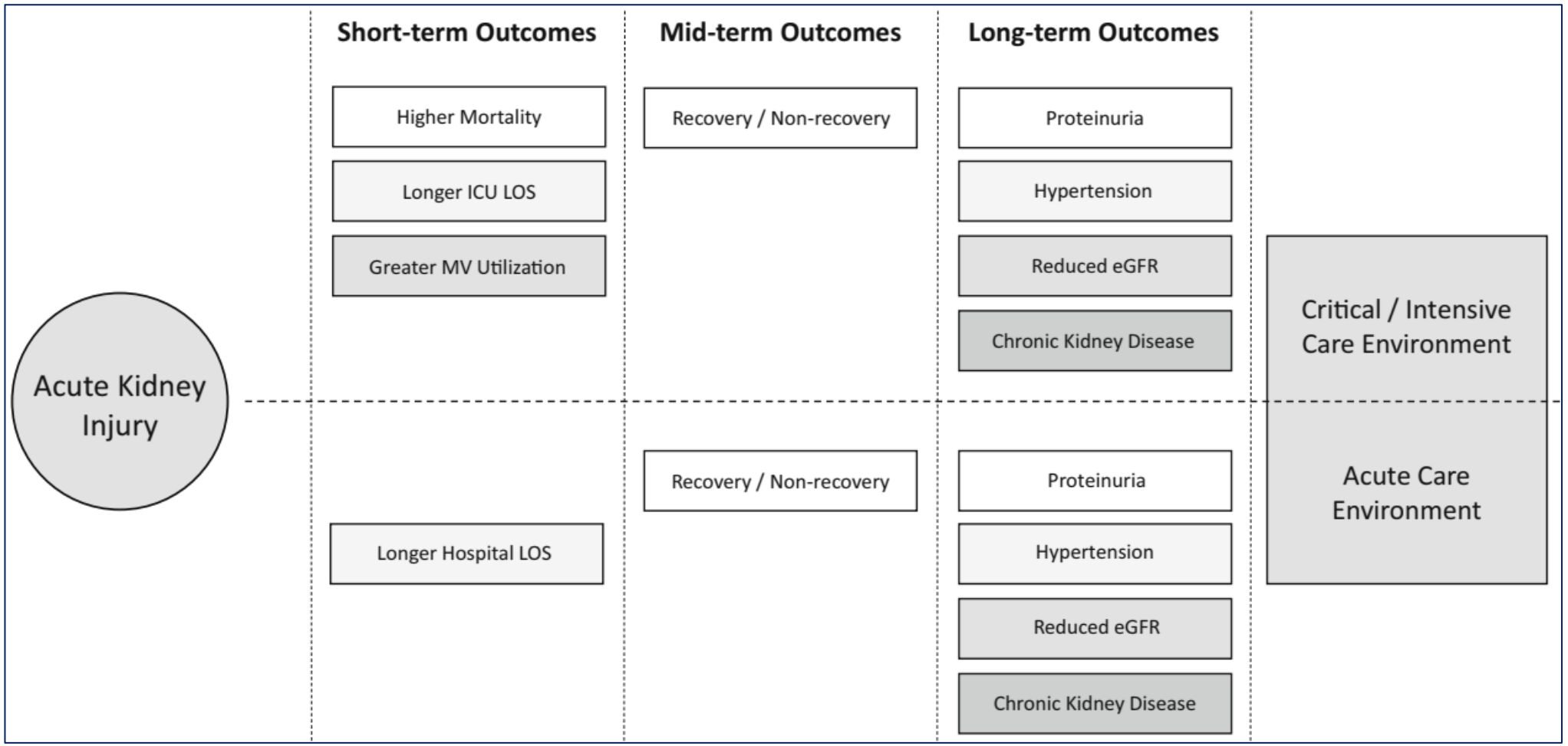
START-AKI trial (N=2927)
Early: Stage 2 or 3 (within 12 h)
Late: urgent indications, persistent AKI >72 h

90 day 44% vs 44%

AKIKI-2 trial (n=278)
Early: stage 3 and receiving vasopressors ± MV + oliguria .72 h or BUN 120 mg/dL
Late: Urgent indications, BUN >140 mg/dL

90 day 44% vs 55%

Outcomes in AKI

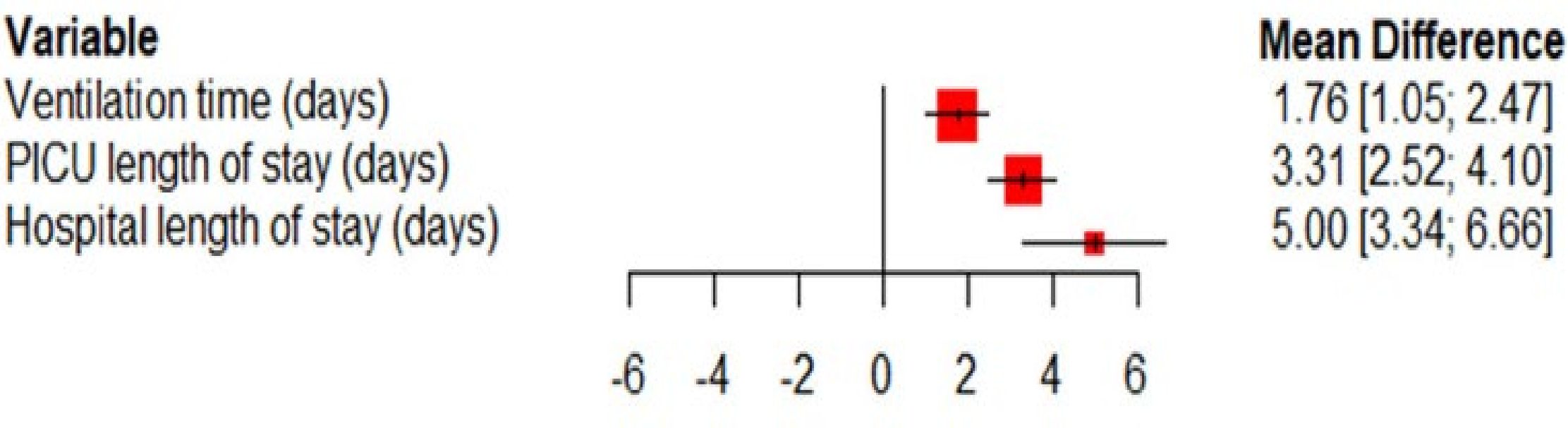


Uber et al Pediatric Nephrology (2020) 35:213–220

Short-term outcomes in AKI

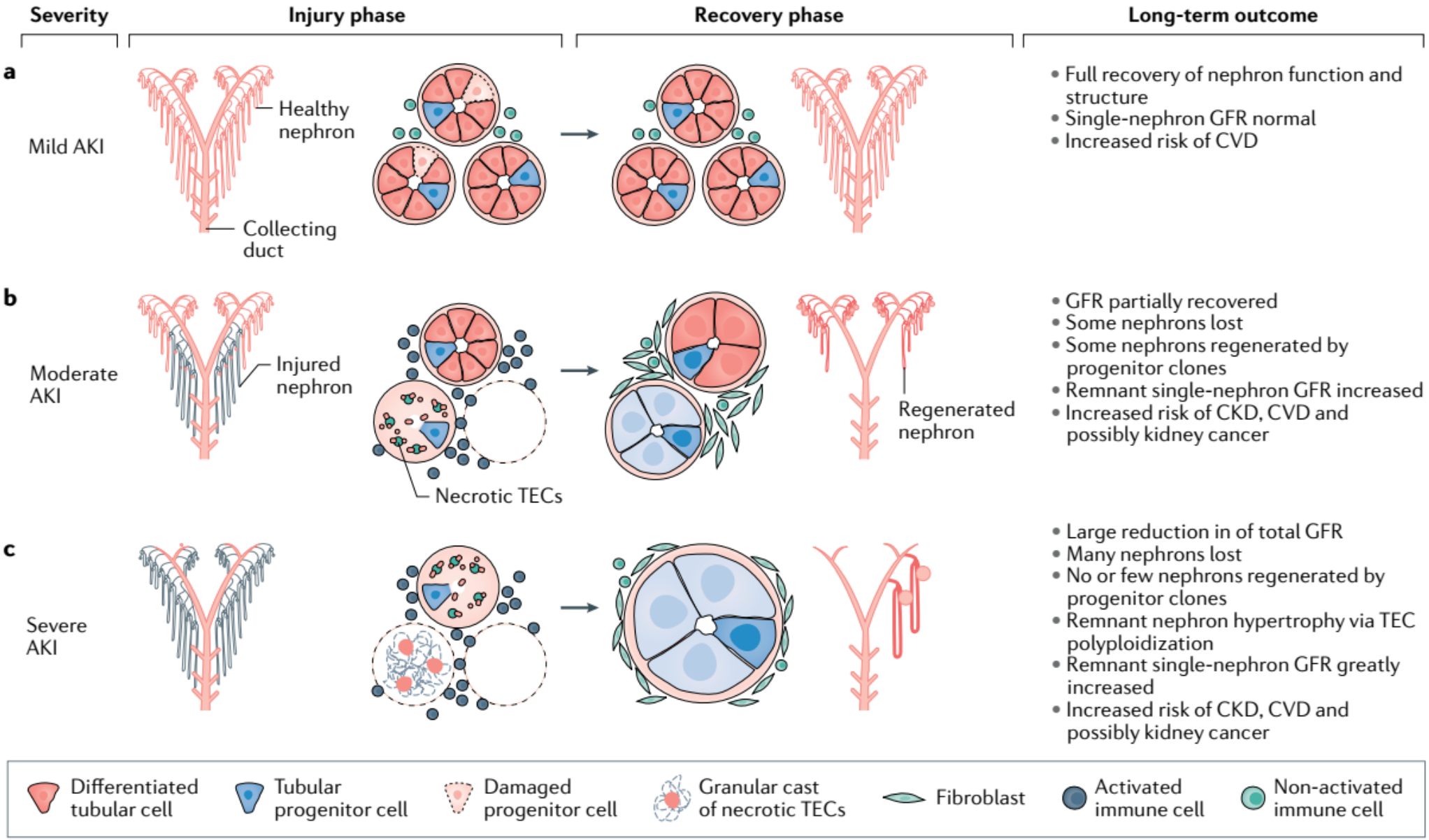
58 studies (18334 children post cardiac surgery)

Development of AKI associates with greater mechanical ventilation time, PICU and hospital length of stay



Eynde et al , Front. Pediatr. 9:733744. doi: 10.3389/fped.2021.733744

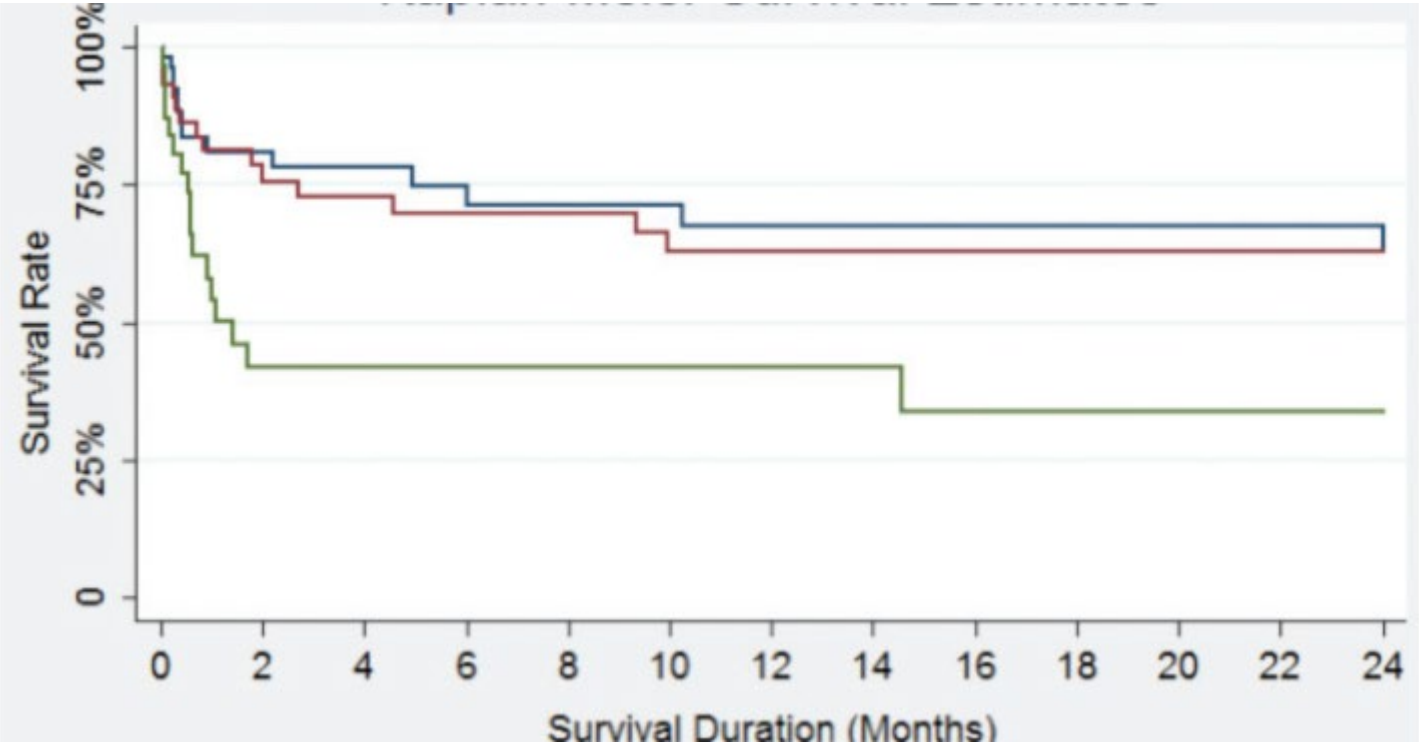
All is not Acute in AKI



Long-term outcomes

Retrospective cohort study 2012- 2013
N= 131 children
Children with AKI in PICU, Follow up: 2 years

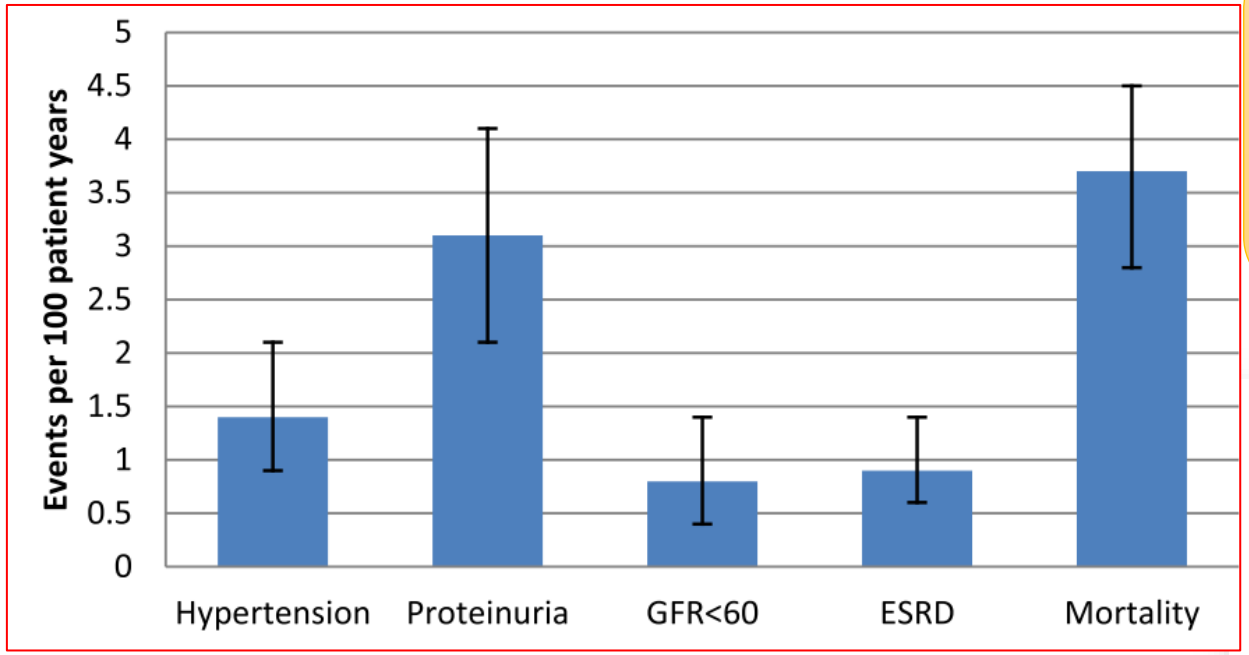
pRIFLE (n=131)	
Risk	42.0 %
Injury	34.4 %
Failure	23.7 %



At end of 24 months follow
Mortality -40%
CKD- 33%
Proteinuria- 33%
Hypertension- 73%

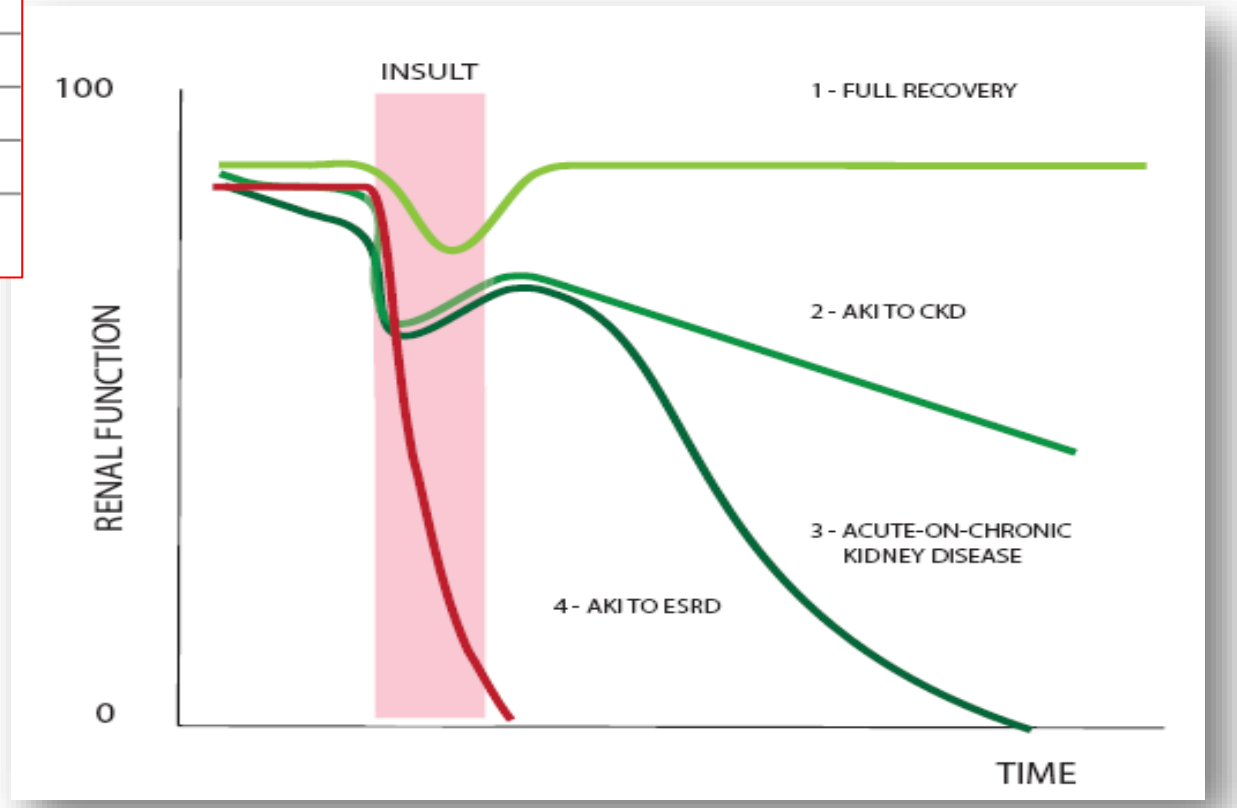
Al-Otaibi et al, Saudi Med J 2017 Feb;38(2):138-142

A considerable proportion of children develop long-term complication following AKI



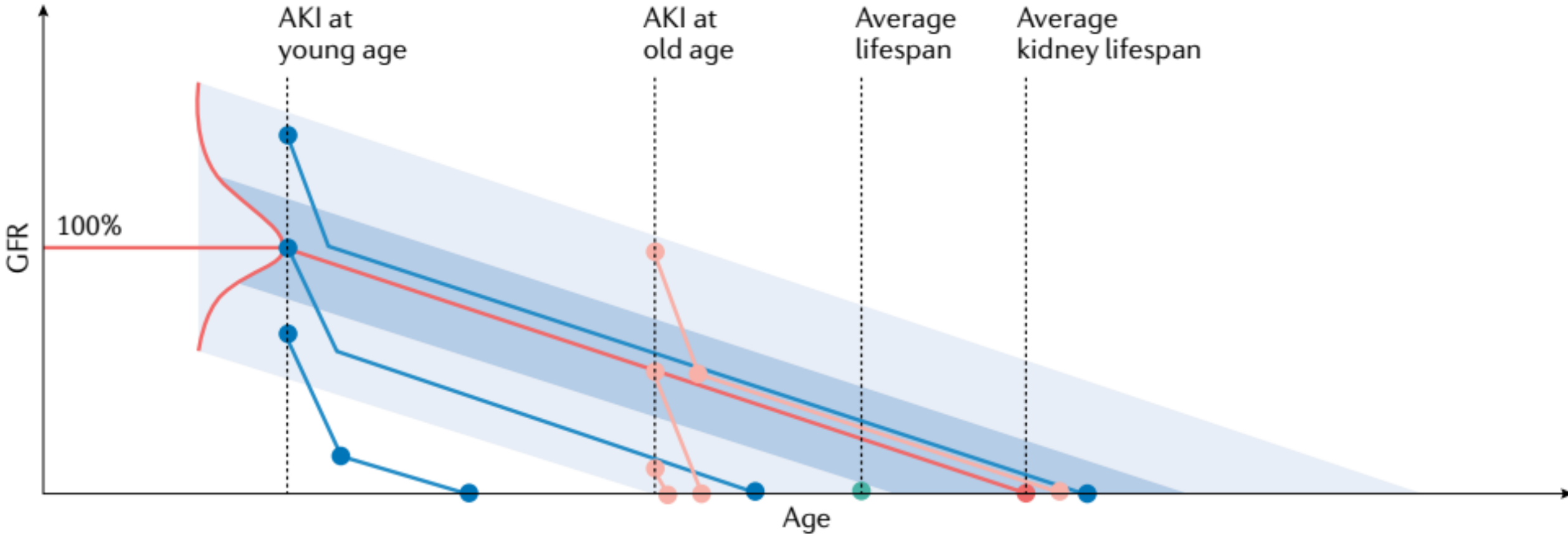
Greenberg *et al. BMC Nephrology* 2014, **15**:184
http://www.biomedcentral.com/1471-2369/15/184

10 cohort studies
N=364 children
Follow up duration mean 6.5 years
(range 2-16 years)



Clin J Am Soc Nephrol 3: 881-886, 2008

Kidney lifespan is determined by nephron endowment and age at time of AKI



*Kellum et al, Acute kidney injury. Nat Rev Dis Primers **7,** 52 (2021)*

Monitoring in AKI survivors

- Should be focused on detection of proteinuria, hypertension and decline in GFR as well growth in children
- First assessment should be made at 3 month
- 3-6 monthly afterwards as per patient risk factors and degree of recovery from AKI

Key messages

- Serum creatinine and urine output: currently used markers for diagnosis both should be used
- Early prediction of AKI is essential to prevent progression; subclinical AKI evolving
- Newer risk-stratification model may help in early recognition
- No role of dopamine and furosemide in prevention or treatment of AKI
- Incremental relationship between severity of AKI and mortality
- AKI is a not one time insult; associates with long term outcomes

Greetings from Command Hospital, Pune

Neonatal AKI….
The hows, whys and whats

Lt Col Suprita Kalra
Consultant & Prof
Pediatrics and Pediatric Nephrology
Command Hospital, Pune

Patient 1

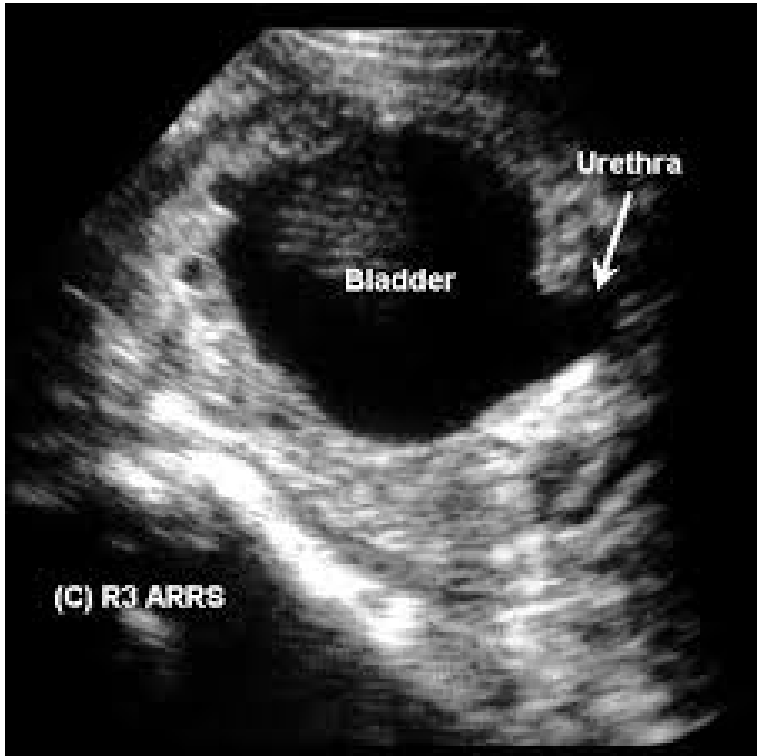
- 3 day old male neonate
- Born at 39 weeks 4 days POG
- Prolonged stage II, fetal distress, MSL
- Born limp, intubated and shifted to NICU
- Ventilated and on inotropes
- Seizures after 12 hrs of birth
- Oligo-anuria since birth
- Rising creatinine, metabolic acidosis

Patient 2

- 12 day old female neonate
- Born to 24 year old primi through SVD
- BW 2800gm
- Discharged at day 3
- Brought back on day 10 with lethargy, poor feeding
- O/E severe dehydration, weight loss of 580gm(20%)
- Serum Na:174meq/l, urea/creatinine:300/10mg/dl

Patient 3

- Male neonate born at 34 weeks POG
- Emergency LSCS
- Indication: severe oligohydramnios
- Antenatal USG: B/L HDN with loss of CMD
- UB distended:
  Keyhole sign +



Patient 4

- Male neonate at 60 h of life
- Born at 27 weeks POG
- Emergency LSCS
- Indication: severe maternal PIH
- RDS; received 2 doses of surfactant
- Mechanical ventilation & inotropic support
- Oligo-anuria since birth
- First creatinine at 48h 1.9mg/dl

NAKI: Survey of Perceptions Amongst Pediatricians and Neonatologists

- n=257 (135 neonatologists & 122 pediatricians)
- Most underestimated risk of AKI
- < 50% aware of AKIN or KDIGO criteria
- 50% unaware of risk of CKD in preterm neonates
- 50% unaware of need to follow up with pediatric nephrologist after NAKI

Sethi SK et al Front Pediatr. 2020 Jan 14;7:553.

Neonatal AKI Magnitude

- AKI incidence 8–40% in NICU
- AKI requiring RRT incidence ≤1%
- Mortality in neonates with AKI 60%
- Gestational risk factors include premature birth, IUGR,LBW

Viswanathan S et al. Pediatr Nephrol. 2012;27(2):303–311
Carmody JB et al. Clin J Am Soc Nephrol. 2014;9(12):2036–2043

- CHD 60% develop postoperative AKI

Alabbas A et al. Pediatr Nephrol. 2013;28(7):1127–1134

AKI in vulnerable groups

1	LBW	Hu Q et al. Sys Review. Front Pediatr. (2021) 9:666507. Askenazi D. Pediatr Nephrol. (2020) 2020:9.	AKI 25-40% Significant association btw LBW, early GA and AKI AKI associated with increased mortality and length of stay
2	CHD	Alten J.Crit Care Med. (2021) Sharma A et al. Kidney Res Clin Pract. (2020)	AKI 52-60% Stage 3 AKI associated with increased mortality aOR 2.44
3	NEC	Bakhoum C . J Matern Fetal Neonatal Med. (2019)	AKI 32-54%
4	Nephrotoxic medications	Salerno S. J Pediatr. (2021)	AKI 17%
5	ECLS	Murphy H et al.Blood Purif. (2021) 18:1–10.	AKI 51-70%

Acute Kidney Injury in Premature and Low Birth Weight Neonates: A Systematic Review and Meta-Analysis

Graphical Abstract

AIM: To summarize the literature and evaluate prevalence, risk factors and mortality of premature and low birth weight neonates

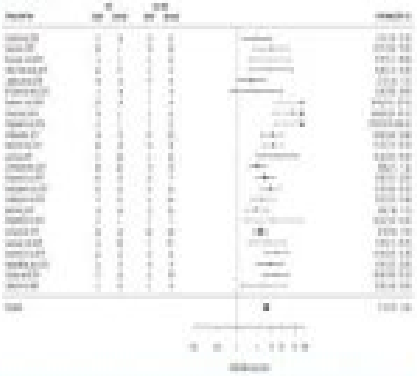
DESIGN & OUTCOMES:

AKI in premature and Low birth weight neonates

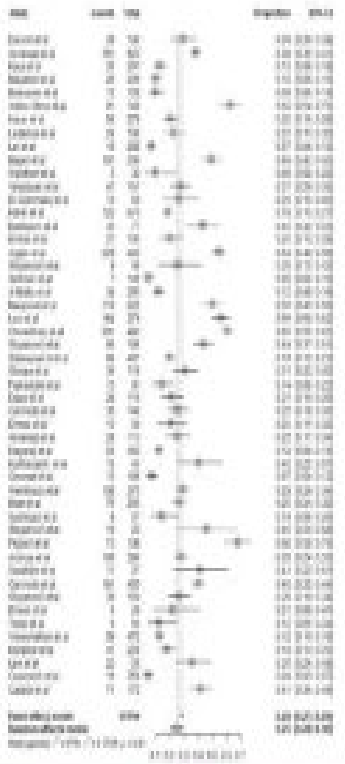
50 articles of 10,744 patients were included

Overall rate of AKI from the pooled results was 25% (95% CI 20–30%)

AKI with higher rate of mortality (OR = 7.13; 95% CI 5.91–8.60; *P*<0.01).



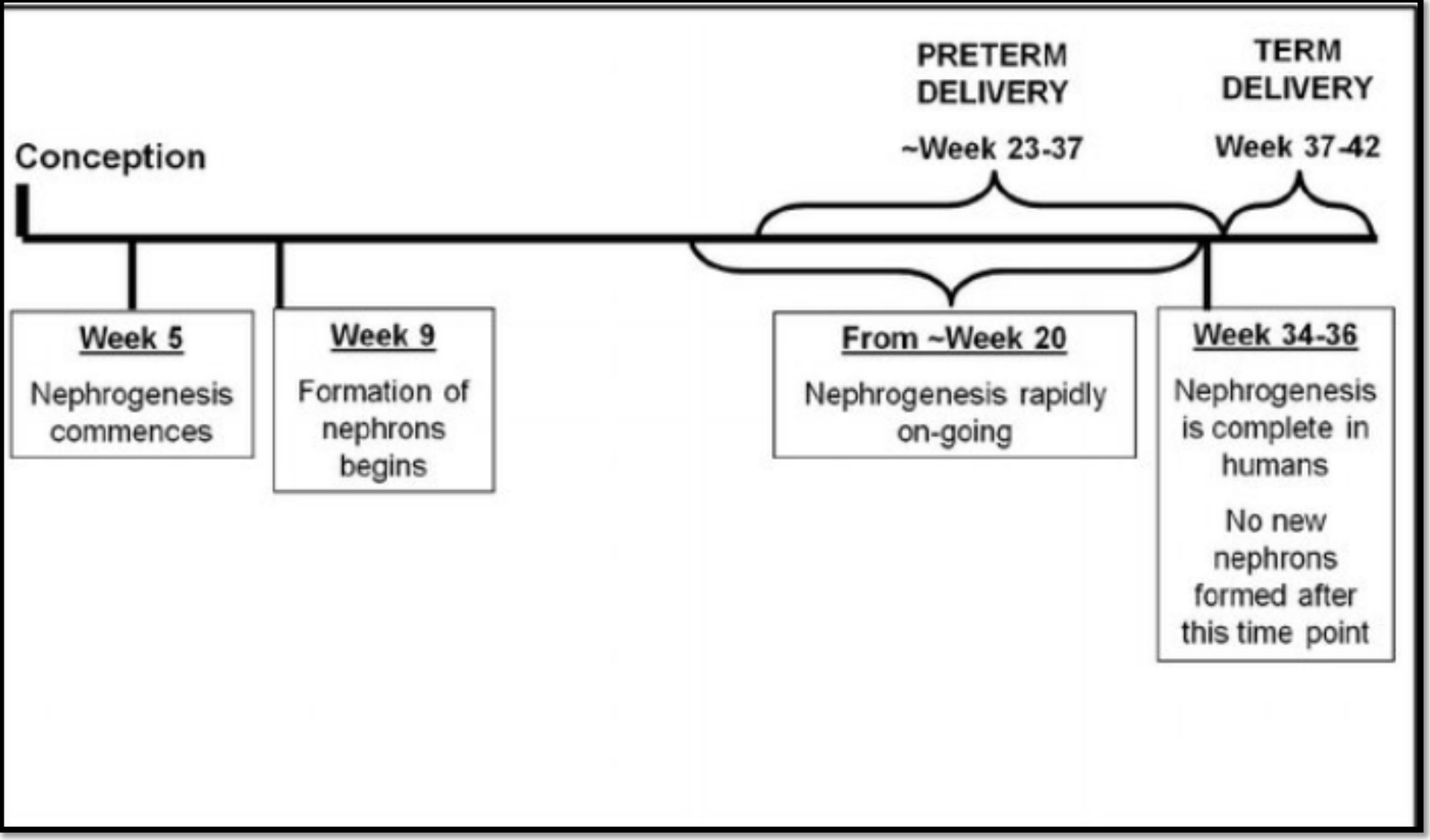
Risk factor of AKI included lower GA, lower Apgar score, mechanical ventilation, lower birth weight and sepsis etc.



CONCLUSION: AKI was prevalent and was associated with high mortality rate among preterm and low birth weight neonates.

Wu et al. 2021

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association



- Increase in BW by 1 kg : 2,00,000 additional nephrons
- Prematurity & LBW impact nephron number & development
- Cationic ferritin-enhanced MRI & radial glomerular count
- Increased risk for AKI and/or CKD

Normal GFR in neonates & children

Age	Mean GFR+/- SD (ml/min/1.73m^2)
29-34 weeks GA- 1 week postnatal age	15+/- 5.6
29-34 weeks GA- 2-8 week postnatal age	28.7+/- 13.8
29-34 weeks GA- above 8 week postnatal age	51>4
1 week term males and females	41+/-15
2-8 weeks term males and females	66+/-25
Above 8 weeks term males and females	96+/-22
2-12 years (males and females)	**133+/-27**
13-21 years (males)	140+/-30
13-21 years (females)	126+/-22

Pediatric and neonatal RIFLE criteria

	Creatinine critreia		Urine out put criteria	
	pRIFLE	**n RIFLE**	**P RIFLE**	**nRIFLE**
Risk	eCCL decrease by 25%	?	UOP<0.5ml/kg/hrx8hr	UO<1.5ml/kg/hr for 24hr
Injury	e CCL decrease by 50%	?	UOP<0.5ml/kg/hrx16hr	UO<1.Oml/kg/hr for 24hr
Failure	eCCL decrease by 75% or CCL<35ml/min/ 1.73m2.	?	UOP<0.3ml/kg/hrx24hr or anuric for 12hr.	UO<0.7ml/kg/hr for24hr or anuric for 12hr.
Loss of function	Persistant failure >4wks	Persistant failure >4wks	Persistant failure >4wks	Persistant failure >4wks
End stage	Persistant failure >3month	Persistant failure >3month	Persistant failure >3month	Persistant failure >3month

Neonatal AKI:KDIGO Classification

Zappitelli M et al. Pediatr Res. (2017) 82:569-73.

Stage	Serum creatinine	Urine output
0	No change in sCr or rise <0.3 mg/dl	≥ 1ml/kg/h
1	sCr rise ≥ 0.3 mg/dl within 48 h or sCr rise ≥ 1.5-1.9 x reference sCr within 7 days	≥ 0.5ml/kg/h but <1 ml/kg/h
2	sCr rise ≥ 2-2.9 reference sCr	≥ 0.3 ml/kg/h and > 0.5 ml/kg/h
3	sCr rise ≥ 3 x 3 reference sCr or sCr ≥ 2.5 mg/dl or receipt dialysis	>0.3 ml/kg/h

For infants up to 120 days

Defn based on Serum Creatinine

- Defn may not be same across gestational age

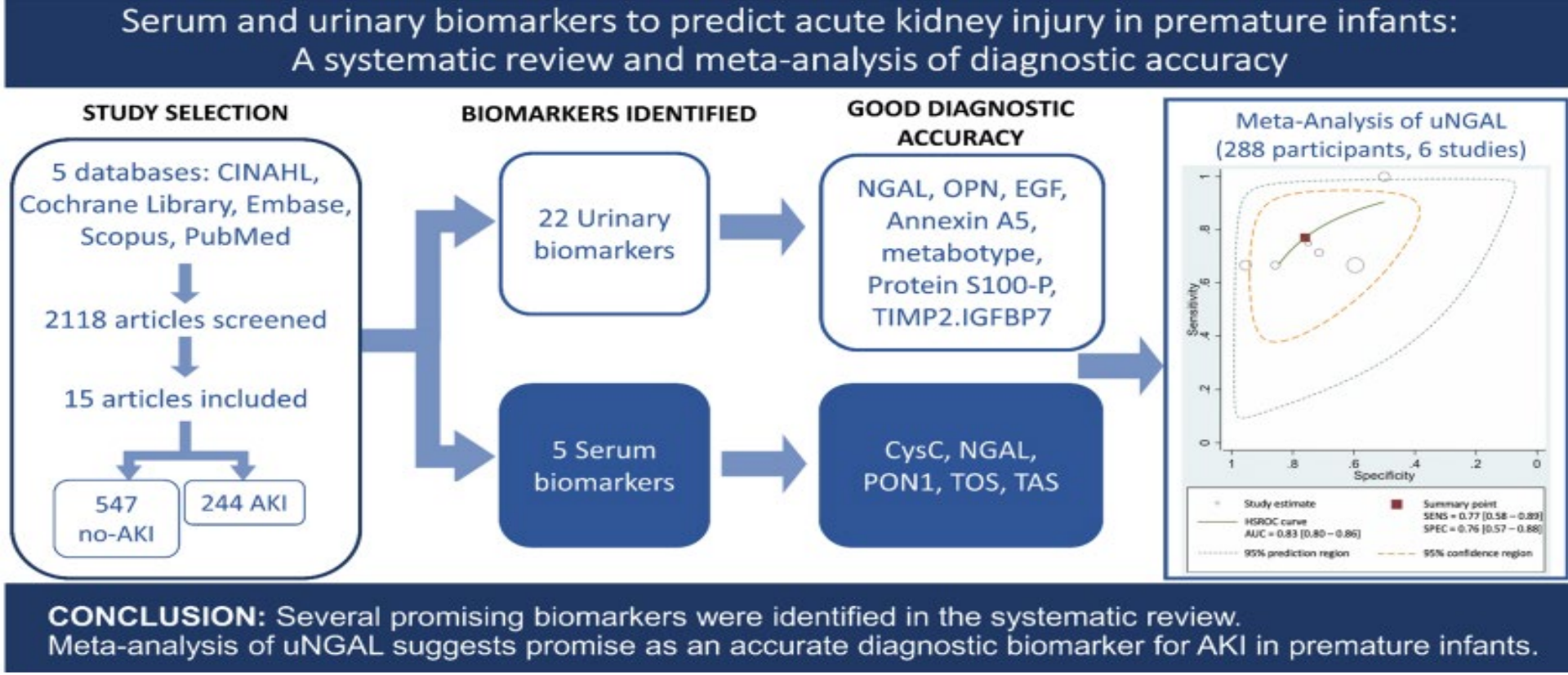
Askenazi D et al for AWAKEN cohort. Pediatr Res. (2019) 85:329–38

- Scr adjusted for TBW more accurate in VLBW
- Fluid-adjusted SCr:

  SCr × [TBW + Current wt – birth wt)]/TBW
- Lower incidence of AKI (18.8% vs 27.9%)

- Term neonates failure of drop of SCr in first postnatal week maybe significant

Gupta C. Pediatr Nephrol.(2016) 31:1167–78.



- In healthy preterms , Calbindin, Collagen IV, FABP1, GST, IP-10, KIM-1, Osteoactivin, Renin, TFF-3, TIMP-1, -1-Microglobulin, Albumin, Clusterin, Cystatin C, EGF, Lipocalin-2/NGAL and Osteopontin using multiplex kits at 72 h & 3 weeks of life.
- Significant increase in concentrations at 3 weeks parallel to rise in GFR
- Cystatin C however did not change

Correa LP. J Pediatr (Rio J). 2021 Sep-Oct;97(5):508-513.

Etiology of neonatal AKI

Multifactorial :

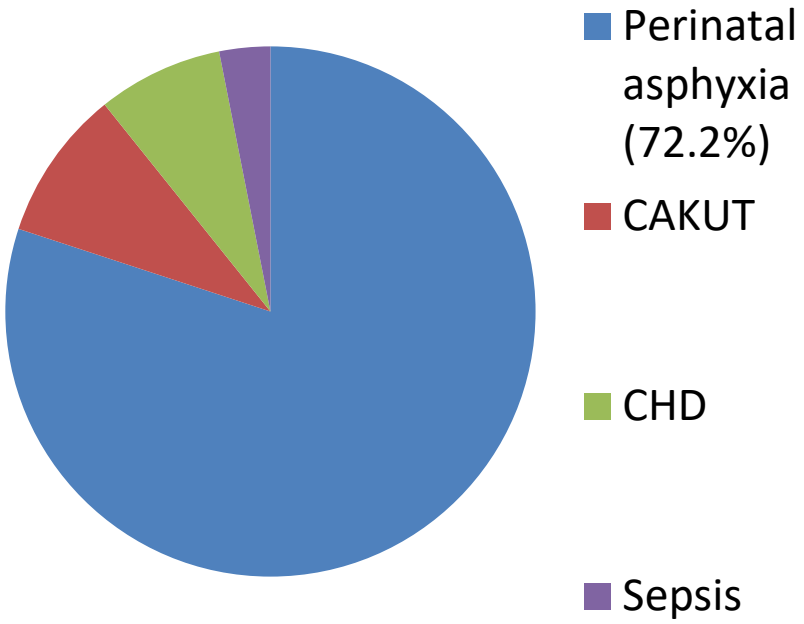
- Intravascular volume depletion: hypovolemia, sepsis
- Ischemia: low cardiac output, vasopressors
- Nephrotoxic medication
- MODS

Additional unique conditions predisposing to AKI

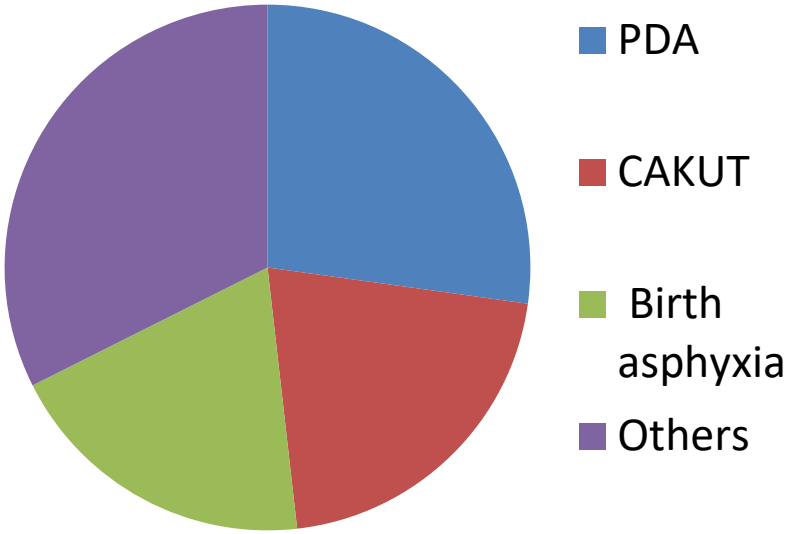
- Maternal medications esp ACEi/ARBs
- Prematurity/IUGR
- Placental blood loss at birth
- Perinatal asphyxia with renal ischemia
- Postnatal infections
- Excessive fluid losses
- Umbilical catheter-associated renal vessel thrombosis

Etiology of NAKI

Term Neonates



Preterm Neonates



Gallo D et al.Neonatology. 2021;118(2):174-179.

Neonatal AKI in developing countries

- Study from Thailand n=139
- Prevalence of NAKI increased from 0.9 to 6.3% during 24-year study period
- Incidence 6.4%
- 39% renal failure in 2 & 65% in 7 days after birth
- Sepsis-30.9%, Hypovolemia-18.7%, CAKUT-12.2%,Birth asphyxia-11.5%

  Prayong Vachvanichsanong et al. NDT, Volume 27, Issue 3, March 2012, Pages 973–977
- n=200 infants with sepsis, AKI in 26%, 15% had oliguria; 45% in 5.5 days

Indian J Pediatr 2006;73

Risk Factors and Outcomes of Early Onset Neonatal AKI
AWAKEN Study

CJASN
Clinical Journal of American Society of Nephrology

Cohort

Neonatal KIDNEY Collaborative

24 NICUs

2110 High Risk Neonates

>48 hr IV Fluids

Day 0 - 7

Outcomes

	Mortality	Hospitalization
		Adjusted OR / Mean Difference
449 AKI		2.8 (1.7-4.7) / 7.3 days (p <0.001)
1661 No AKI	Ref	Ref

Risk ↑

- Transfer from outside hospital
- Epinephrine drip
- High bilirubin
- Children's Hospital
- Inborn errors of metabolism
- Surgical need
- Frequent Creat Monitoring

Risk ↓

- Multiple gestation
- C section
- Antimicrobials, methylxanthines, diuretics, vasopressors

Conclusions AKI in the first postnatal week is common & associated with death and longer hospitalizations. The AWAKEN study demonstrates specific risk factors which can serve as "red flags".

Jennifer Charlton, Louis Boohaker, David Askenazi, Alison Kent, et al., on behalf of the NKC. ***Incidence and Risk Factors of Early Onset Neonatal Acute Kidney Injury***. CJASN doi: 10.2215/CJN.03670318.

Visual Abstract by Divya Bajpai, MD, PhD.

Risk factors and outcomes of acute peritoneal dialysis (PD) in neonates

PROSPECTIVE

Multicenter

TINKER Database
The Indian ICONIC Neonatal Kidney Educational Registry

All admitted neonates <28 days who received IV fluids for at least 48 hours, n=1600

Acute Kidney Injury (AKI per KDIGO criteria) n=491

n=44
9% required PD

Increased risk of needing PD among neonates w

4.95 (2.39-10.27)
p<0.001
Significant cardiac disease

4.77 (1.98-11.51)
p<0.001
Inotropes usage

4.17 (1.00-17.59)
p=0.04
Respiratory support in NICU

3.96 (1.21-13.02)
p=0.03
Necrotizing enterocolitis

3.69 (1.27-10.70)
p=0.02
Fluid overload during 1st 12 hours in NICU

2.72 (1.
p=0
Resuscitat
deliver

AKI neonates with PD (vs. those without PD)

7 vs. 11
p=0.004
Lower median duration of stay in NICU (days)

Conclusions There is a need to keep a vigilant watch in neonates with risk factors for development of AKI and need for peritoneal dialysis.

Sidharth Kumar Sethi, Sanjay Wazir, et al (Corr
Factors and Outcomes of Neonates with Acu
Dialysis: Results from the Prospective TINK
Neonatal Kidney Educational Registry] Stud

Visual Graphic by Edgar Lerma, MD

Nephrotoxic Drugs in NICU

87 % VLBW exposed to nephrotoxic medication & 26 % develop AKI

Rhone et al. J Matern Fetal Neonatal Med. 2014;27D14:1485–90

ACEi	**GFR ↓ due to inhibition of efferent arteriole constriction**
Aminoglycosides	Toxic to proximal tubules, lysosomal accumulation, intrarenal vasoconstriction & local glomerular/ mesangial cell contraction
Amphotericin B	Distal tubular toxicity, vasoconstriction, and decreased GFR
NSAIDS	Decreased afferent arteriole dilatation due to ↓PG production resulting in ↓ GFR
Radiocontrast agents	Renal tubular toxicity secondary to increase in reactive oxygen species;
Vancomycin	Proximal tubular injury

Risk factors for aminoglycoside nephrotoxicity

- Concurrent use of other nephrotoxic medications
- High drug levels
- Prolonged treatment courses
- Repeated treatment courses
- Intravascular volume depletion
- Pre-existing renal dysfunction

Aminoglycosides only if no appropriate, less nephrotoxic alternatives exist

Interventions for Prevention

NINJA: Nephrotoxic Injury Negated by Just-in-time Action

- Prospective quality improvement project
- Non critically ill hospitalized children receiving iv aminoglycoside >3 days or >3 nephrotoxins simultaneously
- Daily serum creatinine in exposed patients
- 1749 patients,2358 hospital admissions,3243 episodes of nephrotoxin exposure
- 575 had AKI episodes over 43-month study period
- Overall exposure rate decreased by 38% (11.63-7.24 exposures/1000 patient days), and the AKI rate decreased by 64% (2.96-1.06 episodes/1000 patient days)

Goldstein et al.Kidney Int. 2016 Jul;90(1):212-21

SYSTEMATIC REVIEW ARTICLE

Front. Pediatr., 18 February 2020 | https://doi.org/10.3389/fped.2019.00568

Efficacy and Safety of Paracetamol for Patent Ductus Arteriosus Closure in Preterm Infants: An Updated Systematic Review and Meta-Analysis

Yingqi Xiao[1], Hui Liu[2], Rujun Hu[1], Qiang You[3], Min Zeng[4] and Xiaolian Jiang[1*]

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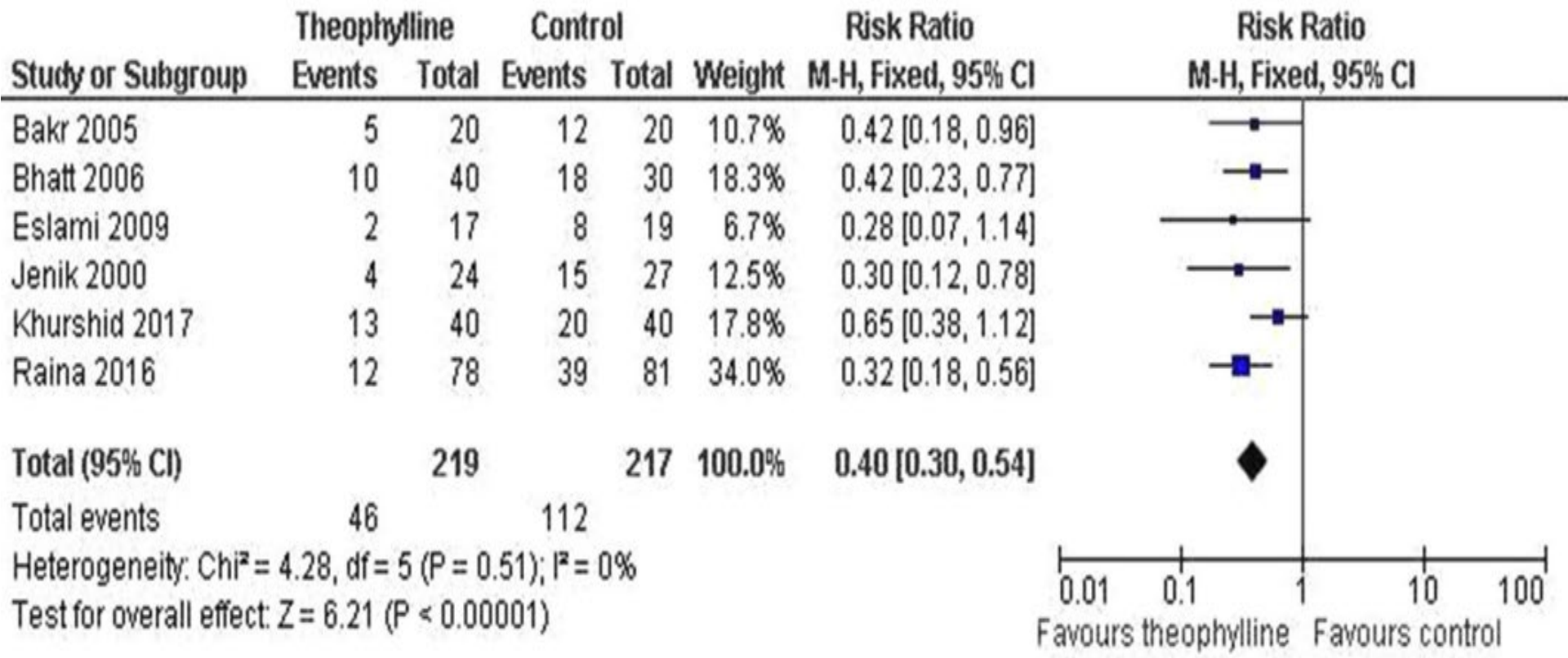
[Intervention Review]

Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants

Arne Ohlsson[1a], Prakeshkumar S Shah[2]



- Six trials,n= 436 term neonates with birth asphyxia
- Received a single dose of theophylline
- Pooled estimate 60% reduction in incidence of AKI (RR: 0.40; 95% CI 0.3 to 0.54; heterogeneity: I^2=0%) decrease in serum creatinine over days 2-5
- No significant difference in all-cause mortality

Bhatt GC, Gogia P, Bitzan M, et al Archives of Disease in Childhood 2019;104:670-679.

Principles of Management

Maintain neonatal homeostasis

- Early recognition of patients at high risk patients & incipient AKI
- Strategies to prevent or minimize progression of AKI
- Fluid & Electrolyte balance
- Nutrition
- KRT when indicated

Story of Biomarkers: the quest continues

Author	Year	Design	Sample, *n*	Biomarkers studied	Findings
Essajee et al[34]	2015	Prospective case control	108	uNGAL	uNGAL was significantly higher in asphyxiated infants with AKI compared with those without AKI
Oncel et al[44]	2016	Prospective case control	61 41 with asphyxia (15 with AKI; 26 without AKI) 20 controls	uNGAL uIL-18	uNGAL and uIL-18 were significantly elevated in infants with asphyxia compared with controls, and also in asphyxiated infants with AKI compared with asphyxiated infants without AKI
Hazle et al[45]	2013	Prospective observational	49	uNGAL uIL-18 uKIM-1 uCys C	Elevated uNGAL, uIL-18, and uCys C at 24 h following cardiopulmonary bypass surgery identified infants at risk for poor outcomes (death, AKI, prolonged intubation, and hospitalization)
Smertka et al[47]	2014	Prospective case control	102 (51 mild sepsis, 22 severe sepsis, 29 no sepsis)	sNGAL uNGAL sCys C	sNGAL and uNGAL were not correlated with AKI in septic term infants, but strongly correlated with inflammatory markers (C-reactive protein and procalcitonin). sCys C was not correlated with AKI in septic infants
Askenazi et al[48]	2012	Prospective case control	33 (9 with AKI, 24 without AKI)	uKIM-1 uCys C uNGAL uOPN	Elevated levels of uCys C was predictive of AKI
Treiber et al[42]	2012	Prospective case control	100 50 asphyxiated	sCys C	sCys C was a more sensitive marker of GFR than SCr in

Noninvasive continuous monitoring of renal oxygen saturation with near-infrared spectroscopy (NIRS)

- Renal tissue oxygenation (RrSO2) monitoring surrogate for local tissue oxygen use
- Lower RrSO2 in preterms who develop AKI on first postnatal day or week

Dorum BA.Pediatr Int. 2021;63(3):290–29

- In postop cardiac patients, NIRS detected decline in RrSO2 before SCr or UOP

Harer MW.Pediatr Nephrol. 2021;36(6):1617–1625

Management of neonatal AKI

- Early assessment for cardiogenic shock & timely PGE1 infusion for duct-dependent CHD
- Rapid but judicious fluid resuscitation and/or inotropes in hypovolemic or septic shock
- Fluid overloaded in first 3 days in NICU higher mortality and longer ventilation

Matsushita FY et al.Eur J Pediatr. (2020) 179:1665–71.

- Re-establishing UOP with diuretics may reduce KRT
- Diuretics help in fluid overload but not outcome of AKI

Am J Kidney Dis 2004;44

Management of neonatal AKI

- Therapeutic hypothermia potential reno-protection

- Single dose of 5 mg/kg IV theophylline within 1st h of life in neonates with severe birth asphyxia
- Caffeine shown to reduce AKI in retrospective study of 140 VLBW
- AKI occurred less frequently if caffeine in first postnatal week

  Secondary analysis of AWAKEN study
- Number needed on caffeine to prevent 1 episode of AKI was 4.3.8

- Metanalysis low dose dopamine no benefit
- Mannitol or Fenoldopam also no benefit

Nutrition of neonate with AKI important:

- Calories needed 100 Kcal/kg/d
- Proteins 1-2 gm/kg/d
- Enteral nutrition with EBM best
- TPN if enteral feeding not feasible

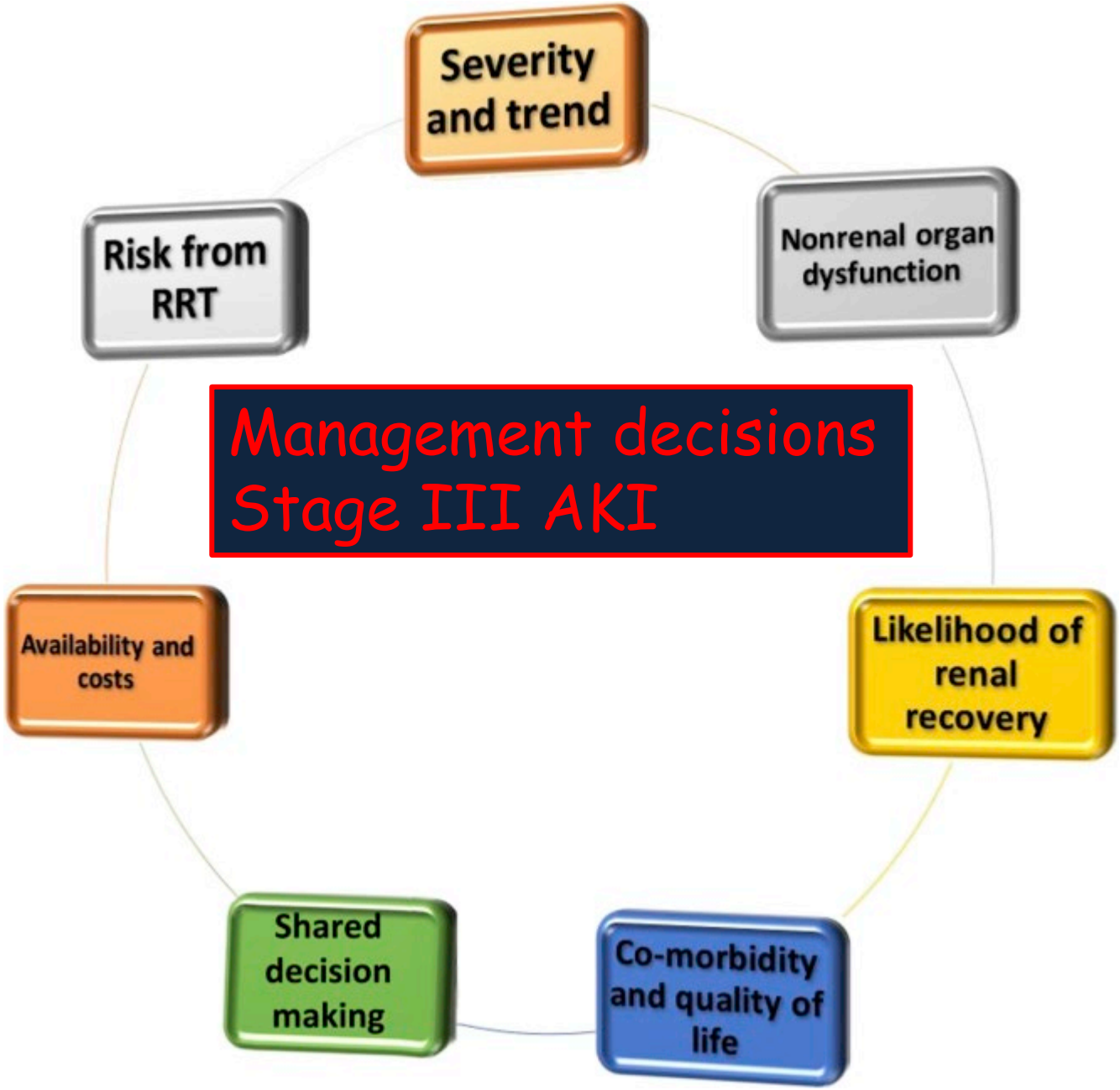
Ann Intern Med 2005;142

KRT in neonates: transition "last-ditch effort" to early Goal directed therapy

Indications for KRT in neonates:

- Refractory acidosis
- Uremia
- Electrolyte abnormalities esp high K
- To make space for nutrition
- Fluid overload
- Hyperammonemia /toxin removal

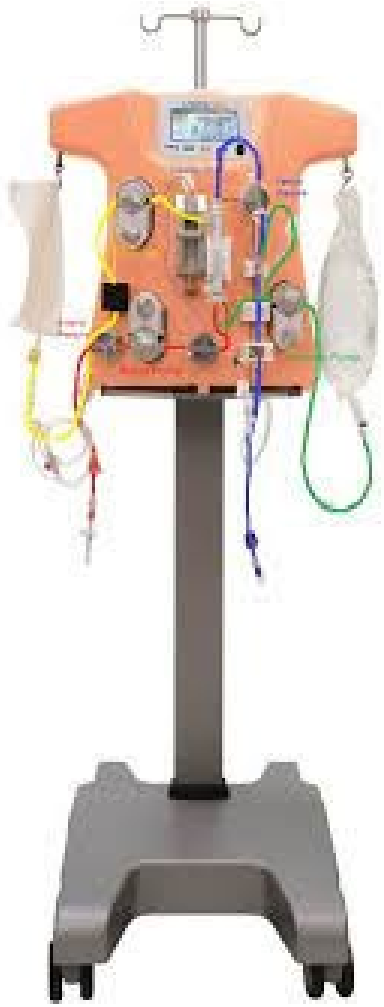
Fluid overload >20% at initiation of RRT independent predictor for mortality


Severity and trend
Nonrenal organ dysfunction
Likelihood of renal recovery
Co-morbidity and quality of life
Shared decision making
Availability and costs
Risk from RRT
Management decisions
Stage III AKI

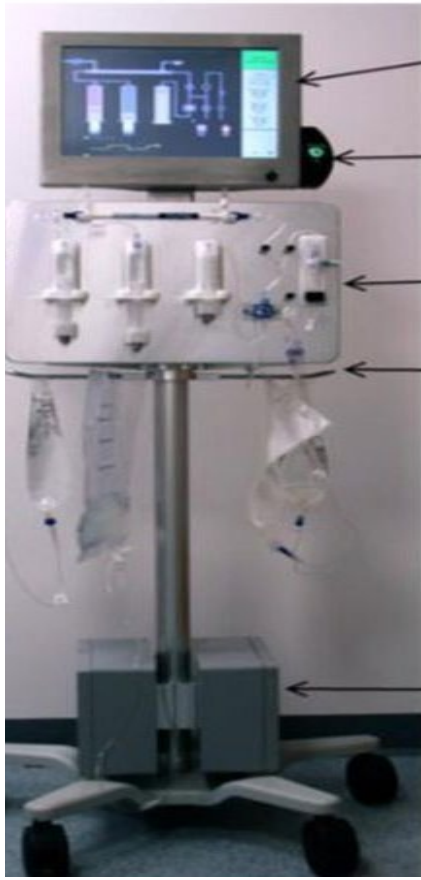
Modalities of RRT

- PD conventionally modality of choice
- HD & CRRT technically difficult
- Few small series

  Wu CY. *Front Pediatr.* 2021;9:769220.
- Vascular access and systemic anticoagulation
- Neonatal CRRT machines: Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM®) and Newcastle Infant Dialysis and Ultrafiltration System (NIDUS®)



CARPEDIEM®



NIDUS®

Original Article

Acute peritoneal dialysis in neonatal intensive care unit: An 8-year experience of a referral hospital

Aslihan Kara [a,*], Metin Kaya Gurgoze [a], Mustafa Aydin [b], Erdal Taskin [b], Unal Bakal [c], Aysen Orman [b]

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Received Dec 19, 2016; received in revised form Jun 8, 2017; accepted Nov 10, 2017
Available online 16 November 2017

Indian Pediatr 2020;57: 420-422

Acute Peritoneal Dialysis in Premature Infants

Meliha Aksoy Okan[1], Sevilay Topçuoglu[1], N Nilgun Karadag[1], Elif Ozalkaya[1], Hande Ozgun Karatepe[1], Gonca Vardar[1], Aysenur Celayir[2] and Guner Karatekin[1]

From [1]Departments of Neonatology and [2]Paediatric Surgery, Zeynep Kamil Maternity and Children's Training and Research Hospital, University of Health Sciences, Istanbul, Turkey.

Long term Outcomes

- Neonates who survive AKI might experience long-term renal dysfunction

Mammen C et al. Am J Kidney Dis. 2012;59(4):523-530.

- AKI significantly associated with increased likelihood of unfavorable outcome at 24 months in term neonates with HIE

Cavallin, F., Rubin, G., Vidal, E. *et al.* *Pediatr Nephrol*. 2020; *Pediatr Nephrol* **35,** 477–483 (2020).**35,** 477–483.

KDIGO practice guidelines recommend all neonates with AKI be evaluated after 3 m for new onset or worsening CKD & thereafter even if CKD not present at that time

Take home messages

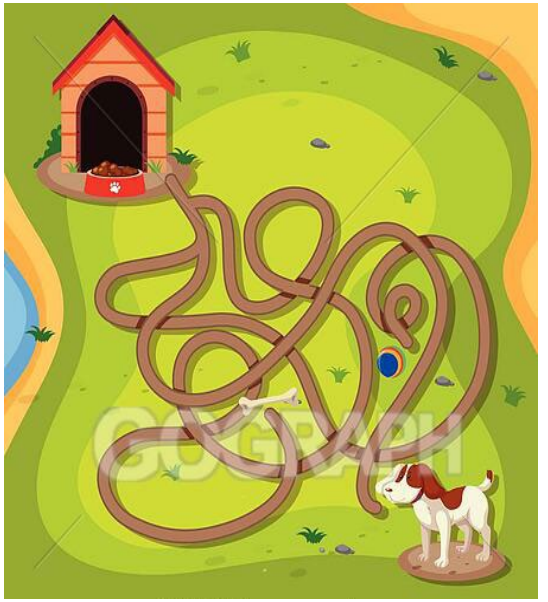
- AKI determinant of morbidity and mortality in critically ill neonates
- Prematurity and LBW are risk factors for AKI
- Nephrotoxic medications increase susceptibility to AKI in critically ill neonates
- Early identification of at risk neonates & timely diagnosis & management including

  KRT improves outcomes
- Neonates post AKI experience

  long-term renal dysfunction and

  should be monitored periodically

  for CKD



Thank you for patient hearing

Any questions????

Case discussion- Sepsis

Dr Sudarsan K

Assistant Professor

Department of Paediatrics

JIPMER, Pondicherry

Dr Georgie Mathew

Associate Professor

Department of Paediatrics

CMC, Vellore

History

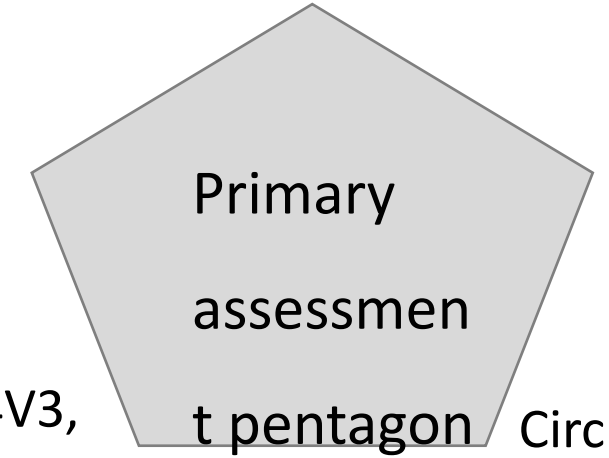
9 mo old infant brought with fever for 3 days, cough and rapid breathing for 2 days

No h/o ear discharge, seizures, diarrhea, rash

Infant is lethargic for the last 24h with decreased feed intake; has not passed urine in the last 10h

Airway: Open, patent

Exposure: Mottled skin



Breathing: RR 56/min, Rt LZ crepts with bronchial breathing, SpO2 91%

Disability: E3M4V3, no FND

Circulation: PR 174/min, CFT 4s, CP++/PP+, cold peripheries, BP 68/40 mm Hg, RBS 52 mg/dL

Focussed examination

CVS: Tachycardia, no murmur

RS: B/L AEE, Rt LZ bronchial breathing with crepts

P/A: soft, non tender, no organomegaly

CNS: No FND or meningeal signs

Head to toe: Periorbital puffiness +

No eschar, rash, petechiae

Weight 7 kg

Imp: Severe pneumonia with septic shock

Management in the casualty

O2 by nasal prongs, 4L/min

Dextrose bolus f/b 100% maintenance IVF

NS bolus 140 ml over 30 min → Tachycardia persisted, BP not improved → Second bolus 140 ml over 30 min → Liver 6 cm below RCM, PR 162/min, BP 69/38 mm Hg

Adrenaline 0.1 mcg/kg/min started and hiked to 0.3 mcg/kg/min

1st dose Ceftriaxone started

catheterized: No urine

Baseline investigations

Hb	8.1 g/dL
TLC	18560
DLC	N86 L12
Plt	1.8 L
Urea	85 mg/dL
Creatinine	0.89 mg/dL
Na/K	138/5.8

pH	7.26
pO2	64
pCO2	50
HCO3	15.7
Lactate	5.6

~~CXR: Rt lower zone patch~~

Revised diagnosis: Severe Pneumonia with septic shock with AKI stage 3

Continues to be anuric 12 hours later

Does the child warrant kidney replacement therapy?

If yes, what and how?

KRT

PD catheter inserted

Rationale

1. Fluid overload state

Fluid in so far: 280 (bolus)+ 70 (drugs)+350 (maintanance) = 700 ml

Anuric

Fluid overload = 700 ml = 10%

2. Acidosis

PD prescription

Reservoir – 10 ml/kg
Dwell volume 600-800 ml/m^2 or 20-40 ml/kg → start with 100-140 ml and go up rapidly to 150-200 ml per cycle , watch for respiratory distress
Dwell duration – short duration for small molecules (water, potassium, acidosis) → 20-30 min per dwell
Anticoagulation – 500-1000 U/L heparin
Potassium – currently no potassium added to dialysate – add when levels are below 4-4.5 mEq/L

Monitoring

Blood gas/potassium levels after 6-8 cycles
Blood sugar monitoring
Leaks around catheter
Peritonitis q48 hourly

Contrast Associated AKI

Case based scenarios

Dr Anshuman Saha

MD, DM (Pediatric Nephrology, SJMCH)

Associate Professor, IKDRC, Gujrat

Dr. Sumantra Kumar Raut

MD, DM (Pediatric Nephrology, AIIMS)

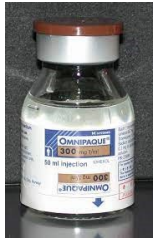
Asst Professor, NBMC, West Bengal

2nd Annual Pediatric Kidney Meet

AIIMS, Jodhpur

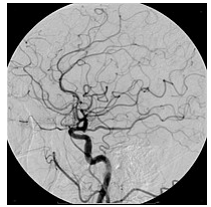
29.01.2023

Introduction



- Contrast associated AKI: 24-48 hrs of radio contrast, not necessary causal
- Incidence: 10-50% (CECT), mostly if premorbid eGFR is low *Radiology, 2013*

- Mostly mild, non oliguric, rapid recovery (<7 days) if not prior CKD
- Renal vasoconstriction (medullary hypoxia, NO, endothelin) OR tubular damage OR both



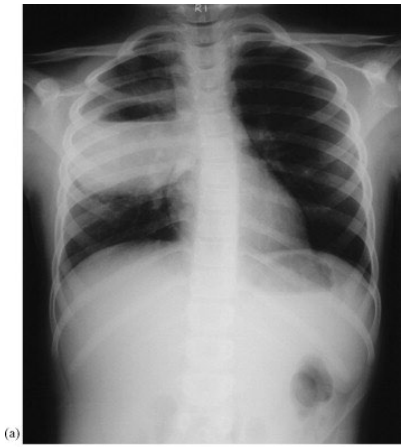
- Prevention >> management
- Avoidance of contrast, low vs iso osmolar dosing ALARA (Iohexol ??)
- Intravenous hydration helps; alkali and NAC doubtful role

Case: 1

5y old boy Rahul admitted in PICU with pneumonia, sepsis, septic shock (Nov 22)

no premorbid illness

Persistent fever after initial improvement



On day 7 of admission:
Resp worsening: 5 litre of O_2 with H3FNC: Spo2 93%

Out of shock (MAP: 78), off inotropes, but on IV maintenance fluid

X Ray reveals a suspected pulmonary abscess (Rt)
No history of contact of Tuberculosis
Undergoes contrast enhance CT chest

Investigations:

	Day 7	Day 9	Day 11	Discharge
Hb	13 g/dl	13.5 g/dl	12 g/dl	12 g/dl
CRP	110	92	75	12
Creat	0.7 mg/dl	1.2 mg/dl	1.0 mg/dl	0.5 mg/dl
Urea	112 mg/dl	113 mg/dl	85 mg/dl	45 mg/dl
Urine output	500 ml	520 ml	750 ml	1.2 l

Q1. What is the provisional diagnosis ??

CIN vs CA-AKI

Multifactorial: Radio contrast, sepsis, shock, other nephrotoxic antibiotics;
Diagnosis of exclusion: non oliguric, mild AKI, rapid onset, rapid recovery, low FENa

Q2. Is it AKI?

Yes: 1.2 → 0.5 (7 d) >> 0.7 → 1.2 (48 hrs) *KDIGO, 2012*

Q3. If yes, which stage of AKI?

1.2 → 0.5 (7 d) : stage 2

Q4. What may be the etiology, pathogenesis of AKI in Rahul ?

Hypovolemia and hypoperfusion of kidney
Volume and osmolality of contrast; Iodinated vs non iodinated contrast
Other conventional risk factors of AKI

Prevention

Euvolemia:

- Adequate hydration; difficult in sick children
- Pre and post 6-12 hrs 1 ml/kg/hr vs pre 1 hr 3ml/kg and post 6 hrs 1.5 ml/kg
- NS > $NaHCO_3$ and IV > oral *NEJM, 2018*

Appropriate contrast type and volume

- Non ionized , Low osmolar (600 mosm/L) vs iso osmolar (300 mosm/L)
- Volume: as low as reasonable
- Try to find alternate mode of investigations (MRI vs CT for abdomen)

Other drugs:

- NAC, fenoldopam, Vit C, diuretics, stop ACEi (under investigations)

Treatment

Conservative management – general principle of AKI

- Fluid, electrolytes
- Antibiotics dose modify
- RRT : rarely needed
- Euvolemia
- Forced diuresis
- NAC-Doubtful role

Summary

- CA AKI rare these days
- Multifactorial in etiology
- Difficult to prove causation

- Maintenance of euvolemia is the key to prevent AKI after contrast exposure
- Treatment is symptomatic and conservative
- Outcome is usually very good

Thank you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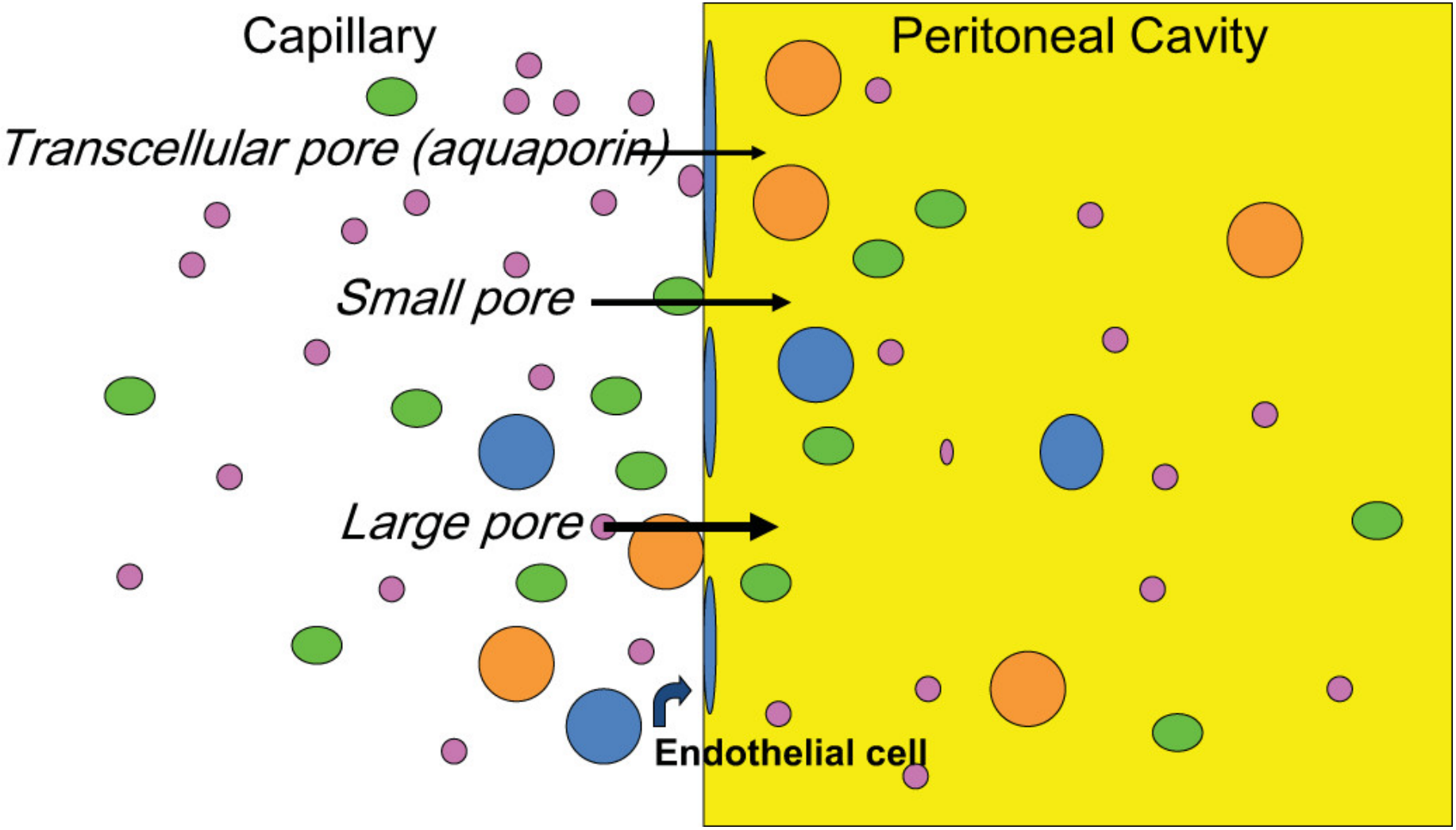
Peritoneal Dilaysis

Dr Aliza Mittal
Associate Professor
Pediatrics

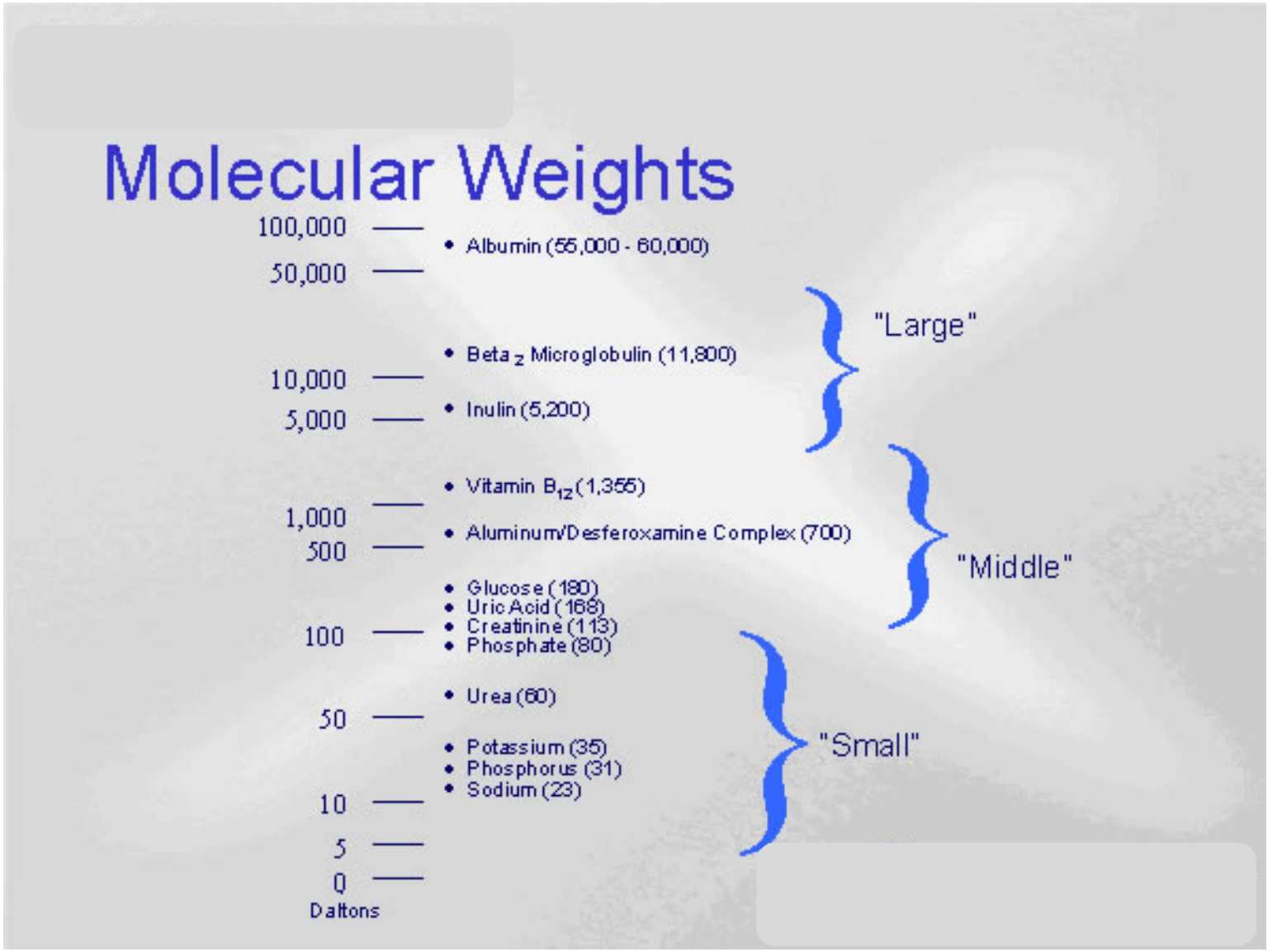
Physiology of Peritoneal Dialysis

- Membrane- interface between blood and dialysate
- PD- Total surface area of peritoneum is roughly equal to that of skin
- **Three pore model-**

Large pores- convective transport of high molecular weight compounds and middle molecular weight uremic toxins
Small pores- low molecular weight compounds –urea
Ultrasmall pores- facilitate transport of water= Aquaporins


Capillary
Peritoneal Cavity
Transcellular pore (aquaporin)
Small pore
Large pore
Endothelial cell

Transport of solute depends on size



Peritoneal Dialysate Fluids

- Dextrose based-low ph
- Biocompatible solutions- have dual chambers to allow separation of dextrose from PD solution- milder and maintain peritoneal integrity
- Icodextrin-High molecular weight water soluble glucose polymers

Composition of PD Fluid

- Osmotic agent- Glucose/Dextrose-1.4-3.9 gm/dl
- Base Lactate- 35-40 mEq/L, Bicarbonate- 34 mEq/L
- Sodium- 132-134 mEq/L
- Calcium- 1.25-1.75 mMol/l(2.5-3.5 mEq/l)
- Magnesium- 0.25-0.75 mMol/L (0.5-1.5 Meq/L)
- Chloride- 95-103.5 mEq/L

Indication to initiate

Urgent indications:

Complications of uremia- pleuritic/pericarditis/Uremic encephalopathy/neuropathy/significant bleeding diathesis

Persistent metabolic disturbances- hyperkalaemia/metabolic acidosis/hypocalcemia/hyperphosphatemia refractory to therapy

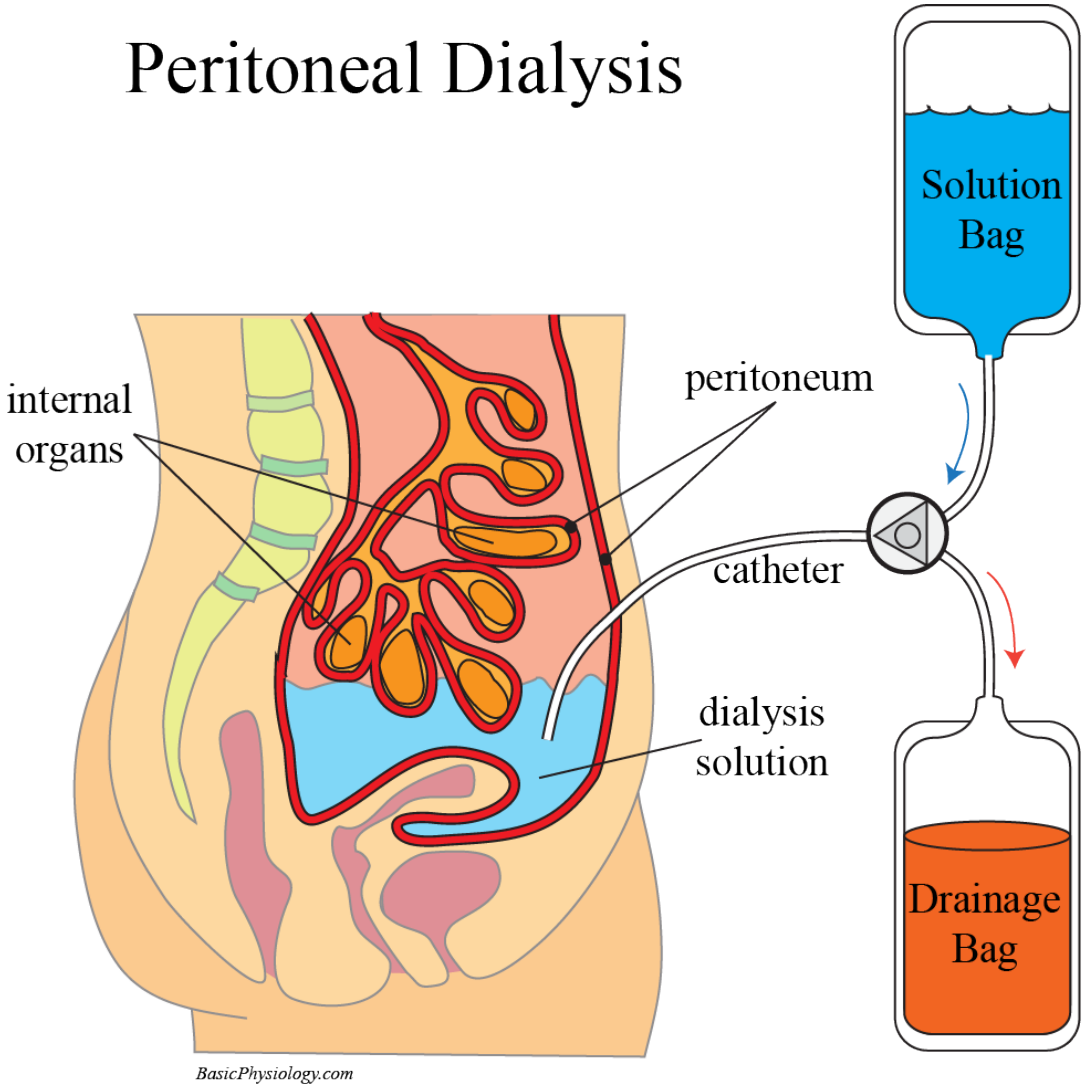
Fluid overload refractory to diuretics

Hypertension refractory to antihypertensive medications

Indications in **Non-urgent cases**

- NKF-KDOQI- GFR <14 ml/min/1.73 msq
- Strongly recommended <8 ml/min/1.73msq
- Growth failure/poor physiological well being/poor nutritional status

Peritoneal Dialysis



PD Prescription

Fill volume
Dwell time/ Duration of therapy
Dialysate Composition

Initial fill volume- low (CAPD)

800-1200 ml/m^2 (20-25 ml/kg upto 30 ml/kg……50 ml/kg in infants)

PD Prescription

- Ultrafiltration-

Depends on cycle **frequency/fill volume/osmolality** of the dialysate and transport capacity of peritoneal membrane- *cannot be precisely controlled*

- Keep IPP- Below 18 cm H2O
- Optimal- <2 yr-8-10 cm H2O, >2 13-14 cm H2O

- Dwell Time- PD using stiff catheter upto 72 hrs
- Long Dwell- better middle molecule clearance and additional sodium removal
- Short dwell- increases UF and urea clearance

- Dialysate: Avoid unnecessary exposure to dextrose to increase UF
- optimise FILL VOLUME

Monitoring

- Assess for fluid overload atleast twice daily
- Strict input –output monitoring
- Look for pericatheter leak
- Look for clinical signs of peritonitis

- Repeat VBG and serum electrolytes after 10 cycles
- Serum electrolyte q 12 hrly
- Urea/creatinine q 24 hrly initially less frequently later
- Watch for hyperglycemia

Examine PD fluid daily for cells

Complications of PD

Non infectious complications-

- Gastrointestinal problems- GER, Delayed Gastric emptying
- Seepage of peritoneal fluid- abdominal wall/pericatheter genital edema
- Obesity/Hyperlipidemia
- Loss of protein , amino acids, immunoglobulins

Catheter-related mechanical problems occurs in 10-25% patients

Clin J Am Soc Nephrol 2012

- Mechanical complications of increased intraperitoneal pressure- hernias, leaks, edema, backpain
- Malfunction/Catheter migration/Obstruction
- Intra-luminal or extra luminal blockage or Loss of reservoir

- can be dislodged by injecting **NS/Dialysate** using 50 ml syringe under moderate pressure using push and pull maneuver
- Treat **Constipation**
- Fibrin – 500-1000 U/L Heparin is added to each dialysate
- Thrombolytics- Urokinase or recombinant TissuePlasminogen activator can be used
- Guide wire manipulation

Dialysate leakage

Any dialysate loss from the peritoneal cavity other than via the lumen of the catheter

When to suspect leak??

- External fluid at wound or exit-site
- Reduced exchange outflow volume
- Weight gain
- Abdominal swelling and edema/increased girth
- Scrotal, penile, or labial edema
- Unilateral pleural effusion

Decrease the dialysate volume
Resuturing the pericatheter area
Reinsertion of PD catheter

Infectious Complications

- Catheter **exit site/Tunnel infections** and peritonitis
- Common organisms- Staph and Pseudomonas
- Cloudy effluent with or without fever and abdominal pain
- Eosinophilic peritonitis- Hypersensitivity of peritoneum to dialysis system

Peritoneal effluent leucocyte count >100 cell/cumm with 50% neutrophils is presumptive

***Perit Dial Int* 2014 &**
ISPD guideline 2016

Isolation of organism

Blood-culture bottle should be preferred technique

Sampling and culture methods should be reviewed if >15% of peritonitis episodes are culture-negative

ISPD guideline 2016

Empirical antibiotic therapy

Start immediately after sending specimen for organism isolation

Should cover both gram-positive and gram-negative bacteria

Cochrane Library

Cochrane Database

Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients (Review)

Campbell D, Mudge DW, Craig JC, Johnson DW, Tong A, Strippoli GFM

Pre-procedure vancomycin compared reduce risk of peritonitis :RR 0.08, (95% CI 0.01 to 0.61)

Systemic prophylactic antibiotics is recommended **prior** to catheter insertion **(1A)**

ISPD guideline 2016

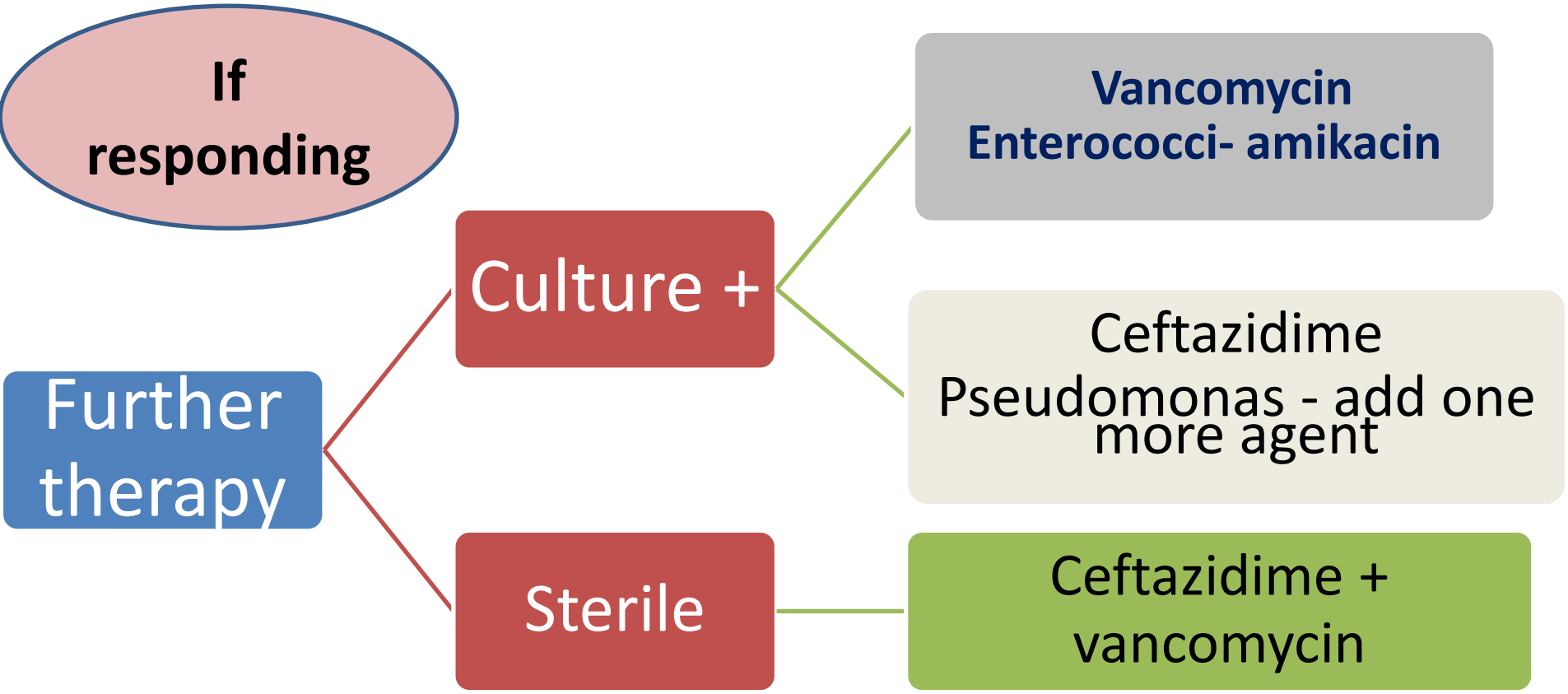
Single dose of 10 mg/kg vancomycin 30-60 min before catheter insertion

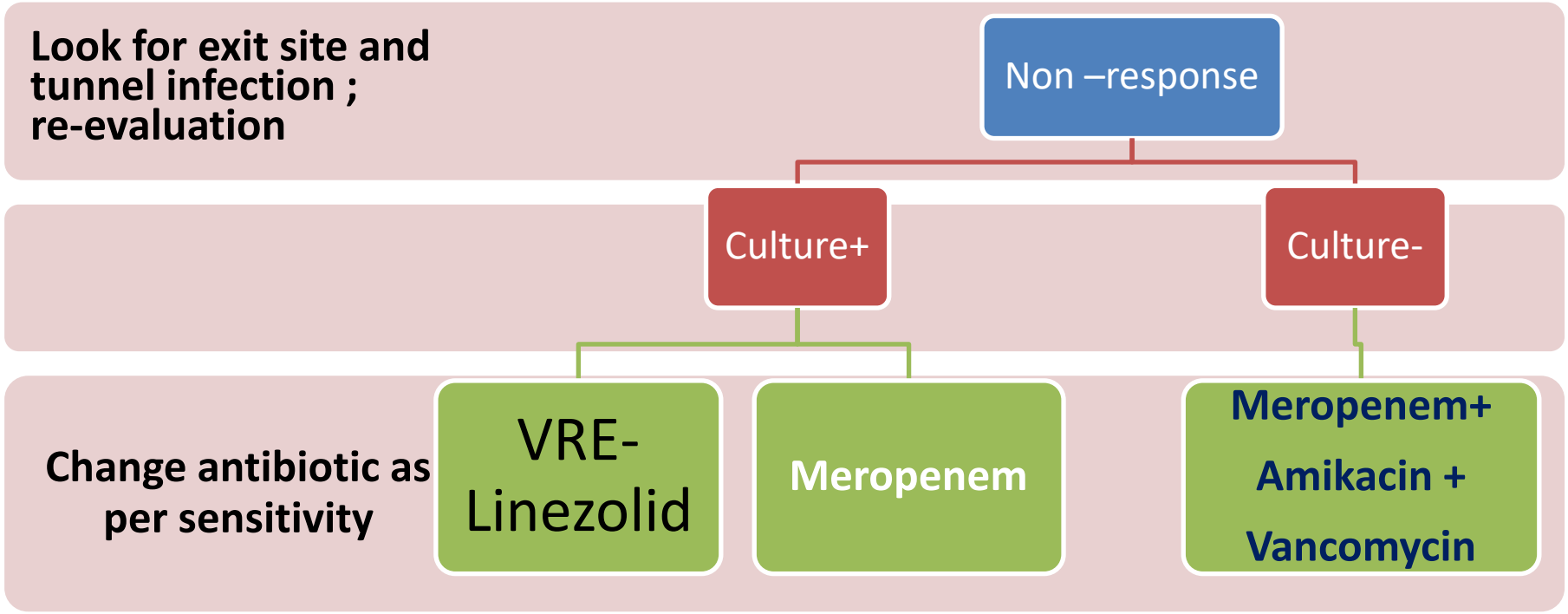
Response to therapy assessed at 48-72h

Absence of pain, fever, tenderness

Clearing of effluent cloudiness

Drop in dialysate white cell count by >50%





Failure to response by 5 days on appropriate antibiotics: remove catheter

ISPD guideline 2016

HEMODIALYSIS

Timing of Hemodialysis Initiation

- Patients who **reach CKD stage 4** (GFR , 30 mL/min/1.73 m^2 education about kidney failure and options for its treatment (Not Graded)

- The decision to be based **primarily upon an assessment of signs and/or symptoms a**ssociated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy **rather than on a specific level of kidney function in the absence of such signs and symptoms.** (Not Graded)

KDOQI HD Adequacy guideline 2015 update AJKD

Physiology of Hemodialysis

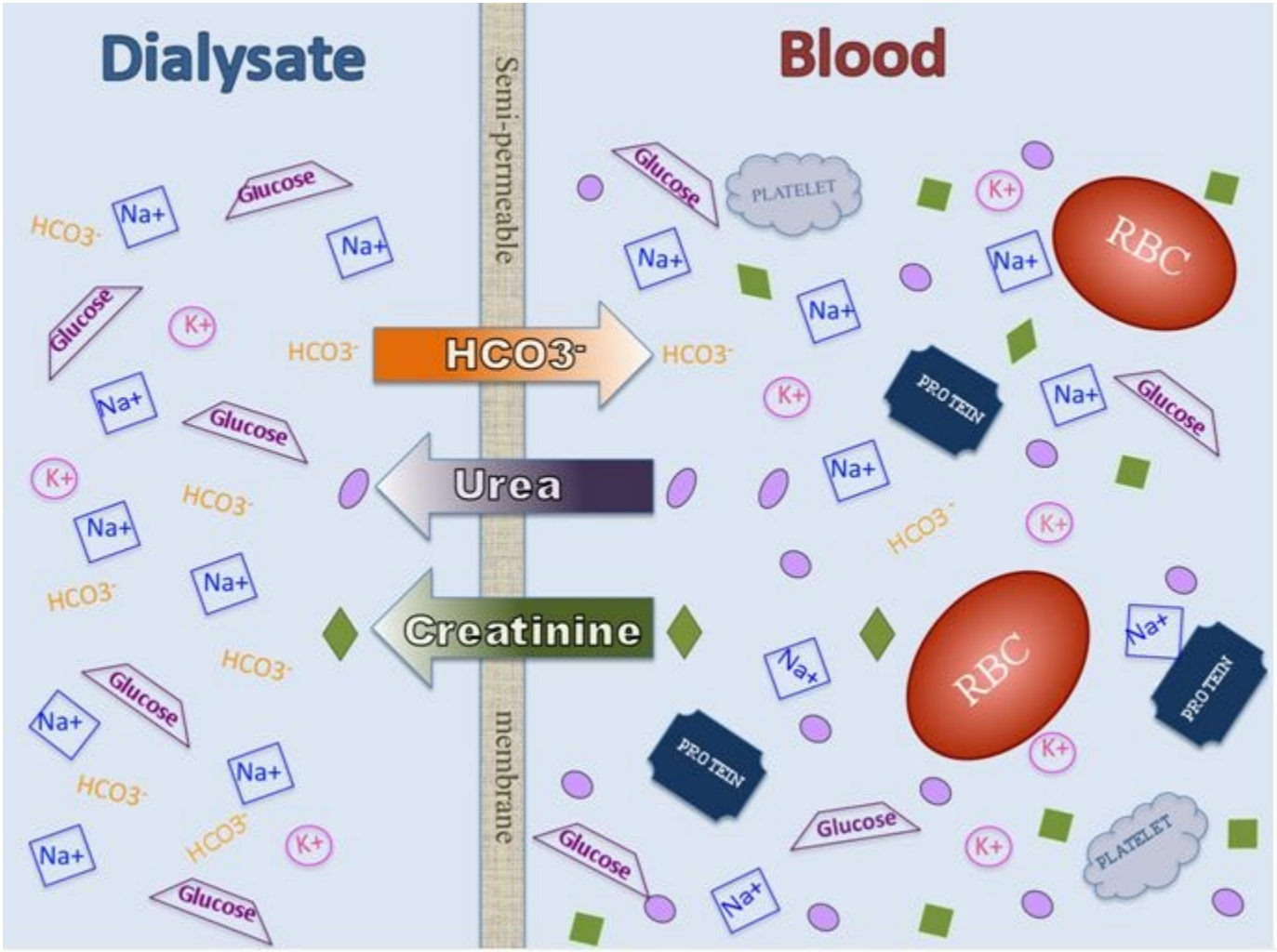
Dialysate

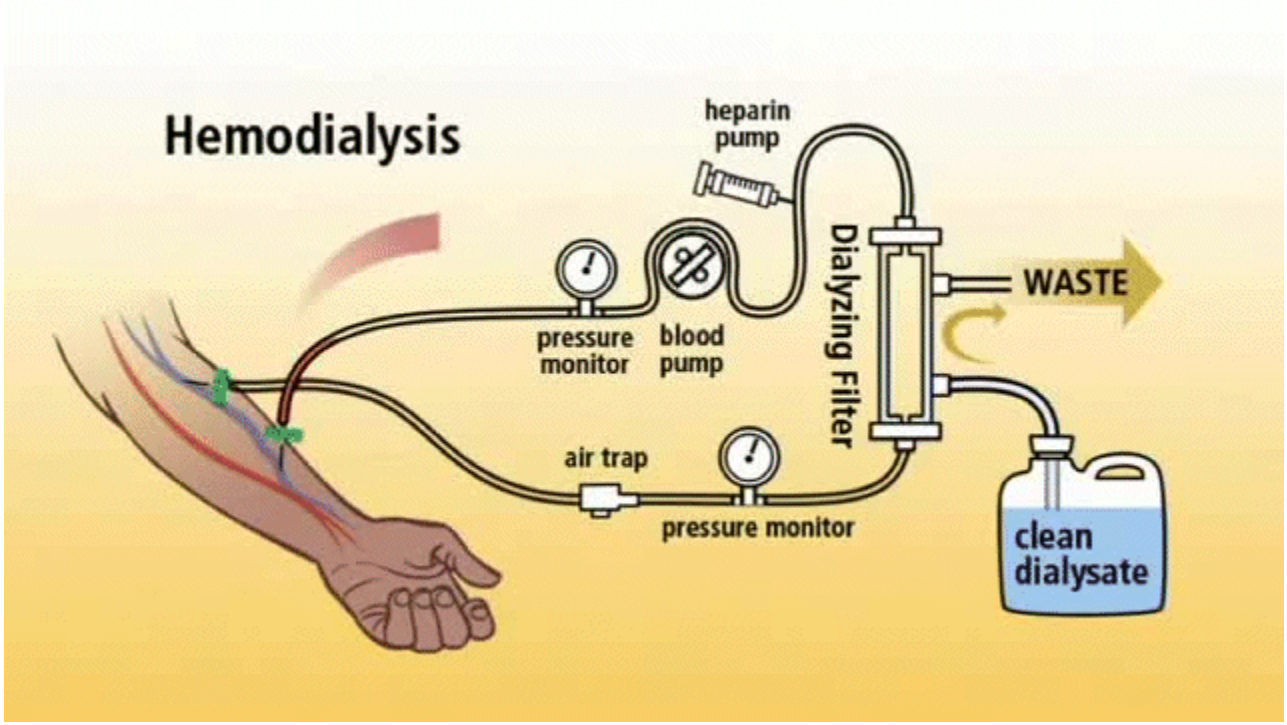
Dialysate delivered at a rate of 500ml/min

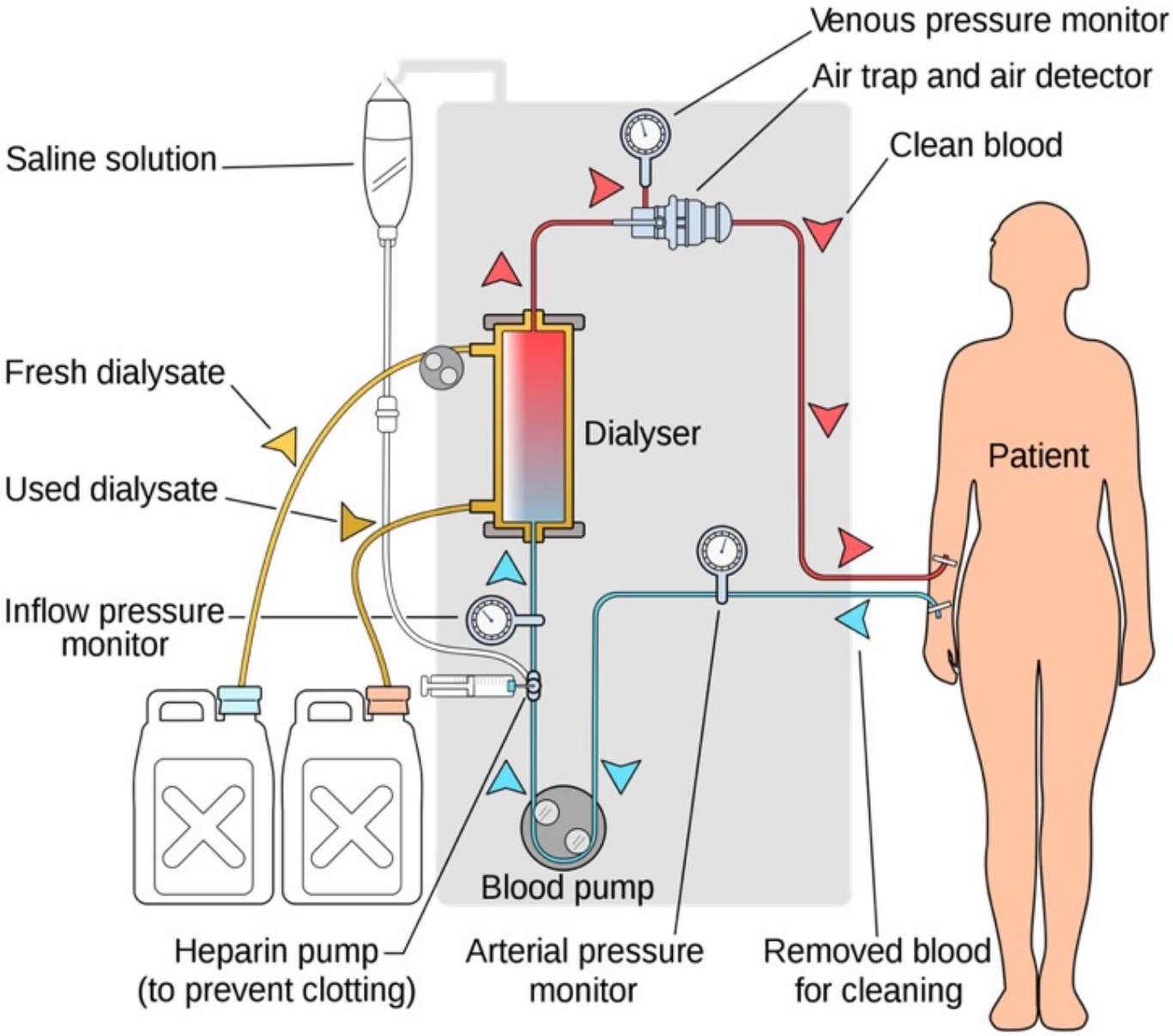
- **120 liters of dialysate / 4-hour session!!**
  - Concentrated solutions mixed with water
  - Usually 1:34 or 1:40
  - Conductivity is a measurement of electric conductivity of Na to check if dilution is correct
  - With proper dilution conductivity = 13-15
  - Serious hyponatremia or hypernatremia occurs if dilution is incorrect

Dialysate

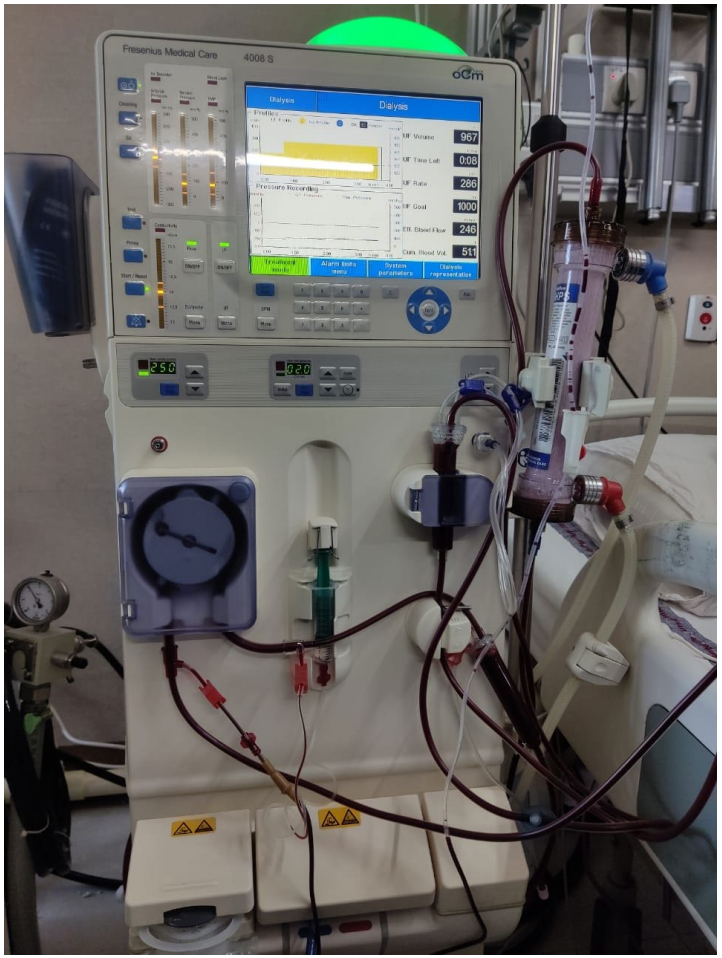
solute	blood	dialysate	direction
UREA	**high**	**zero**	**To Dx**
OTHER TOXINS	**high**	**zero**	**To Dx**
Sodium	**135-140**	**135-140**	**NO**
Potassium	**Above 5**	**1.4-3.0**	**To Dx**
Magnesium	**Above 1**	**0.5-1.0**	**To Dx**
glucose	**+/-140 (8)**	**180 (10)**	**+/-**
chloride	**100-119**	**100-119**	**NO**
Ionized Calcium	**4.5-5 mg/dl** **2-2.5mEq/L**	**5-6 mg/dl** **2.5-3 mEq/L**	**+/-**


Dialysate
Blood
Semi-permeable membrane
HCO3-
Urea
Creatinine
Glucose
Na+
K+
PLATELET
RBC
PRO TEIN

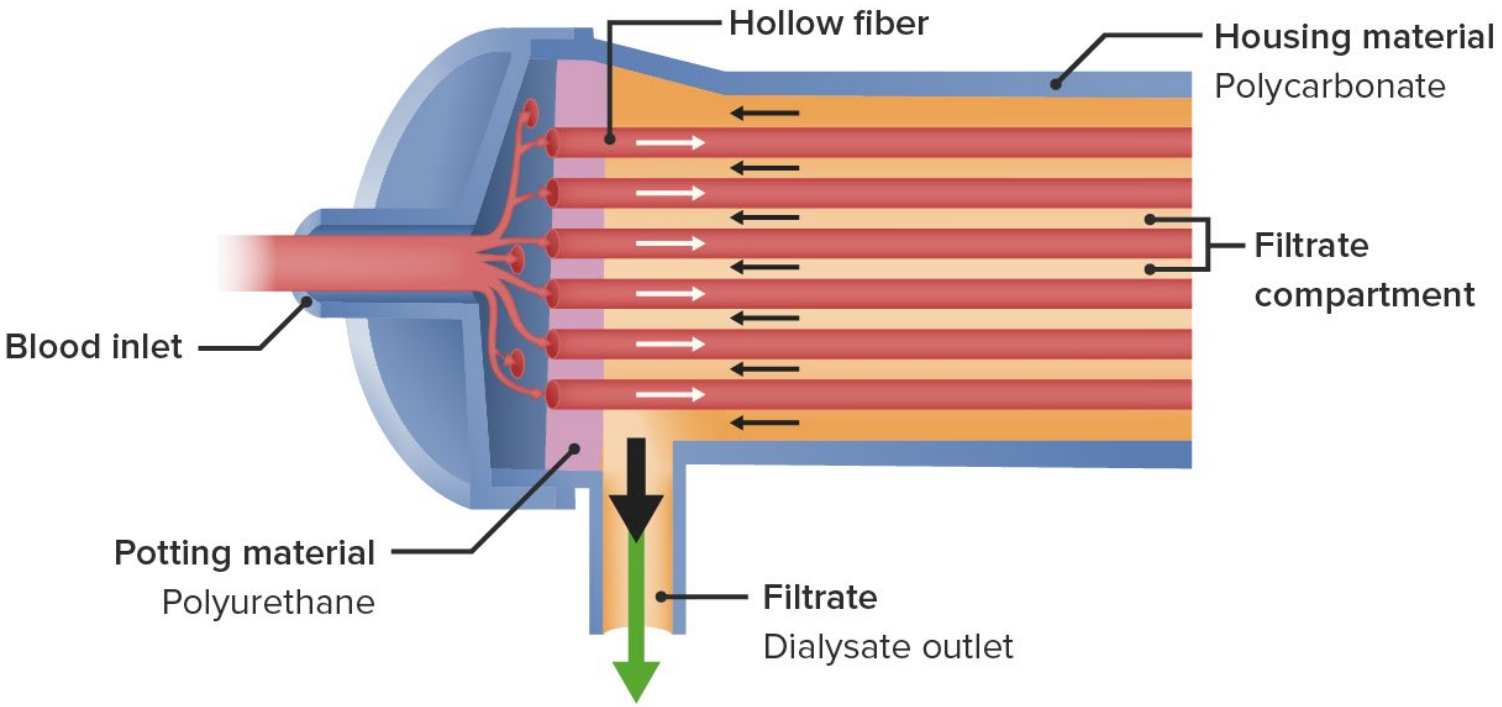

Hemodialysis
heparin pump
Dialyzing Filter
WASTE
pressure monitor
blood pump
air trap
pressure monitor
clean dialysate


Venous pressure monitor
Air trap and air detector
Saline solution
Clean blood
Fresh dialysate
Dialyser
Patient
Used dialysate
Inflow pressure monitor
Blood pump
Heparin pump (to prevent clotting)
Arterial pressure monitor
Removed blood for cleaning


AquaWTU


Fresenius Medical Care
4008 S
Dialysis
Dialysis
Pressure Recording
UF Volume
967
UF Time Left
0:08
UF Rate
286
UF Goal
1000
ETI. Blood Flow
246
Cum. Blood Vol.
511
Treatment mode
Alarm limits menu
System parameters
Device representation

Hollow fiber structure



The wavy structure of the hollow fibres reduces dialysate channelling and enhances solute transport.

Spacing between the wavy fiber structures keeps the individual fibers apart, preventing dialyzate channeling and facilitating a uniform flow of dialyzate within the fiber bundle

The consistent dialysate flow around each fiber ensures every single performs at maximum efficiency, resulting in enhanced solute transport


UF Volume
973
UF Time Left
0:06
UF Rate
286
UF Goal
1000
Eff. Blood Flow
246
Cum. Blood Vol.
515
Dialysis representation

Equipment and consumables needed

Equipment

Dialysis Machines

Reverse Osmosis system

Water treatment area

Monitors

Lab support

Weighing machine

Consumables

Dialysers

Dialysis Tubings (pediatric and adult size)

Part and part B dialysis solution

Resuscitation trolley with drugs

Anticoagulant

Saline

Low flux dialyzers

Dialyser size	F3	F4	F5	F6
Effective surface area m^2	0.4	0.7	0.9-1.0	1.3
UF coefficient (K_{UF}) mL/hr/mm TMP	1.7	2.8	4-4.2	5.5
Blood prime volume (mL)	20-30	42-44	60-63	82-84
Max UF ml/hr	800	1600	2450	3300
KoA (mL/min)	290	440	557	670

High flux and high efficiency dialyzers

Type	High flux dialysers			High efficiency		
Dialyser size	F40S	F50S	F60S	F4HPS	F5HPS	F6HPS
Effective surface area m^2	0.7	1.0	1.3	0.8	1.0	1.3
UF coefficient (K_{UF}) mL/hr/mm TMP	20	30	40	8	10	13
Blood prime volume (mL)	42-44	60-63	82-84			
KoA (mL/min)	N/A	589	709	494	604	731

Table 6. Descriptive Nomenclature for Various HD Prescriptions

Proposed Name	Time of Day	Duration (h/session)	Frequency (sessions/wk)
Conventional HD	Daytime	3-5	3-4
Frequent HD[a]			
Short	Daytime	<3	5-7
Standard	Daytime	3-5	5-7
Long	Nighttime	>5	5-7
Long HD[b]			
Long thrice weekly	Nighttime or daytime	>5	3
Long every other night	Nighttime	>5	3.5
Long frequent	Nighttime	>5	5-7
Treatment Location			
In-center	Outpatient treatment in a hospital or dialysis facility		
Home	HD treatment in the patient's home		
Level of Assistance			
Fully assisted	HD treatment is performed entirely by a health care provider		
Partially assisted	The patient performs some (but not all) aspects of the HD treatment him or herself (eg, cannulation of fistula, connection/disconnection, setting machine, monitoring blood pressures), while other aspects are performed by a health care provider		
Self-care (with or without an unpaid caregiver)	The patient performs all aspects of the HD treatment him or herself, with no assistance from a health care provider; this may be done with or without the assistance of an unpaid caregiver		
Blood flow rate			
Standard	≥300 mL/min		
Low flow	<300 mL/min		
Dialysate flow rate			
Standard	≥500 mL/min		
Low flow	<500 mL/min		

Abbreviation: HD, hemodialysis.

[a]Short and standard daily HD are usually delivered in-center, while long-nocturnal HD is usually delivered at home.

[b]Long—thrice weekly HD may be delivered in-center or at home, while long every other night and frequent HD are usually delivered at home.

Manpower

- Dialysis Nurses
- Residents/Doctors
- House keeping staff
- Staff for regular servicing and upkeep of the equipment
- Ward staff

Patient preparation for Dialysis

Timing of initiation of dialysis-CKD

Guideline	GFR which is absolute indication of starting dialysis	GFR at which dialysis is considered (esp. if complications present)
KDOQI	<8 mL/min/1.73 m^2	<15 mL/min/1.73 m^2
CARI	<6 mL/min/1.73 m^2	<10 mL/min/1.73 m^2
European guidelines	<6 mL/min/1.73 m^2	8-10 mL/min/1.73 m^2
Canadian society of nephrology	<6 mL/min/1.73 m^2	<12 mL/min/1.73 m^2
BAPN	<6 mL/min/1.73 m^2	<15 mL/min/1.73 m^2

Preparing the patient for dialysis

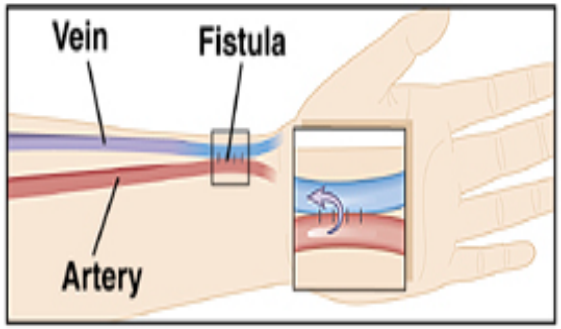
- Counsel the relatives and Written and informed Consent [before every session of Hemodialysis in case of MHD]
- **Clinical Examination**: Assessment of weight gain/fluid overload/acid-base- electrolyte status/pallor/BP …..
- Basic investigations to ensure safety of dialysis(PT/INR, Viral markers, platelet counts)

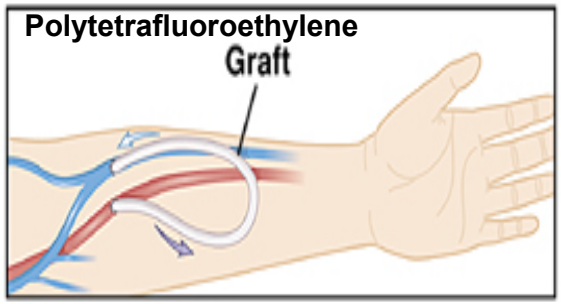
Vascular Access

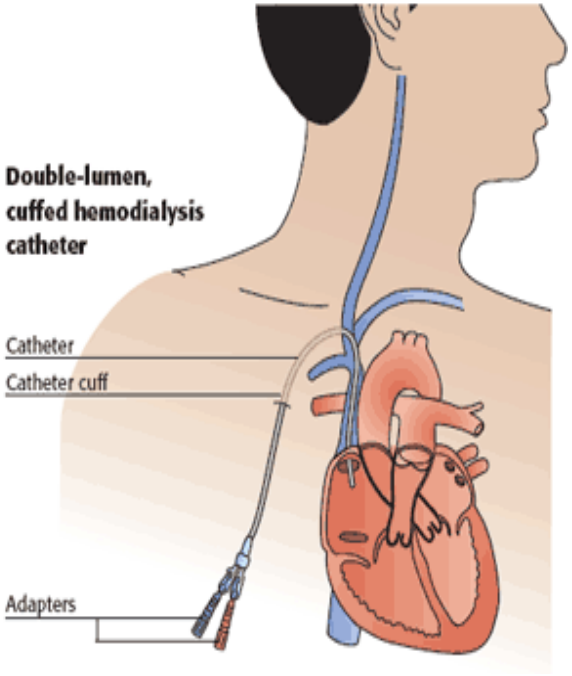
- Flow rate adequate for the dialysis prescription, has a long use-life, and has a low rate of complications (e.g. infection, stenosis, thrombosis, aneurysm, and limb ischemia)
- Most often used **access-central venous catheter (CVC)** as opposed to an AVF or arteriovenous graft (AVG)
- Usage rates -89% <13 years
- 64% in those 13–19 years of age

National Kidney Foundation-Dialysis Outcomes Quality Initiative (1997) NKF-DOQI clinical practice guidelines for vascular access. Am J Kidney Dis 30:S150–S19

Hemodialysis Vascular Access







Vascular Access Guidelines

- **Arm veins suitable for placement of vascular access should be preserved, regardless of arm dominance.**
- Arm veins, particularly the cephalic veins of the non-dominant arm should not be used.
  - **Avoid PICC lines**
- **Dorsum of the hand** could be used for IV.
- A Medic Alert bracelet should be worn to inform hospital staff to avoid IV cannulation of essential veins.
- **Subclavian vein catheterization should be avoided** for temporary access in all patients with CKD (➔ stenosis ➔ preclude use of ipsilateral arm for vascular access)

SAVE the Non-Dominant ARM for Vascular Access

- When GFR < 30 mL/min
  - No BP measurement
  - No IV
  - No Blood Draws

On Non-Dominant Arm

- Place vascular access within a year of hemodialysis anticipation …

Typical Dialysis Prescription

- **Vascular access**
- **Dialyser**
  - Size: Dialyser surface area: 0.8 -1.0 * patient's surface area *(as in table)*
  - Type: Decided on the basis of ultrafilterate removal required and clearance of middle molecules required (high vs low efficiency and high vs low flux)
  - Blood tubing: Decided on the basis of patient size
- **Priming:** Prime with blood or 5% albumin if total extracorporeal blood volume >10% of patients blood volume OR < 20 kg patient
- **Blood flow rate (Q_B):** 5–7 mL/ min/ kg in small children QB is determined using body weight (BW, kg): (BW+10)* 2.5=QB (mL /min)
- **Dialysate flow rate(Q_D):** 500 mL/min [or 2 times the BFR]
- **Ultrafiltration volume:**
  - Should not exceed 1.5 ±0.5% of body weight per hour
  - No more than 5% BW loss per whole session
  - BVM (blood volume monitor) guided removal: not more than 8% rise in Hct during one session
  - Adjust by dry weight and interdialytic weight gain
- **Anticoagulation : Heparin/saline**
- **Duration:** (in patients with minimal RRF): at least 4 hours, shorter dialysis at initiat
- **Schedule**:
  - Three times a week
- Parameters of dialysis adequacy should be checked monthly

Major complications of HD

- Intradialytic Hypotension- 25-55%
- Muscle cramps – 5-20%
- Nausea & Vomiting – 5-15%
- Headache 5%
- Chest Pain & Back Pain 2-5%
- Itching 2-5%
- Disequilibrium syndrome
- Dialyser Reactions
- Hemolysis
- Air Embolism

Bregman H, Daugirdas JT, Ing TS. Complications during hemodialysis. In: Handbook of Dialysis, Dauugirdas JT, Ing TS (Eds), Little, Brown, New York 1994. p.149.

Hemodialysis(HD) prescription

Georgie Mathew

CMC Vellore

Components of a HD prescription

- Time
- Dialyzer (membrane, surface area, configuration) & circuit
- Dialysate flow rate
- Blood flow rate
- Dialysate composition
- Dialysate temperature
- Ultrafiltration rate
- Frequency
- Anticoagulation
- Intradialytic medications
- Adequacy

Timing of haemodialysis initiation

Inform and ***prepare*** patients at GFR of 30 mL/min per 1.73 m^2

- Vein preservation
- Fistula creation
- PD insertion
- Palliation

Guideline	Consider HD
KDOQI	<15
CARI (Australia)	<10
European	8-10
Canada	<12
BAPN (Britain)	<15

KDOQI HD Adequacy guideline 2015 update AJKD

Case scenario 1

10 yr/M
Excessive tiredness for 2 weeks
Reduced urine output for 1 week
Breathing difficulty for 1 day

On examination
Short stature, pallor and rickets
Tachypnea
HR 120/min, BO 146/88 mm Hg
JVP elevated with hepatomegaly
Weight 30 kg, BSA 0.98 m^2

Parameter	Value
Creatinine	9.9 mg/dL
Urea	345 mg/dL
Electrolytes	137/5.6/12 mEq/L
Ca/PO_4	8.5/7.7 mg/dL
Parathormone	215 pg/mL
CBC	6.5/7800N70/188k

Uremia
Acidosis

Anemia
Hyperkalemia

How will you proceed?

Stabilization - airway

Blood transfusion?

Antihypertensives?

Furosemide?

Ultrasound

Bilateral shrunken kidneys

Dialysis

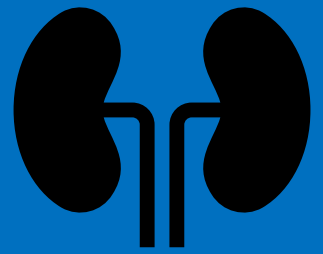
Consent

Blood borne virus screen

Vascular access – avoid right femoral

Blood priming – severe anemia and if circuit volume (dialyzer + tubings)

Dialysis prescription



Short duration for first session? Or 4 hours?

Dialysis disequilibrium syndrome – aim for urea reduction to ~30%

Potassium ? 1.5 or 3.5?

Qb 5-8 or 3-5 ml/kg/min?

Qd = 2-3*Qb

Ultrafiltrate? Maximum 1-3% per hour

IsoUF mode

HD prescription for case 1 - Weight 30 kg

Parameter	Criteria	Prescription
Qb	3-5 ml/kg/min	100-150 ml/min
Qd	6-10 ml/kg/min	200-300 ml/min (400-500)
Duration	1-2 hours	1-2 hours
Dialyzer	80-100% of BSA	F4 (or F5)
Potassium	1.5-2 mEq/L	1.5-2 mEq/L
Anaemia	Blood priming (10 ml/kg)	300 ml packed red cells
Ultrafiltrate	3-5% of body weight	1000-1500 ml
Anticoagulation	Platelets >150,000/mm^3	Heparin 20-40 U/kg stat

Case scenario 2

4 yr/M
Bowing of legs for 2 years
Polyuria, polydipsia

On examination
Weight 10 kg, BSA 0.7 m^2
Short stature, pallor and rickets
Tachypnea
HR 140/min, BO 126/68 mm Hg
USG – bilateral shrunken kidney

Parameter	Value
Creatinine	4.9 mg/dL
Urea	205 mg/dL
Electrolytes	137/3.8/16 mEq/L
Ca/PO_4	8.5/5.9 mg/dL
Parathormone	215 pg/mL
CBC	12.5/7500N50/78k
Uremia	Acidosis

HD prescription for case 1 - Weight 10 kg

Parameter	Criteria	Prescription
Qb	3-5 ml/kg/min	30-50 ml/min
Qd	6-10 ml/kg/min	60-100 ml/min (400-500)
Duration	1-2 hours	1-2 hours
Dialyzer	80-100% of BSA	F3 (or F4)
Potassium	3.5 mEq/L	3.5 mEq/L
High ECV	Priming	Albumin 5%
Ultrafiltrate	May not be needed	~100-200 mL
Anticoagulation	Platelets 50-100k/mm^3	Heparin 10-20 U/kg stat

Ultrafiltration

- Not >5% of body weight in a single dialysis session (~1% per hour)
- Pulmonary edema not more than 4L
- 10 ml/kg/hr in volume overloaded patients
- Consider the saline flush at the end (~0.2 L)
- Initial dialysis 2 hr - Iso- UF can be performed for 1-2 hrs, removing 2-3 kg fluid.

Case scenario 3 – maintenance HD

10 yr/M – child in case 1 – 6 mo later

Diagnosed end stage kidney disease

On maintenance hemodialysis

Right sided permacath

On examination

Weight 30 kg, BSA 1 m^2

HR 90/min, BO 116/68 mm Hg

Interdialytic weight gain 1 kg

Parameter	Value
Creatinine	3.9 mg/dL
Urea	105 mg/dL
Electrolytes	137/4.2/22 mEq/L
Ca/PO_4	8.5/4.3 mg/dL
Parathormone	215 pg/mL
CBC	10.6/7500N50/212k

HD prescription for case 3 - Weight 30 kg

Parameter	Criteria	Prescription
Qb	5-7 ml/kg/min	150-210 ml/min
Qd	10-15 ml/kg/min	300-450 ml/min
Duration	4 hours	4 hours
Dialyzer	80-100% of BSA	F4 (or F5)
Potassium	3.5 mEq/L	3.5 mEq/L
Priming	ECV not high	Not needed
Ultrafiltrate	Intradialytic weight gain	1000 ml
Anticoagulation	Platelets >150k/mm^3	Heparin 20-40 U/kg stat f/b 20 U/kg/hr
Erythropoietin stimulating agents at end of HD session		

Other additions to the prescription

Antibiotics in case of catheter related blood stream infection

Sodium profiling – for hyponatremia, hypernatremia and intradialytic hypotension (IDH)

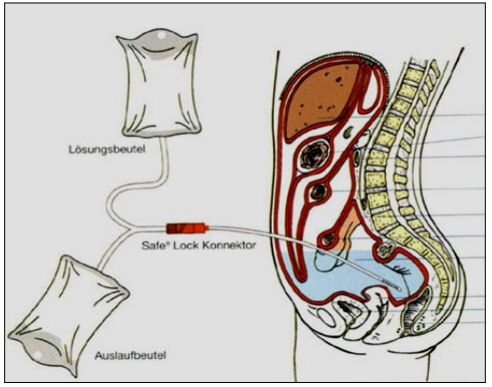
Iron infusions

Dialysate temperature – 36.5 deg C for IDH

TYPICAL PRESCRIPTION

- **Dialyser**
  - Size: Dialyser surface area: 0.8 -1.0 * patient's surface area *(as in table)*
  - Type: Decided on the basis of ultrafilterate removal required and clearance of middle molecules required (high vs low efficiency and high vs low flux)
  - Blood tubing: Decided on the basis of patient size
- **Priming:** Prime with blood or 5% albumin if total extracorporeal blood volume >10% of patients blood volume OR < 20 kg patient
- **Blood flow rate (Q_B):** 5–7 mL/ min/ kg in small children QB is determined using body weight (BW, kg): (BW+10)* 2.5=QB (mL /min)
- **Dialysate flow rate(Q_D):** 300-500 mL/min
- **Ultrafiltration volume:**
  - Should not exceed 1.5 ±0.5% of body weight per hour
  - No more than 5% BW loss per whole session
  - BVM (blood volume monitor) guided removal: not more than 8% rise in Hct during one session
  - Adjust by dry weight and interdialytic weight gain
- **Anticoagulation**
- **Duration:** (in patients with minimal RRF): at least 4 hours
- **Schedule**:
  - Three times a week
- Parameters of dialysis adequacy should be checked monthly

CHANGES IN PD PRESCRIPTION FOR AKI



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AIIMS, Jodhpur
29.01.2023

Dr. Sumantra Kumar Raut
MD, DM (Pediatric Nephrology, AIIMS)
Consultant Pediatric Nephrologist
Asst Professor and In-Charge, Nephrology
NBMC, West Bengal

Case 1

2y boy Rahul, 10 kg, admitted in PICU with sepsis, AKI, UO 0.2ml/kg/hr, puffy+++, ventilated, MAP 78 mmHg

Day 1= Ur/Cr: 180/3.2
Na/K: 155/ 5.5
pH/HCO3: 7.2/11

Hb 6.8
INR: 2.5

RRT: Y/N?? YES

If yes why??? K^+, HCO3, PRBC

Prescription ??

Dextrose? **2.5%**

IN/Dwell vol? 210ml

Out vol? 220 ml

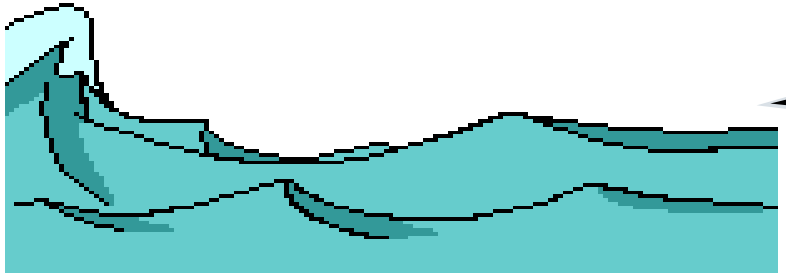
Catheter? Stiff/soft

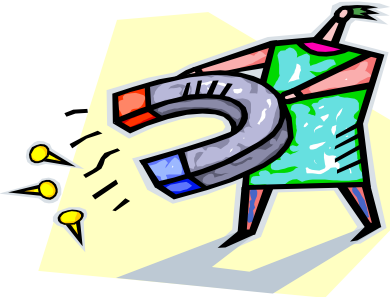
Dwell time?? 30' for 6-8hrs →60' for rest

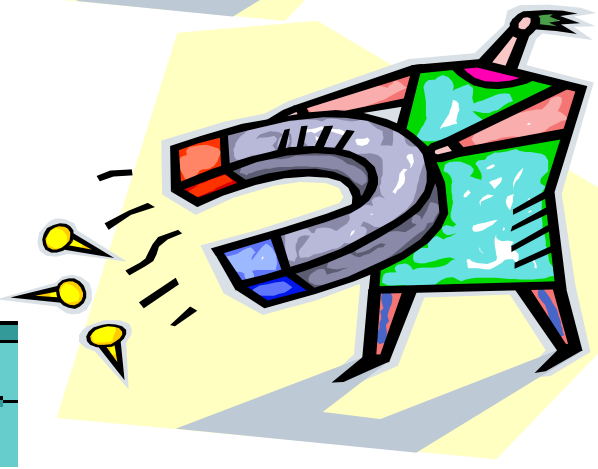
UF 160 ml + 160ml=320ml on day 1 → CBG 310 mg/dl

How to manage ??? baby still 10 % fluid overloaded

Osmotic Pressure of Dextrose Solution





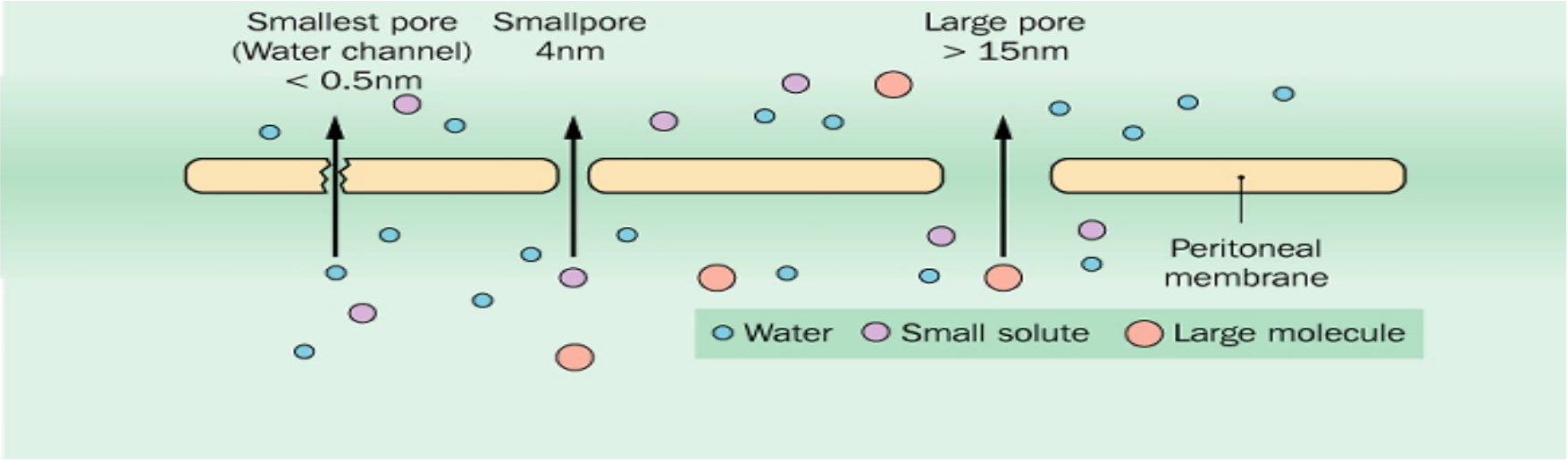


1.5 % Solution

2.5 % Solution

4.25 % Solution

Model of transport- “3 pore” model



Ultrapores
Radius <0.8 nm

allowing ‘sieving’ of water
similar to aquaporins

Numerous inter-endothelial pores
Radius 4-8 nm

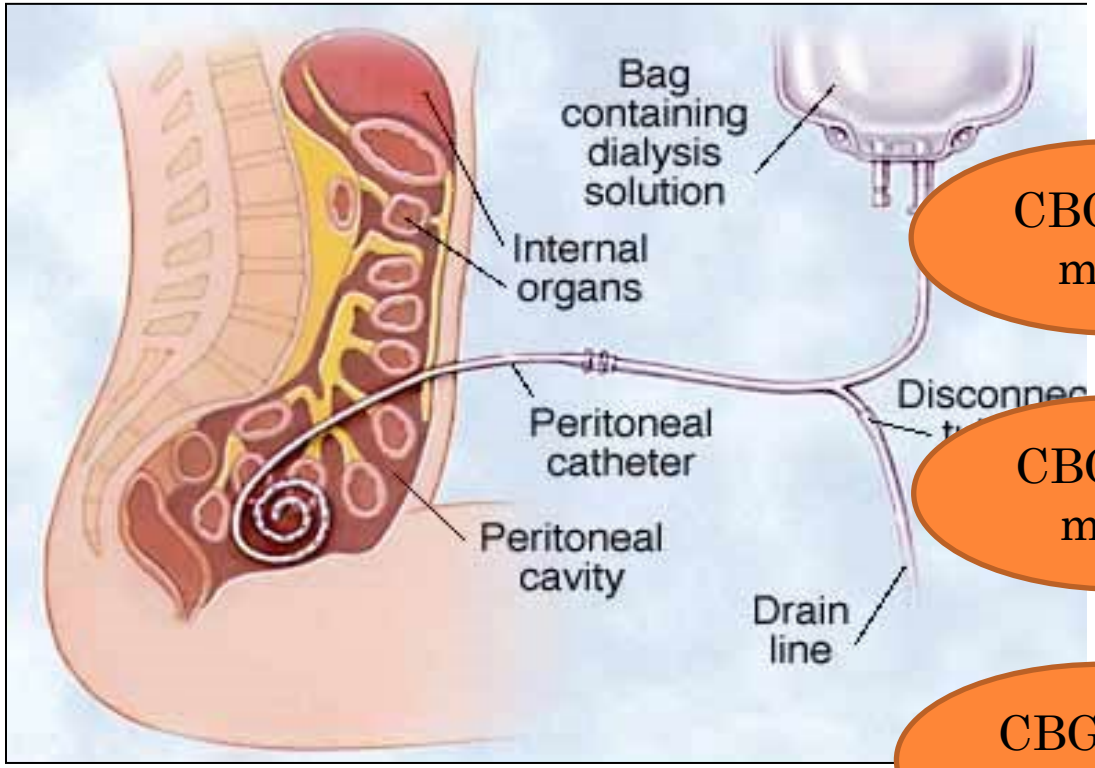
small solutes (Ur, Cr, Na, K, water)
Diffusion/ ultrafiltration

Endothelial clefts
Radius 20-40 nm

Macromolecules (proteins)
Convection

Principles of peritoneal dialysis

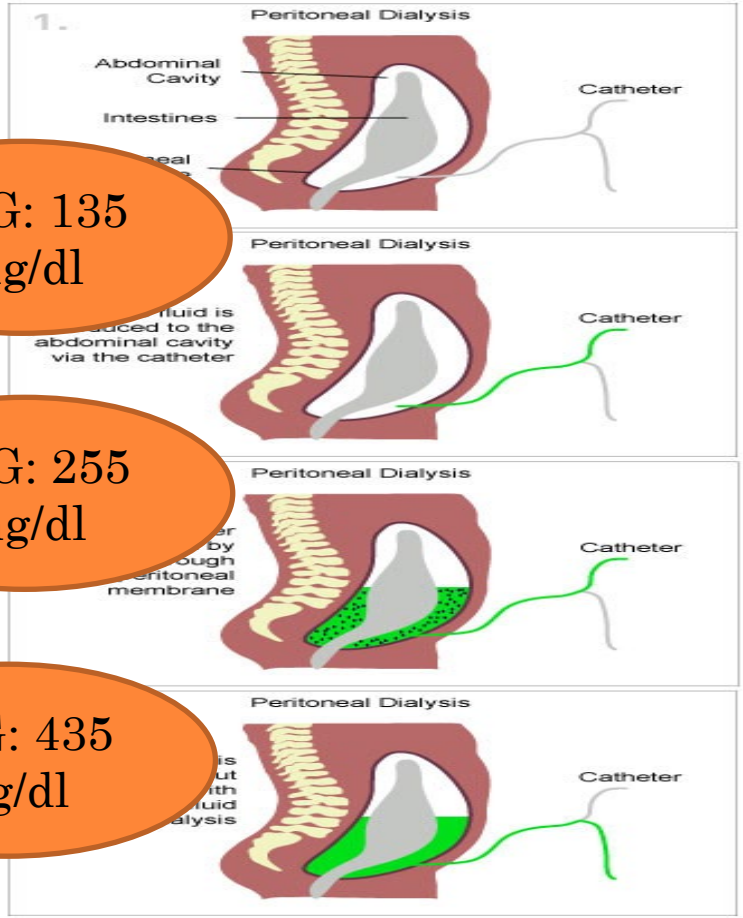
F → D → D
Sugar



CBG: 135 mg/dl

CBG: 255 mg/dl

CBG: 435 mg/dl



A special fluid is instilled through a permanent catheter in the lower abdomen

Thank you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PD prescription modification in Hypernatremic Dehydration

Sudarsan K

Assistant Professor

Department of Pediatrics

JIPMER, Pondicherry

Case history

7 month old girl presented with

- Loose stools for 3 days
- Vomiting for 3 days
- Poor feeding and lethargy for 1 day

- Mother gives history of decreased urine output for the past 24h
- No h/o blood or mucous in stools, fever, seizures

Examination

Vitals- HR:165 bpm; RR:54/min; BP: 65/32 mm Hg; peripheries cold

GPE- Depressed AF, sunken eyes, dry oral cavity, scaphoid abdomen, perianal rash

Systemic exam-

CVS: Tachycardia, no murmur

Chest: clear, no added sounds

P/A: no HSM, scaphoid abdomen, perianal rash

CNS: Lethargic E3M3V2, no FND or meningeal signs

Wt: 5 kg

Imp: AGE with severe dehydration

Emergency stabilization

- 4L/min oxygen by face mask
- 100 ml NS bolus
- 500 ml RL correction over 6h
- Maint IVF: 500 ml/day
- Catheterised: nil urine (Anuric for the last 12h)

Revised diagnosis: AGE with severe dehydration with AKI stage 3

Labs

Hb	7.2 g/dL
TLC	22350
DLC	N68 L30
Plt	1.2 L
Urea	104 mg/dL
Creatinine	**2.3** mg/dL
Na/K	**188**/4.0

pH	**7.14**
pO2	87
pCO2	33
HCO3	11.6
Lactate	6.4

Can we manage this infant with just fluid correction?

Does she need dialysis?

This infant needs dialysis as she is anuric with severe hypernatremia so cannot handle with fluid management alone

Indications for dialysis

- Oligoanuria
- Fluid overload with LV failure
- No improvement despite fluid management or worsening sensorium or serum Na >180-190 mEq/L
- Other associated metabolic abnormalities like hyperkalemia

PD prescription modifications in hypernatremic dehydration

- Increase Na in PD fluid to keep difference between serum and PD fluid

  Na to less than 10-15 mEq/L

- PD fluid contains **130** mEq/L Na

- Add 3%NS to PD fluid to increase Na concentration in PD fluid

  (**1ml 3%NS = 0.5 mEq/L)**

Na: 188

- So in this child, add 90 ml 3%NS per litre PD fluid to increase PD fluid

  Na to 175 mEq/L

KRT…

- PD catheter inserted and PD initiated
- Fluid used: 1.5% PD fluid with 90 ml 3%NS per L PD fluid
- Dwell volume: 150 ml
- Duration: 1 h cycles initially then slowly increased

Wt: 5 kg

Labs 24 h later

Na **177** mEq/L	K 3.5 mEq/L	urea/creat: 56/1.9
pH 7.35	HCO3 18	

Subsequent course…

Day of hospital stay	3% NS to be added to PD fluid	PD fluid Na value (mEq/L)	Serum Sodium values (mEq/L)
At admission			188
Day 2	90	175	177
Day 3	70	165	168
Day 4	50	155	153
Day 5	30	145	142
Day 6	-	130	135

Wt: 5 kg

Slow correction of sodium is necessary

Change in PD prescription for hypokalemia

- PD fluid has no added K
- After 12-24h, hypokalemia sets in
- Add KCl to PD fluid (1ml inj KCl raises K by 2 mEq/L)
- So if patient's K is 2.5 and we need to maintain serum K at 3.5-4 mEq/L, add 2 ml KCl to 1L to PD fluid and titrate further based on serum values

Thank you