Kidney Stones in Children

- Abdulla M Ehlayel, MD, FAAP

- IPNA Teaching Course, Amman, Jordan
- December 5th, 2024

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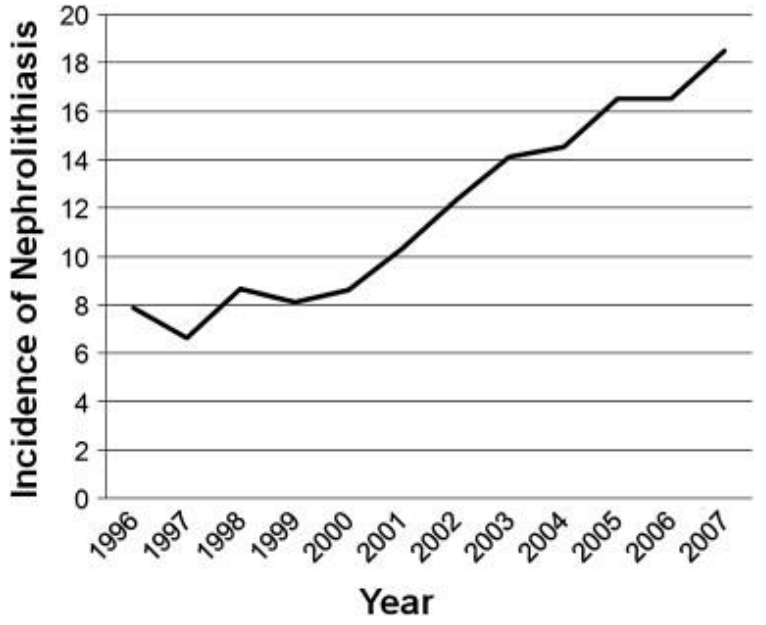
Outline

- Epidemiology and Risk Factors
- Clinical Presentation and Diagnosis
- Acute Management of Kidney Stones
- Prevention of Recurrent Stones

Incidence and Prevalence

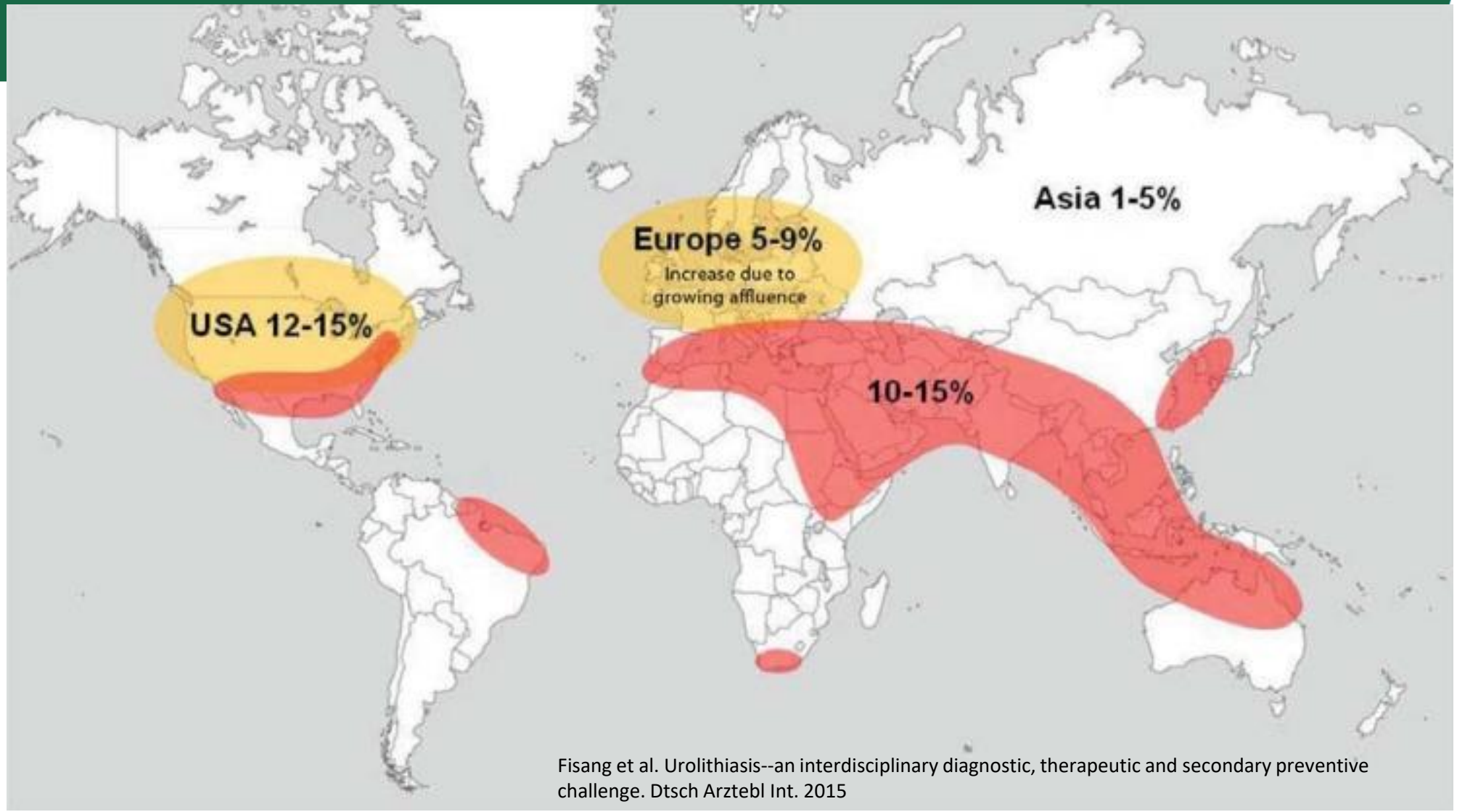
- Kidney stones is a common disease in adults affecting ~9% in US, increased from 5%
- Increasing incidence in children as well, overall lower than adults
- Highest incidence in adolescents



Sas et al. Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr. 2010

VanDervoort et al. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol. 2007

“Stone Belt”

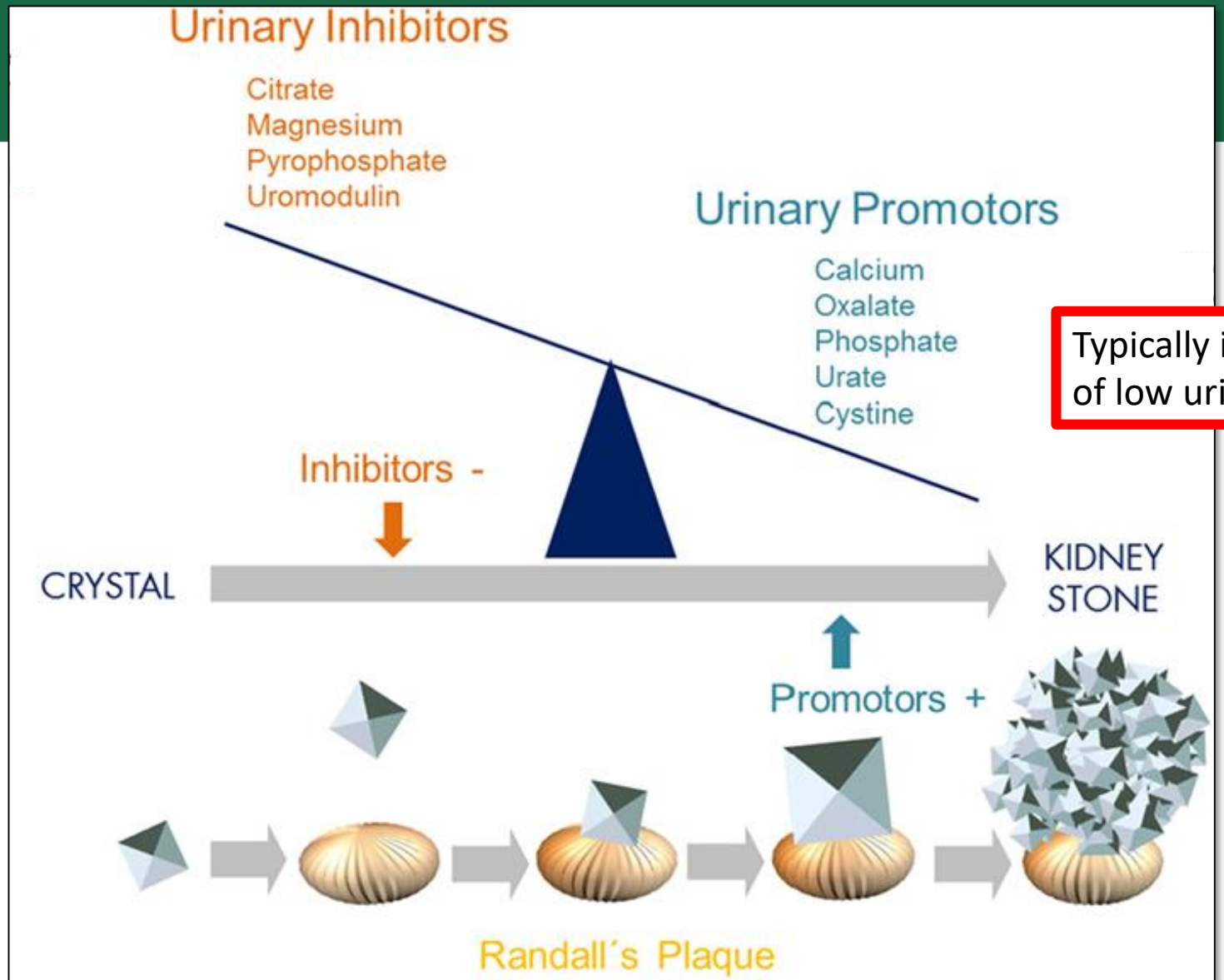


Fisang et al. Urolithiasis--an interdisciplinary diagnostic, therapeutic and secondary preventive challenge. Dtsch Arztebl Int. 2015

Risk Factors

- Metabolic Abnormality
- Urinary Tract Infection
- Structural Abnormality

Metabolic Abnormality

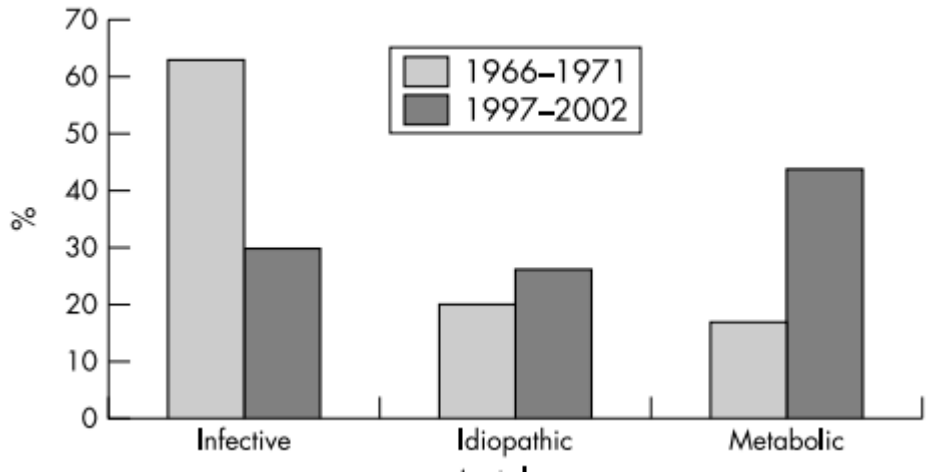


Typically in the setting of low urine flow rate

Halbritter et al. Update on Hereditary Kidney Stone Disease and Introduction of a New Clinical Patient Registry in Germany. Front Pediatr. 2018

Urinary Tract Infections

- 20-25% of children with stones have UTI
- 80% of stones with UTI occur in males
- UTI with stones decreasing



Coward et al. Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child. 2003

Structural Abnormality

Approx 10-25% of children with stones have a renal or urological abnormality. Accompanied by stasis.

- Medullary sponge kidney
- ADPKD
- UPJ obstruction
- Neurogenic bladder
- Horseshoe kidney

Vulnerable Population

- Preterm Infants
- Lymphoproliferative and myeloproliferative disorders
- Intestinal malabsorption: Cystic Fibrosis, IBD, bowel resection
- Medications: topamirate, zonasimide, ketogenic diet, steroids, furosemide, calcineurin inhibitors

Genetic Diseases

Gene symbol[a]	Gene name	Disease entity	MIM phenotype #	Mode	Reference
ADCY10	Adenylate cyclase 10	Idiopathic (absorptive) hypercalciuria, susceptibility	143870	AD	(11)
AGXT	Alanine-glyoxylate aminotransferase	Primary hyperoxaluria (PH), type 1, PH1	259900	AR	(12)
APRT	Adenine phosphoribosyltransferase	Adenine phosphoribosyltransferase deficiency, APRT	614723	AR	(13)
ATP6V0A4	ATPase, H+ transporting, lysosomal V0 subunit a4	dRTA	602722	AR	(14)
ATP6V1B1	ATPase, H+ transporting, lysosomal, V1 subunit B1	dRTA with deafness	267300	AR	(15)
CA2	Carbonic anhydrase II		259730	AR	(16)
CASR	Calcium-sensing receptor	lcemia, AD	601198	AD	(17)
CLCN5	Chloride channel, voltage-sensitive 5		300009/310468	XR	(18)
CLCNKB	Chloride channel, voltage-sensitive Kb		607364	AR	(19)
CLDN16	Claudin 16	and NC, FHHNC	248250	AR	(20)
CLDN19	Claudin 19	and NC with ocular	248190	AR	(21)
CYP24A1	Cytochrome P450, family 24, subfamily A,	tile hypercalcemia	143880	AR	(22)
FAM20A	Family with sequence similarity 20, memb	fect, and NC	204690	AR	(23)
GRHPR	Glyoxylate reductase/hydroxypyruvate red		260000	AR	(24)
HNF4A	Hepatocyte nuclear factor 4, alpha		125850	AD	(25)
HOGA1	4-Hydroxy-2-oxoglutarate aldolase 1		613616	AR	(26)
HPRT1	Hypoxanthine phosphoribosyltransferase	ficiency, HPRT-related gout	300323	XR	(27)
KCNJ1	Potassium inwardly rectifying channel, subfamily J, member 1	Bartter syndrome, type 2	241200	AR	(28)
MAGED2	Melanoma antigen, family D, 2	Bartter syndrome, type 5	300971	XR	(29)
OCRL	Oculocerebrorenal syndrome of Lowe	Lowe syndrome/Dent disease 2	309000/300555	XR	(30)
SLC12A1	Solute carrier family 12, member 1	Bartter syndrome, type 1	601678	AR	(31)
SLC26A1	Solute carrier family 26 (sulfate transporter), member 1	Ca-oxalate-NL	167030	AR	(32)
SLC22A12	Solute carrier family 22 (organic anion/urate transporter), member 12	Renal hypouricemia, RHUC1	220150	AD/AR	(33)
SLC2A9	Solute carrier family 2 (facilitated glucose transporter), member 9	Renal hypouricemia, RHUC2	612076	AD/AR	(10)
SLC34A1	Solute carrier family 34 (sodium phosphate), member 1	Hypophosphatemic NL, osteoporosis-1, NPHLOP1/Fanconi renotubular syndrome 2	612286/613388	AD/AR	(34)
SLC34A3	Solute carrier family 34 (sodium phosphate), member 3	Hypophosphatemic rickets with hypercalciuria	241530	AR	(35)
SLC3A1	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	Cystinuria, type A	220100	AR	(36)
SLC4A1	Solute carrier family 4, anion exchanger, member 1	Primary dRTA, dominant/recessive	179800/611590	AD/AR	(37)
SLC7A9	Solute carrier family 7 (glycoprotein-associated amino acid transporter light chain, bo, +system), member 9	Cystinuria, type B	220100	AD/AR	(38)
SLC9A3R1	Solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1	Hypophosphatemic NL, osteoporosis-2, NPHLOP2	612287	AD	(39)
VDR	Vitamin D (1,25-dihydroxyvitamin D3) receptor	Idiopathic hypercalciuria	277440	AD	(40)
XDH	Xanthine dehydrogenase	Xanthinuria, type 1	278300	AR	(41)

Primary Hyperoxaluria
Cystinuria
Dent Disease
FHHNC
APRT Deficiency

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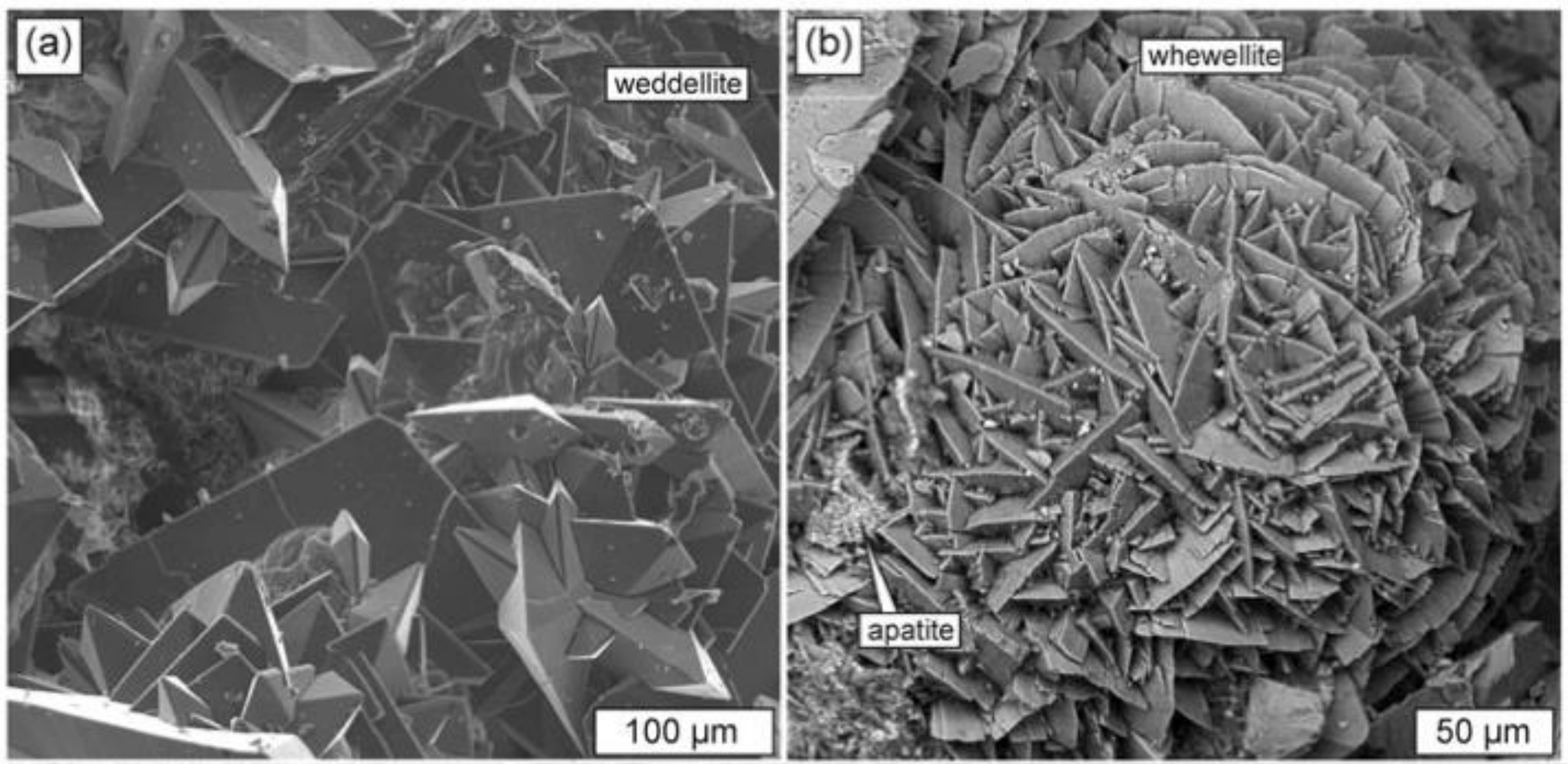
Kidney Stone- Electron Microscope

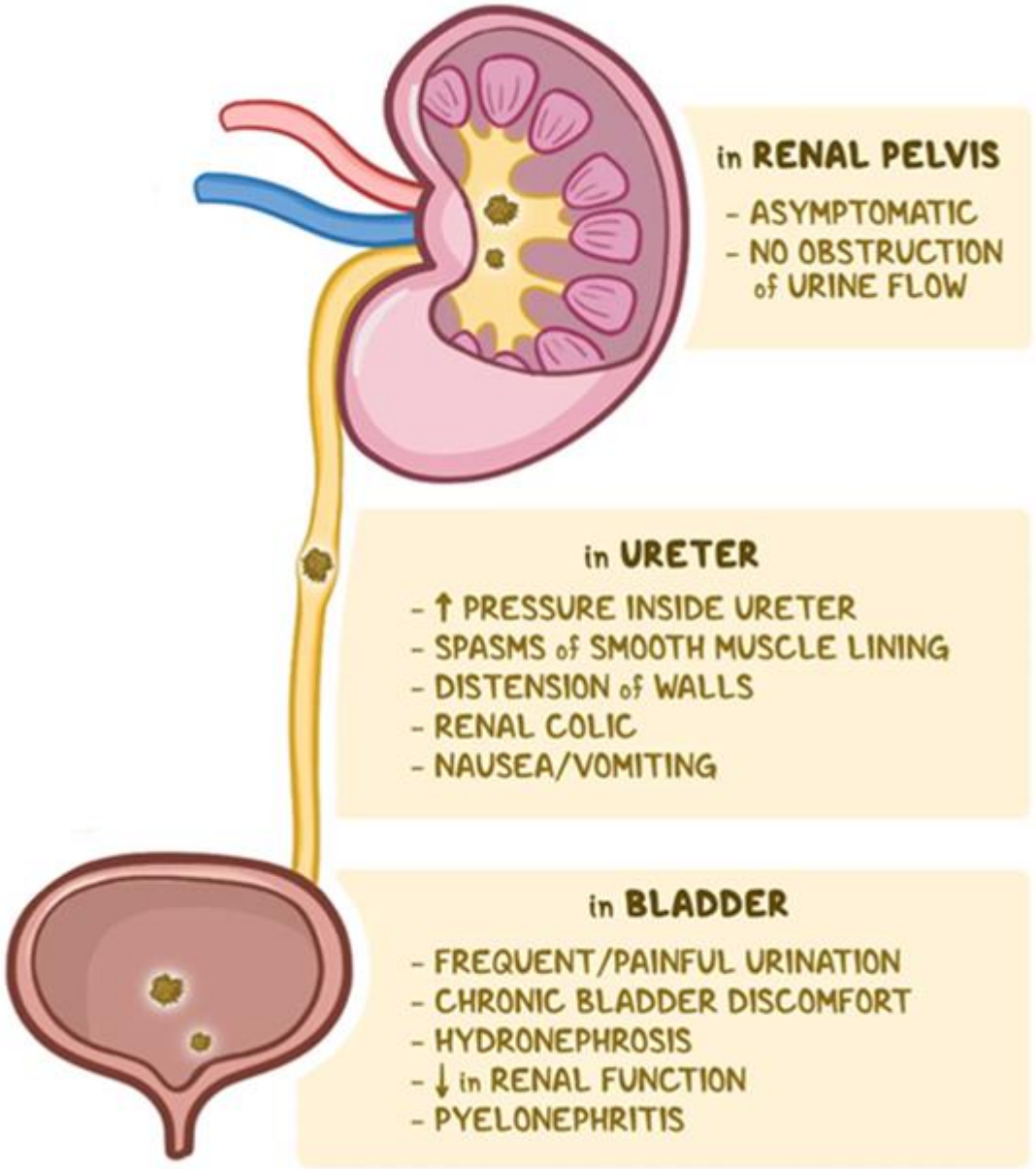


Racek et al. Scanning electron microscopy in analysis of urinary stones. Scand J Clin Lab Invest. 2019

Acute Clinical Presentation

- Acute, severe flank pain that radiates to the groin.
- May also have hematuria and/or dysuria.
- In younger children (<5 years), may be non-specific.
- Infants may present with UTI.

Symptoms also depend on location of the stone



Frequency of Presenting Symptoms

Symptom	Presenting Symptom
Pain	50-75% (less common in younger children)
Gross hematuria	30-55%
Dysuria, Urgency	10%
Nausea, Vomiting	10%

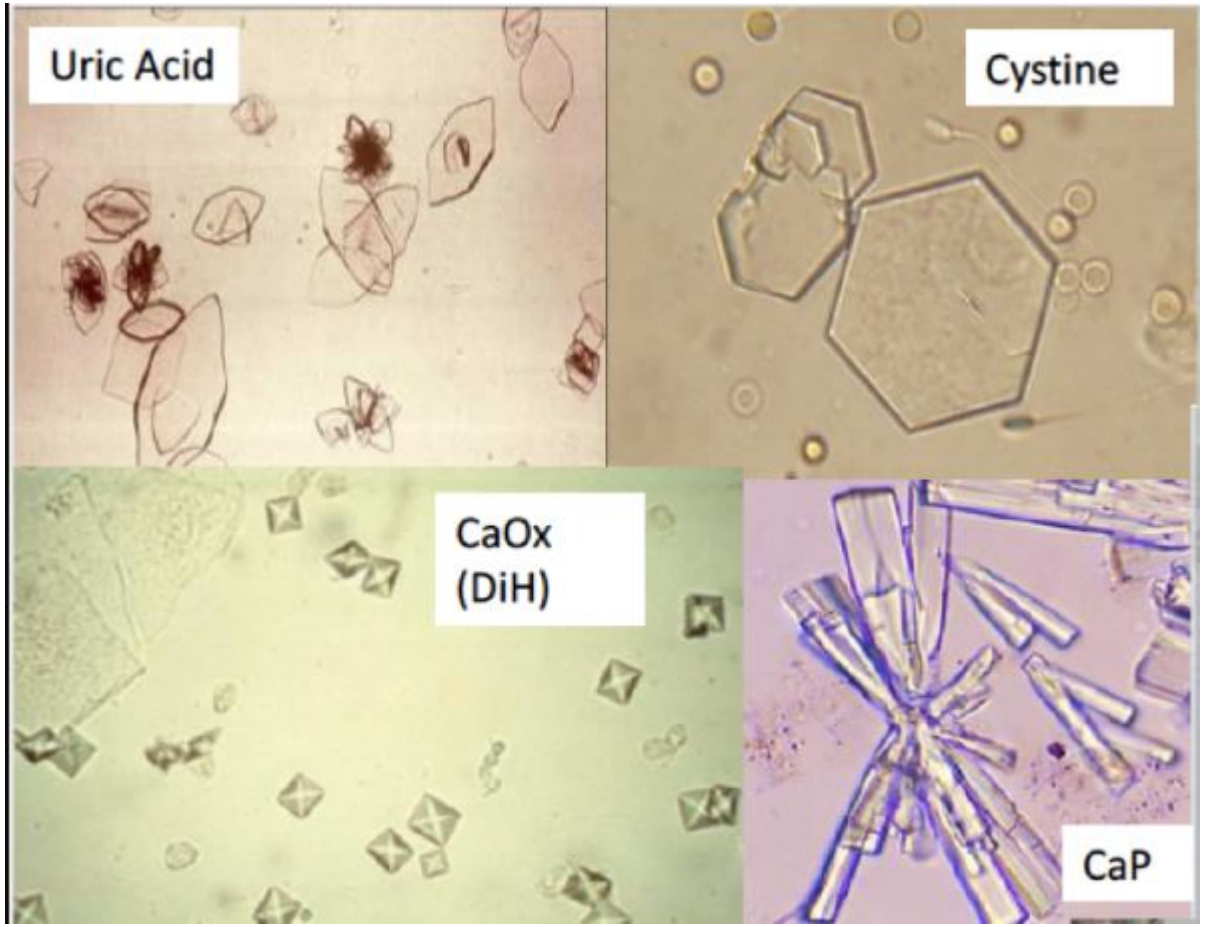
Diagnosis

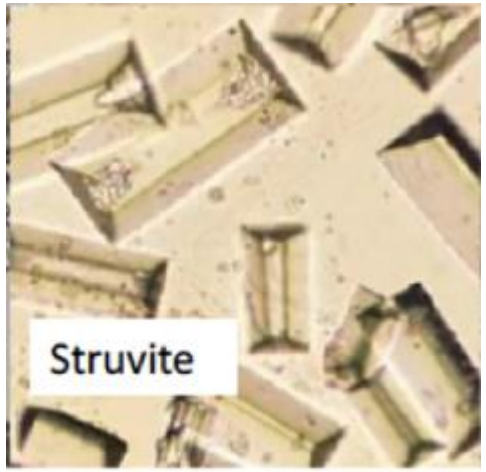
Stones are diagnosed with imaging **or** if patient passes a visible stone

Urinalysis usually provides indirect evidence of stones:

- Hematuria (RBC on microscopy)
- Pyuria
- Crystals

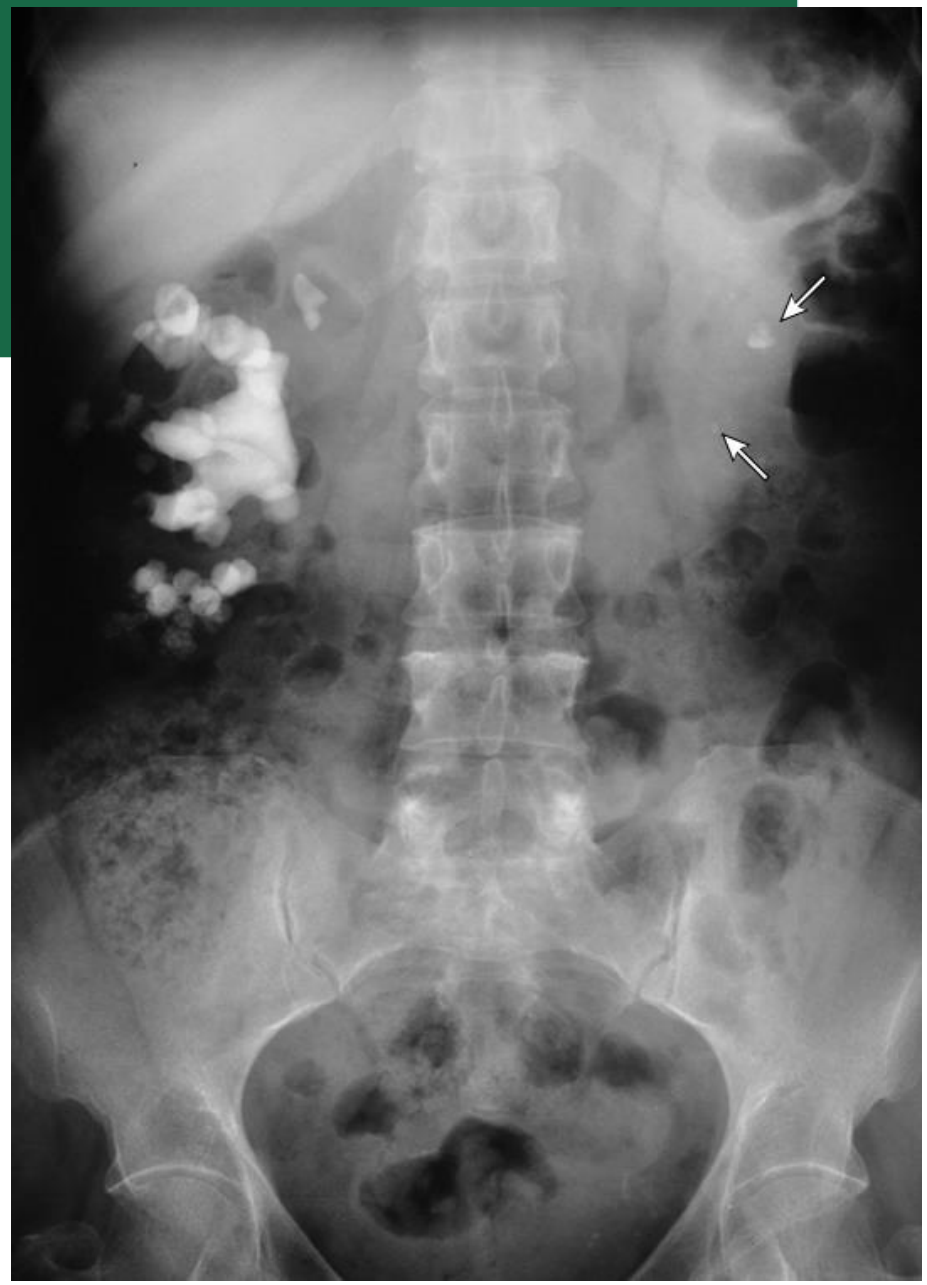
Urine Crystals





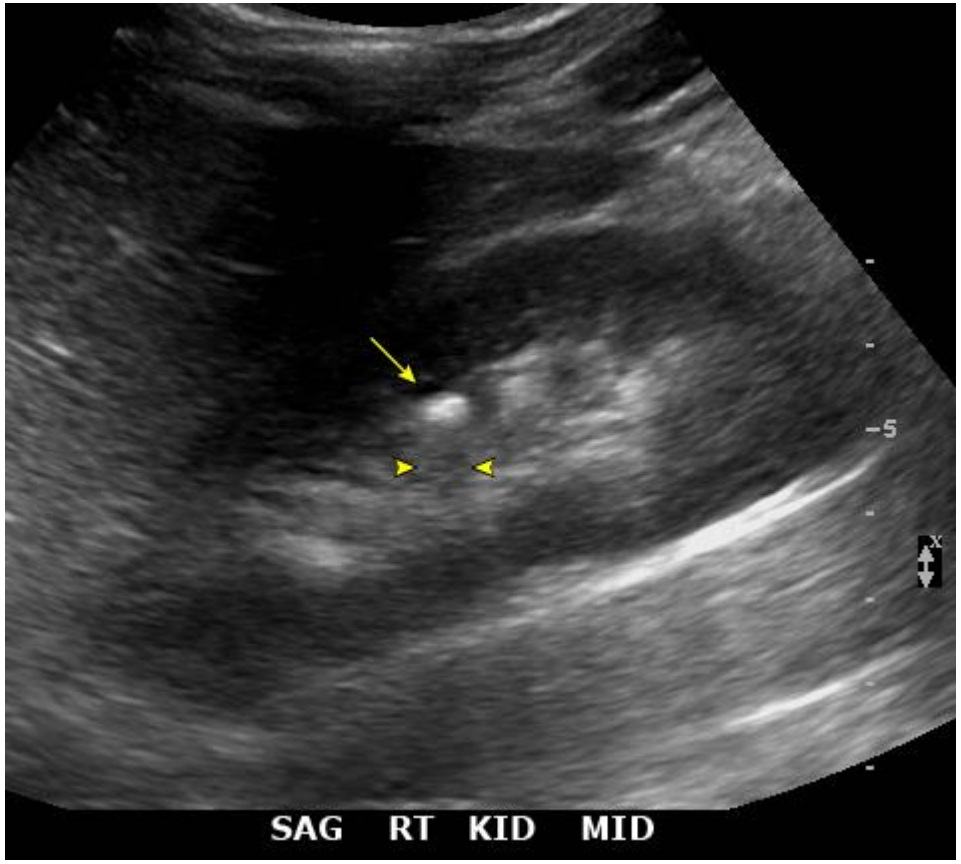
Abdominal X-ray

- Typically insufficient
- Sensitivity 45-58%
- Radiolucent stones (e.g. uric acid stones) and small stones (<5 mm) are often missed
- Useful for follow up and ESWL



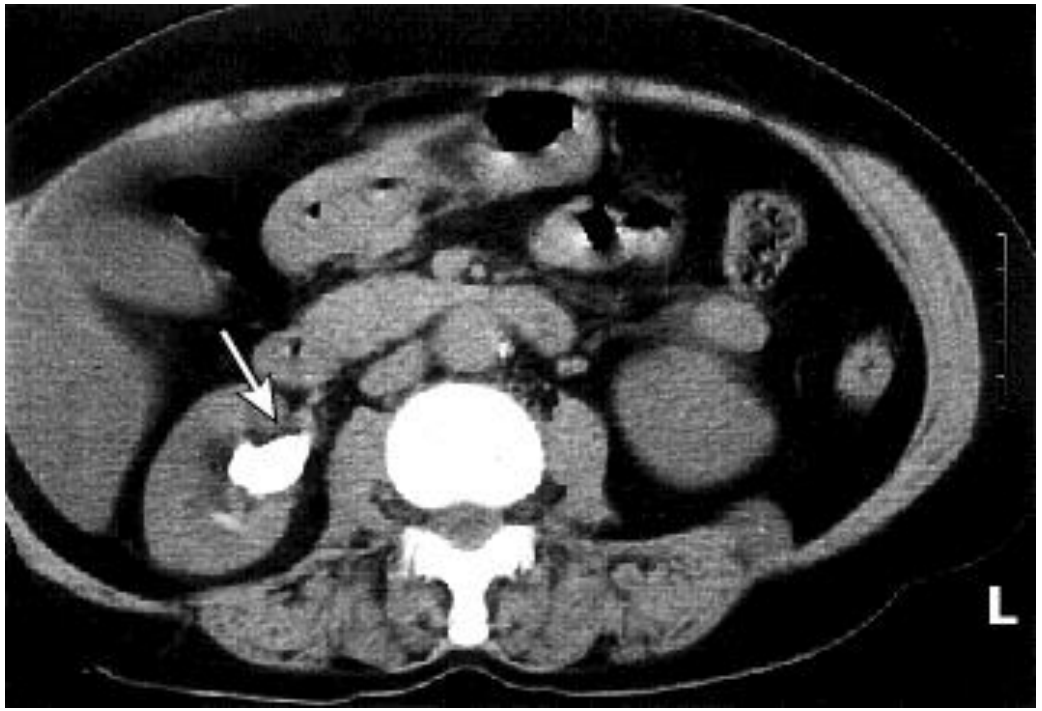
Ultrasound

- Ultrasound is the **INITIAL** imaging study of choice
- Sensitivity >70%
- Specificity 70-95%
- OPERATOR DEPENDANT



CT Scan

- “Gold standard”
- Sensitivity and specificity >90%
- Concern for radiation
- Indicated if US is nondiagnostic with high clinical suspicion



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Medical Management

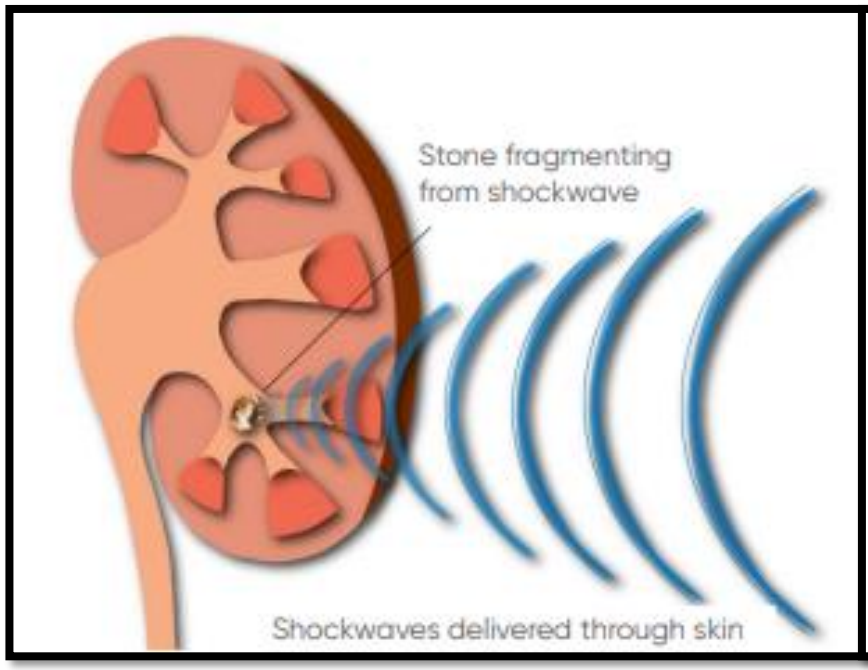
Pain management and **hydration** are the cornerstone of managing acute renal colic.

Typically managed in coordination with urology.

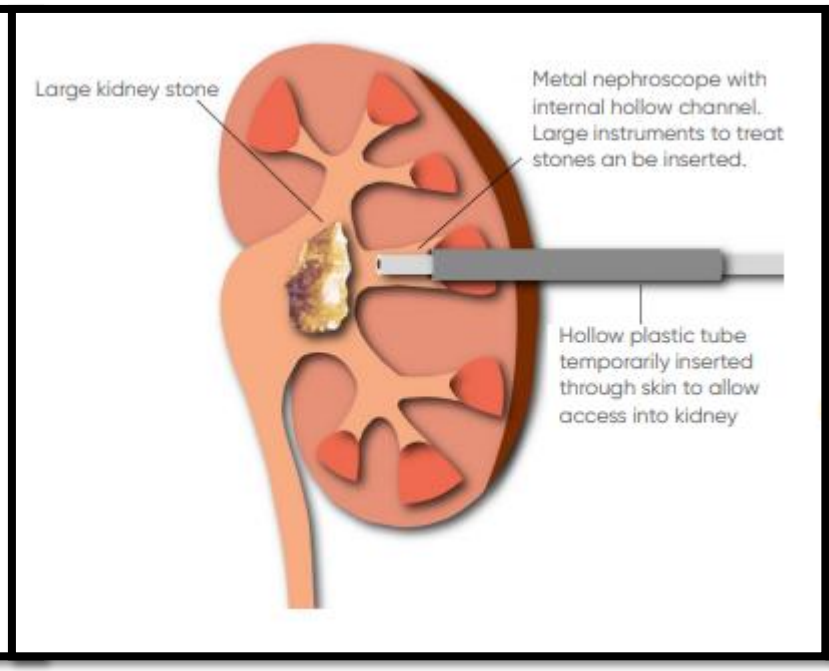
Medical expulsion therapy: use of alpha blockers (e.g. tamsulosin) to facilitate passage of ureteral stone.

- Uncomplicated ureteral stone
- ≤10 mm in diameter

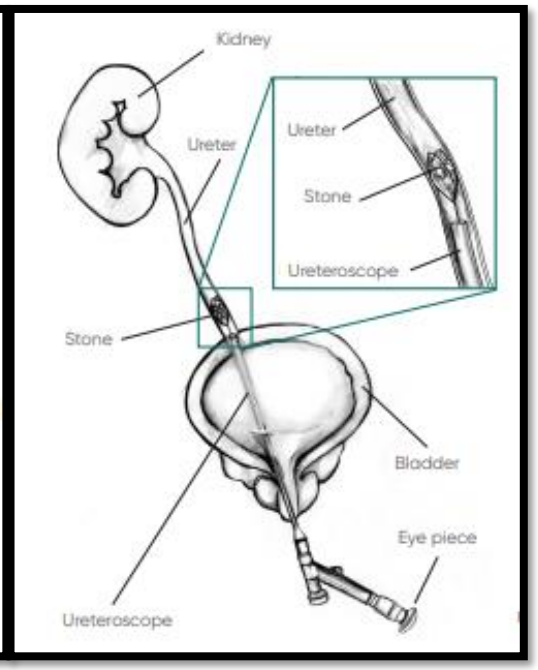
Surgical Intervention



Shock wave lithotripsy
80-83%



Percutaneous nephrolithotomy
70-97%



Ureteroscopy
85-88%

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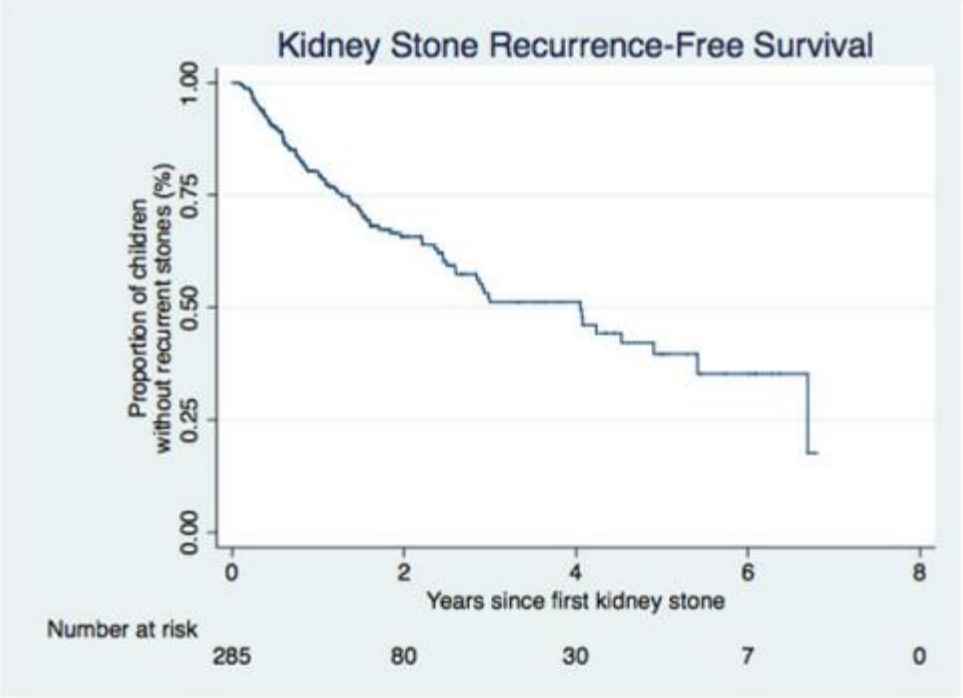
Recurrent Stones

- Kidney stone recur frequently
- Probability of symptomatic stone recurrence ~50% at 3 years
- Goal is to identify and treat modifiable risk factors
- Typically managed by nephrology



Tasian et al. Kidney Stone Recurrence among Children and Adolescents. J Urol. 2017

Evaluation

Serum	Urine (24-hr or spot)	Stone Analysis
Kidney Function Lytes: • Potassium, HCO3 • Calcium, Phosphate • Magnesium • Uric Acid	Urine Volume, pH Lytes: • Calcium, Phosphate • Oxalate • Citrate, Cystine • Uric acid	Identify composition of stone

Strategies for Prevention

1. Increase fluid intake
2. Dietary Changes
3. Medications

Increase Fluid Intake

- Low urine volume is most crucial risk factor for *any* kidney stone
- Dehydration higher with certain occupations and environmental conditions
- Goal fluid intake at least maintenance (2-2.5 L/day or 2000 ml/m^2)

Linder et al. The effect of work location on urolithiasis in health care professionals. Urolithiasis

Fluid Recommendations

Suitable Beverages

- Fluid that increases urine volume: coffee, tea
- Fluid that increases urine pH and citrate: Orange juice, lemonade, grapefruit

Unsuitable Beverages

- Sugar-sweetened soft drinks

Dietary Changes

- Dietary changes depend on the metabolic abnormality identified
- Low sodium diet is beneficial in calcium based stones
- In general, calcium or protein restriction is not recommended

Dietary Changes

Urinary Risk Factor	Limit	Recommendation
Urine volume	Urine volume < 2.0 L/24 h	Fluid intake that achieves urine volume ≥ 2.0 to 2.5 L/24 h Neutral and alkalizing beverages
Hypercalciuria	Calcium > 5 mmol/24 h	Calcium intake: 1000 to 1200 mg/day Protein intake: 0.8 to 1.0 g/kg normal body weight/day Sodium chloride intake: < 2g/day Increased intake of vegetables and fruits
Hyperoxaluria	Oxalate > 0.5 mmol/24 h	Low dietary oxalate intake Calcium intake: 1000 to 1200 mg/day (IH) Avoid Vitamin C supplements!
Hyperuricosuria	Uric acid > 4 mmol/24 h	Protein intake: 0.8 to 1.0 g/kg normal body weight/day Reduced dietary purine intake Increased intake of vegetables and fruits
Hypocitraturia	Citrate < 1.7 mmol/24 h	Protein intake: 0.8 to 1.0 g/kg normal body weight/day Increased intake of vegetables and fruits

Siener R. Nutrition and Kidney Stone Disease. Nutrients. 2021

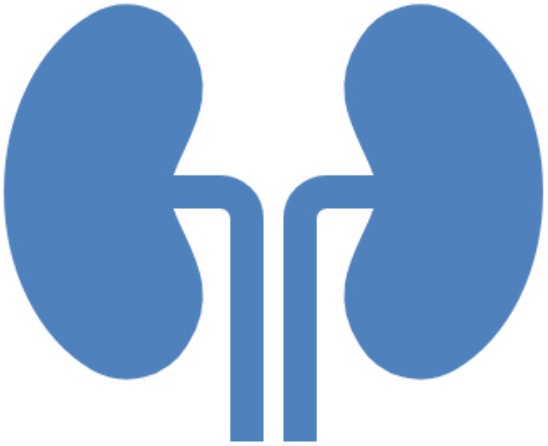
Medication

- Indicated if fluid and dietary changes are ineffective at controlling stones
- Type of medication is used based on the underlying metabolic abnormality
- Specific medications are indicated for some conditions with genetic etiology

Summary

- Incidence of kidney stones is increasing in children
- Risk factors include UTI, metabolic and structural abnormalities
- Symptoms depend on the patients age and location of the stone
- US is the initial imaging of choice
- Fluid intake and dietary changes decrease risk of recurrence

Questions?



IPNA

International Pediatric Nephrology Association

Chronic kidney disease; definition, complications & treatment

Sermin Saadeh, M.D.
Consultant, Pediatric Nephrology
The first IPNA teaching course in pediatric nephrology / the Hashemite University
Amman/Jordan
5/12/2024

Burden of CKD

A life-long condition associated with substantial morbidity, decreased quality of life and premature death

The expected remaining lifetime for a child with end-stage renal disease (ESRD) treated with dialysis estimated to be approximately 18 years

A growing global public health issue with varying estimates of its prevalence. However, growing incidence worldwide.

Definition of CKD

According to KDIGO, CKD in children > 2 years of age defined as either:

1.1: DEFINITION OF CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (*Not Graded*)

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

volume 3 | issue 1 | JANUARY 2013
http://www.kidney-international.org

Diagnostic exceptions for children

The following exceptions or allowances:

(a) The criteria for duration >3 months does not apply to newborns or infants <3 months of age.

(b) The criteria of a GFR <60 ml/min/1.73 m2 does not apply to children <2 years of age as neonates are born with a GFR of around 60, which increases to normal values in the first 2 years of life,

(c) A urinary total protein or albumin excretion rate above the normal value for age may be substituted for albuminuria ≥30 mg/24 h.

(d) All electrolyte abnormalities are to be defined considering age normative values.

How do we measure GFR in pediatrics?

BEDSIDE SCHWARTZ EQUATION (CREATININE)
GFR=0.413*Ht (cm) /Scr (mg/dL)

Adv Chronic Kidney Dis. 2017 Nov; 24(6): 348–356.
Measurement and Estimation of Glomerular Filtration Rate in Children. Ayesa N. Mian and George J. Schwartz

- Creatinine-Cystatin C-based CKiD equation (2012)

Stages of CKD

1.2.3: Assign GFR categories as follows (*Not Graded*):

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

1.2.4: Assign albuminuria* categories as follows (*Not Graded*):
*note that where albuminuria measurement is not available, urine reagent strip results can be substituted (Table 7)

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

volume 3 | issue 1 | JANUARY 2013

http://www.kidney-international.org

Causes of CKD

- CAKUT (50-60%)
  - Vesicoureteral reflux, obstruction, or infections (25%)
  - Hypoplasia or dysplasia (11%)
- Glomerulopathies (5-15%)
- Monogenic causes of CKD estimated at ~20%

Progression of CKD

- CKD progression is influenced by the severity of the initial renal damage, extent of nephron loss, and the age of nephron loss, which limits renal reserve.
- An increased risk with superimposed acute kidney injury from infections, dehydration, drugs, or toxins.
- The extent of injury can result from;
  - a single episode, as seen with acute glomerulonephritis
  - continuous injury from vesicoureteral reflux, chronic infections, obstructive uropathies
  - recurrent injuries from diabetes, lupus, or chronic glomerulopathies.
- Periods of rapid growth, such as with infancy and puberty may result in deterioration of function.

Pattern and timing of CKD progression in hypo/dysplasia

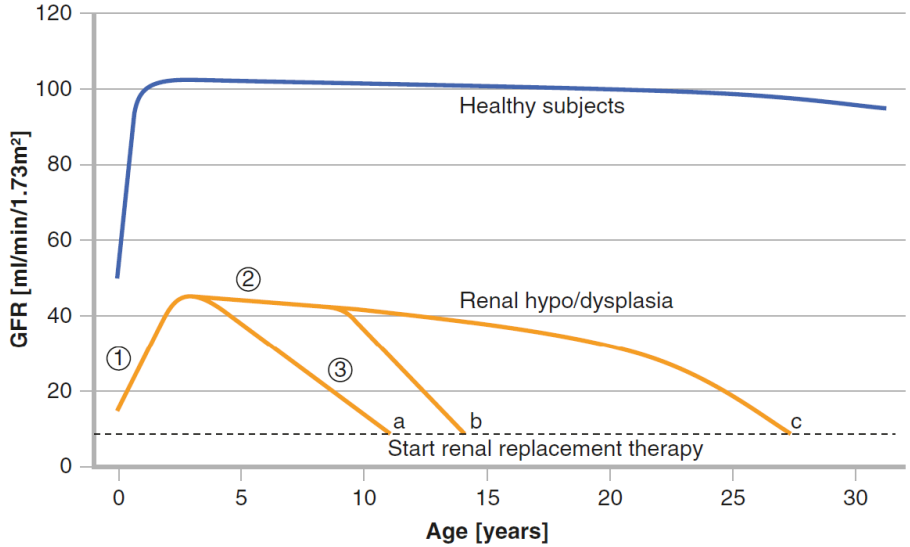


Fig. 53.1 Natural time course of renal disease progression in children with renal hypodysplasia. ① Denotes period of improving renal function during infancy, ② period of stable renal function, ③ period of renal function deteriorating toward ESRD. Third phase is characterized either by rapid decline soon after infancy (**a**) or at early pubertal age (**b**), or by steady slow decline of renal function (**c**) (Used with permission of Springer Science + Business Media from Gonzalez Celedon et al. [10])

- Correlates of deteriorating renal function were proteinuria, hypertension, past febrile urinary tract infections and lower GFR at onset.

- The progression phase started just after infancy in 48% and around puberty in 23% of patients. In 30% kidney function remained stable even beyond puberty.

Gonzalez Celedon C, Bitsori M, Tullus K. Progression of chronic renal failure in children with dysplastic kidneys. Pediatr Nephrol. 2007;22:1014–20.

Glomerular vs non-glomerular progression

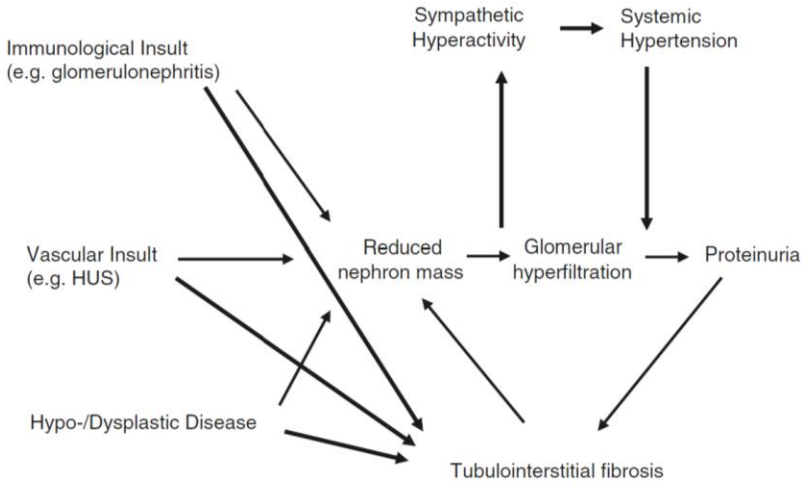
- Children with glomerular disease are estimated to have a 43% shorter time to a composite event of KRT or a 50% GFR reduction or GFR <15 ml/min/1.73 m2 than children with non-glomerular disease. (Ckid and ESCAPE trial)

- Children with mild-to-moderate CKD without proteinuria the median time to attainment of the composite endpoint was longer than 10 years

- Children within the highest risk group, defined by CKD stage IV and gross proteinuria;
  - 50% of children with non-glomerular CKD reached the composite endpoint within 1.3 years and with glomerular CKD within 0.8 years.

Pathophysiology of progression

- According to the Brenner hypothesis any critical loss of functioning renal mass, irrespective of the nature of the initial injury, leads to glomerular hyperfiltration with an increased single-nephron glomerular filtration rate
- The remaining nephrons lose their ability to autoregulate glomerular pressure, resulting in transmission of systemic hypertension to the glomerulus.
- Increased intraglomerular pressure induces proteinuria, which is the pathophysiological link between glomerular, interstitial and tubular damage. The degree of proteinuria in glomerular diseases correlates with the rate of renal failure progression.



Pathophysiological consequences of hypertension and proteinuria

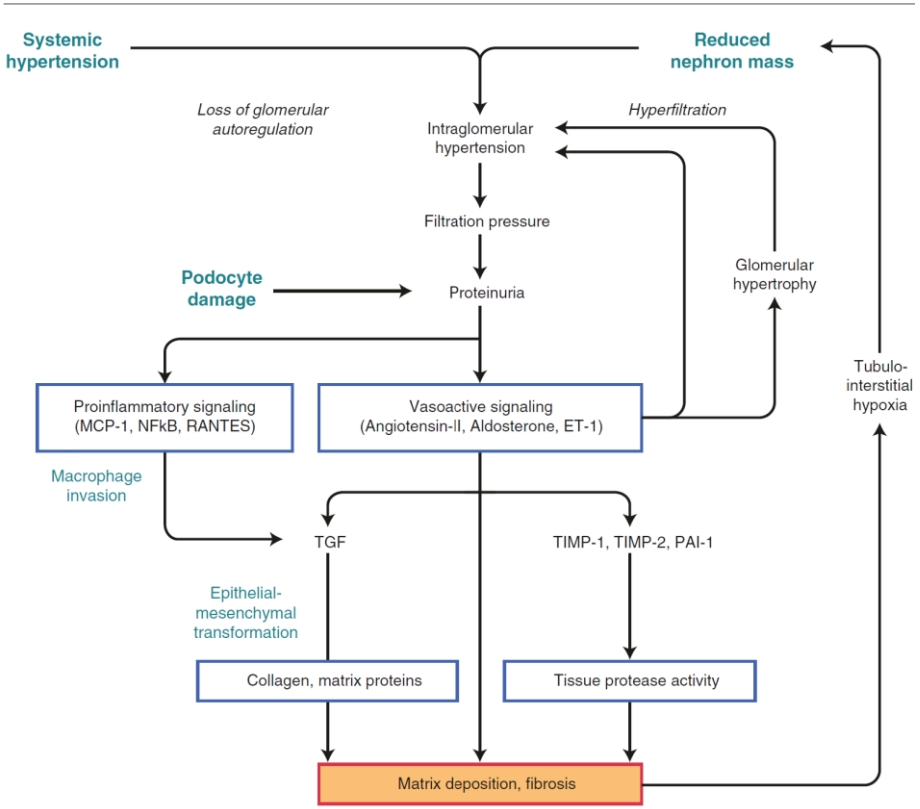


Fig. 53.4 Pathophysiological consequences of hypertension and proteinuria in chronic kidney disease

- Pediatric Kidney disease, second edition. Chapter XII

Modifiable vs non-modifiable risk factors for CKD progression

Non- modifiable

- Glomerular diseases have faster progression of disease compared to non-glomerular
- The presence of two variants of APOL1 genotype in children of Black race
- Genetics; the progression phenotype can be linked to the underlying genetic defect; i.e children with the nephronophthisis complex, those with mutations in the NPHP1 gene have ESRD at a mean age of 13 years, compared to 8 months in NPHP2 and 19 years in NPHP3 mutation carriers
- Age; the younger the age at which a significant loss of renal mass occurs may influence the degree of glomerular hypertrophy.
- Preterm birth and low birth weight due to low nephron mass

Modifiable

- Proteinuria
- Hypertension
- Anemia
- Acidosis
- diabetes

Renoprotective strategies

Blood pressure control;

- The ESCAPE Trial (Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients) provided evidence that intensified blood pressure control targeting for a 24-h mean arterial pressure below the 50th percentile, yields superior long-term nephroprotection compared to a higher target range (50th–95th percentile)

- Within 5 years of observation, the risk of losing 50 % eGFR or progressing to end-stage renal disease was reduced by 35 % (from 42.7 to 29.9 %) in the strict blood pressure control arm
- This has led KDIGO guidelines to recommend intensive lowering of ambulatory BP to <50th percentile

- ESCAPE Trial Group, Wühl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, Testa S, Jankauskiene A, Emre S, Caldas-Afonso A, Anarat A, Niaudet P, Mir S, Bakkaloglu A, Enke B, Montini G, Wingen AM, Sallay P, Jeck N, Berg U, Caliskan S, Wygoda S, Hohbach-Hohenfellner K, Dusek J, Urasinski T, Arbeiter K, Neuhaus T, Gellermann J, Drozdz D, Fischbach M, Möller K, Wigger M, Peruzzi L, Mehls O, Schaefer F. Strict blood–pressure control and progression of renal failure in children. N Engl J Med. 2009;361(17):1639–50.

Renoprotective strategies

Proteinuria

- Its reduction is associated with a slowing of GFR loss
- In children there is evidence from the ESCAPE trial that residual proteinuria during ACE inhibition is quantitatively associated with renal failure progression.
- Even in children with normal kidney function persistent nephrotic-range proteinuria is a risk factor for progressive renal injury; therefore, early detection and therapeutic intervention is mandatory.

- *ACE inhibitors* (*ACEi*) and more recently, *angiotensin II type I receptor blockers* (*ARB*), are pharmacotherapeutics of first choice in both adults and children with chronic kidney disease.

Other antihypertensives

- In CKD patients, RAAS antagonists are combined with a diuretic or with a calcium channel blocker, whereas their combination with a β-blocker usually does not exert an additive effect on blood pressure control.

- Calcium channel blockers can achieve BP control but failed to reduce progression of chronic renal failure. Dihydropyridine CCBs (amlodipine, isradipine) may even induce or aggravate proteinuria

- β-blockers have been shown to be also effective in lowering BP in CKD patients. Metoprolol and atenolol demonstrated beneficial effects on the decline of renal function in CKD patients. Newer β-blockers such as carvedilol have even improved antiproteinuric effects, probably due to sympathicoplegic effects.

sodium glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors (gliflozins)

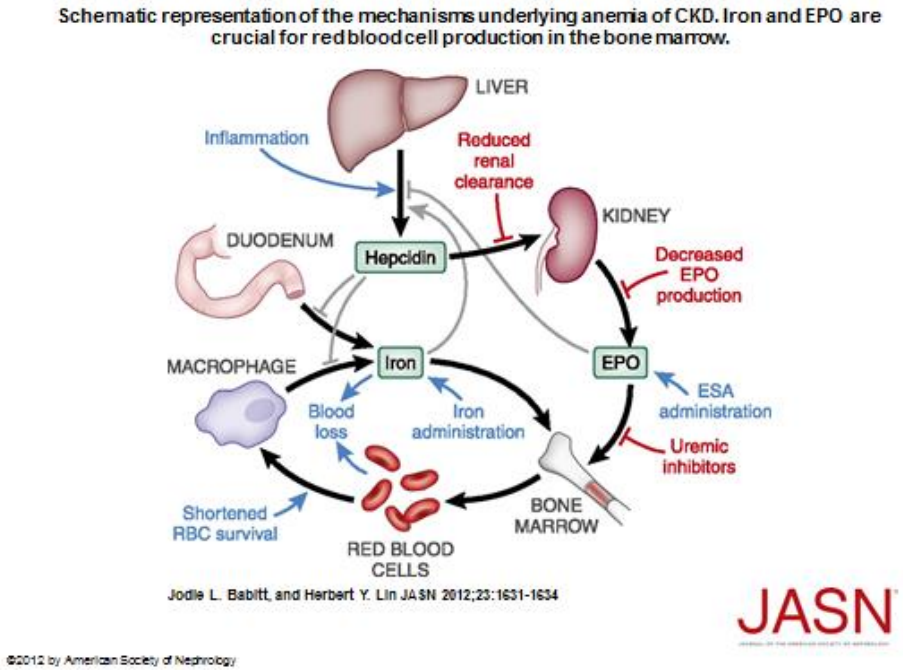
- Apart from the glucose lowering effects, SGLT2 inhibitors also decrease BP, body weight, and albuminuria.
- Large clinical outcome trials with the SGLT2 inhibitors dapagliflozin, canagliflozin, or empagliflozin in T2DM have demonstrated potent long-term renoprotective effects of SGLT2 inhibition, including reductions of 30–50% in albuminuria or proteinuria and clear beneficial effects on hard renal outcomes such as doubling of serum creatinine, eGFR decline, attainment of KRT, or death due to renal disease.
- These nephroprotective effects are based on a decrease of sodium delivery to the distal tubule and reduced glomerular blood flow leading to reversal of glomerular hypertension and hyperfiltration

Other renoprotective strategies

- Studies have suggested beneficial effect to;
  - Dietary phosphate restriction
  - Non-hypercalcemic doses of vitamin D therapy
  - Treatment of acidosis
  - ESA therapy has beneficial tissue-protective effect

Complications of CKD; Anemia

- Elevated hepcidin levels
- Decreased Epo production
- Uremic inhibitors of erythropoiesis
- shortened RBC lifespan, and increased blood loss
- malnutrition
- Iron deficiency
- Inadequate dialysis
- Hyperparathyroidism and myelofibrosis
- Nutritional deficiencies; B12, folate, carnitine, vitamin C, copper



Complications of CKD

Anemia

Effects on the child

- Fatigue
- Impaired cognition
- Sleep disturbances
- Decreased exercise tolerance
- Depression
- Poor appetite
- Cardiovascular complications, such as left ventricular hypertrophy and heart failure

Complications of CKD

Anemia Treatment

- The Kidney Disease Outcomes Quality Initiatives recommend targeting hemoglobin levels between 11 and 13 g/dL (110-130 g/L) to reduce the need for transfusions; to lessen; and to enhance overall quality of life.
- Anemia is best managed with recombinant human erythropoiesis-stimulating agents and iron supplementation.

Anemia Treatment

Epoetin:

- Short-acting achieve maximum efficacy when dosed 1–3 times weekly and demonstrate a longer half-life when given subcutaneously (19–24 h) than intravenously (6– 8 h)

Darbepoetin alfa

- Has equivalent efficacy as to maintain hemoglobin when dosed weekly or every other week in children with CKD
- Darbepoetin alfa may be administered intravenously or subcutaneously

Iron supplementation

- For all pediatric CKD patients with anemia not on iron or ESA therapy, KDIGO recommends oral iron (or IV iron in children on hemodialysis) administration when < TSAT is 20% and ferritin is 100 ng/ml
- For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, KDIGO recommends oral iron (or IV iron in children on hemodialysis) administration to maintain TSAT >20% and ferritin >100 ng/ml

Complications of CKD

Nutrition and Growth

Pathophysiologic features;

- Anorexia, increased energy expenditure despite adequate caloric intake, and muscle wasting
- Contributing factors; systemic inflammation, or endocrine disturbances

Malnutrition in infants

- Contributors; altered taste, oral food aversions, gastroesophageal reflux, delayed gastric emptying, elevated cytokine levels, and alterations in appetite-regulating hormones, such as leptin and ghrelin.
- Aggressive nutritional management with the guidance of qualified dieticians is critical.
- Placement of gastrostomy tubes, particularly in infants and small toddlers, is often necessary to provide adequate nutrition

Sodium supplementation

- Infants and children with renal dysplasia or obstructive uropathy often have an inability to resorb sodium from their urine with sodium excretion paralleling their urine output.
- These polyuric patients may easily be sodium deficient without replacement being given. This may also be seen in patients with salt-losing tubulopathies like Bartter's and Fanconi syndromes.
- Acidosis from bicarbonate losses would not necessarily be seen this early in CKD (GFR nearly 50% of normal).
- Hypophosphatemia may be present from tubular losses and could also affect linear growth although likely not to the same extent as sodium loss. Folate deficiency is also not typically a problem, especially in a patient receiving supplemented formula

Complications of CKD

Fluid and electrolyte abnormalities

- CKD secondary to congenital anomalies of the kidneys and urinary tract are at risk for hypokalemia, hyponatremia, and urinary concentrating defects.
- Patients with early CKD can present with a non-gap metabolic acidosis, but as the disease progresses this metabolic derangement becomes an increased anion gap acidosis.
- Hyperkalemia may become worse with progression of renal disease or in patients receiving ACE inhibitors or angiotensin-receptor blockers for hypertension

Complications of CKD

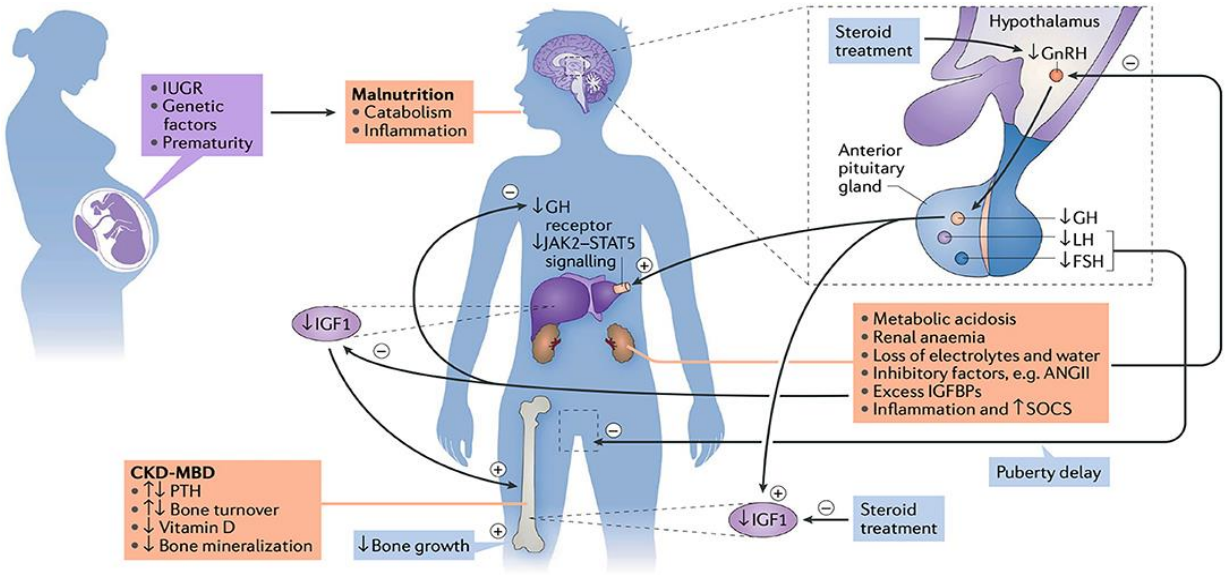
Failure to thrive

- One of the most apparent effects of CKD in children; the mean height of children with CKD is 1.5 SDs below the mean.

- Contributing factors; age at the onset of CKD, duration of CKD, metabolic acidosis, treatment modalities for primary renal disease (corticosteroids), associated genetic disorders, protein-calorie malnutrition, residual urine volume, and hormonal disturbances of the gonadotropic axis (LH and FSH) and somatropic axis (GH, IGF1, and thyroid hormone).

- Short stature is the most common concern associated with low health-related quality of life among survivors of pediatric-onset CKD.
- Optimization of growth can be achieved with appropriate caloric intake and the use of growth hormone replacement.

Growth pathophysiology in CKD



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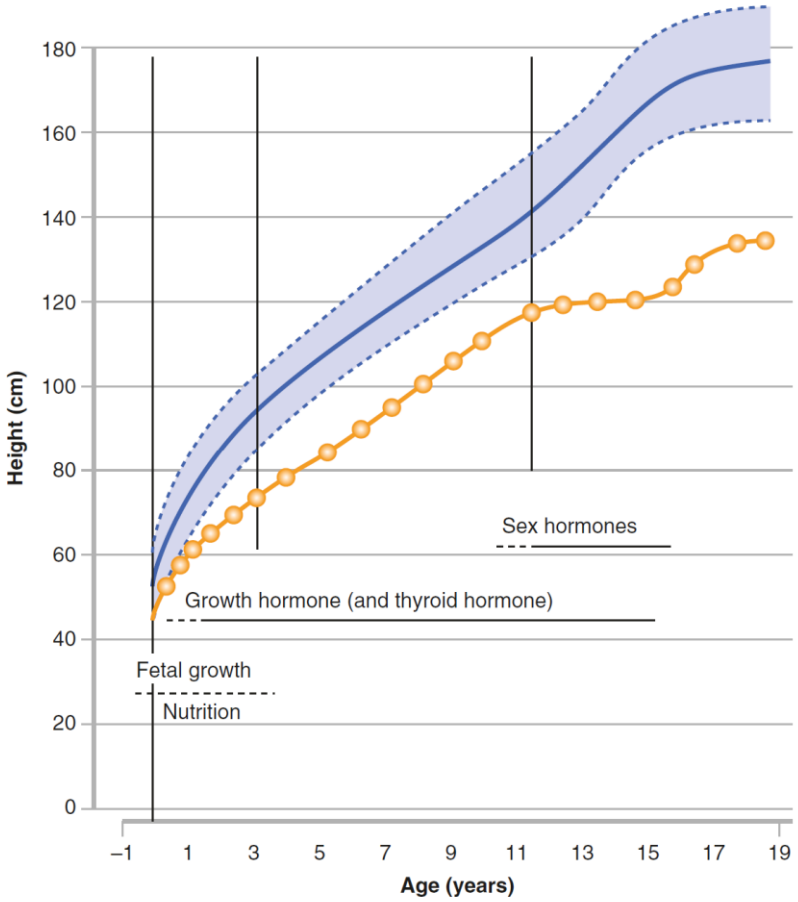
| https://doi.org/10.3389/fped.2020.00399

Strategies for Optimizing Growth in Children With Chronic Kidney Disease

Dieter Haffner*

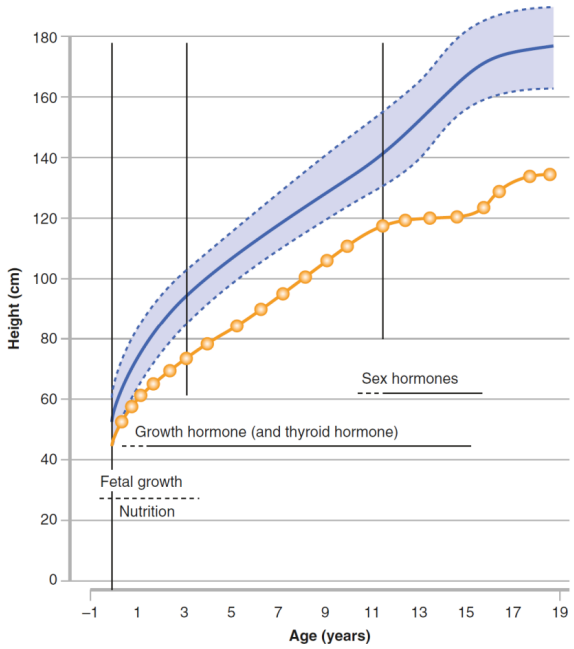
Growth in CKD

- Typical growth pattern in childhood vs CKD



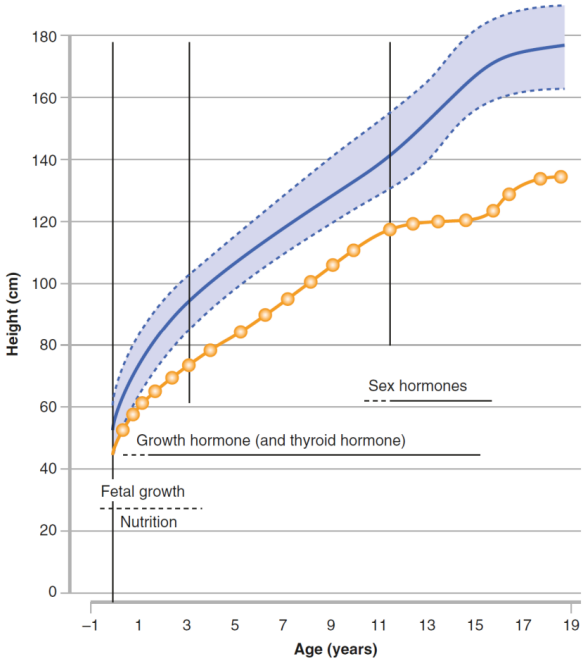
Growth during infancy

- One third of growth occurs during the first two years of life
- Can lead to irreversible loss of growth potential
- It depends mainly on nutritional intake
- Factors to considers;
  - Congenital renal disease resulting in salt-losing nephropathies
  - Feeding intolerance or recurrent vomiting
  - Catabolic episodes; acute illness, infections



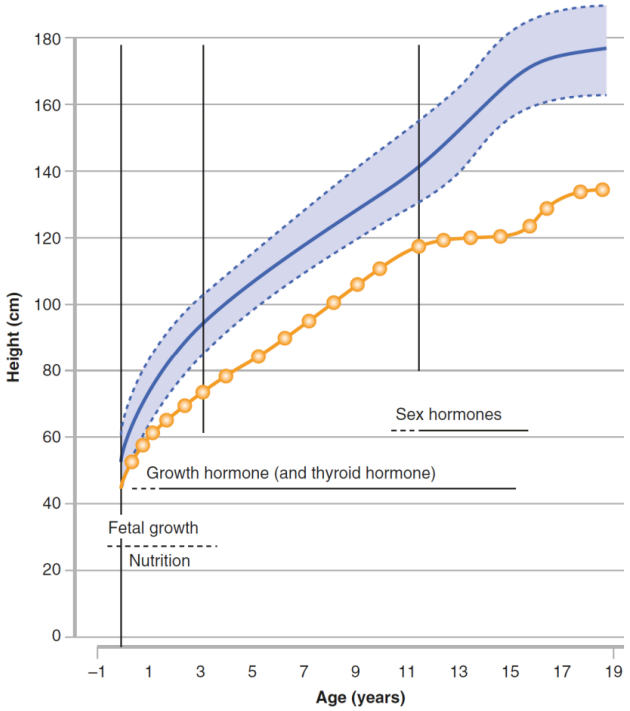
Mid-Childhood growth

- Percentile parallel growth
- Stable if GFR > 25 ml/min/1.73m2
- Dependant on somatotropic hormone axis
- Administration of growth hormone will improve final height



Pubertal growth in CKD

- Signs of puberty as well as growth spurt are delayed by about 2 years
- Height velocity and duration of the spurt is reduced as well
- Results in 50% reduction in total pubertal height increase
- Menarche occurs only in 50% of patient treated with dialysis by 15 years of age



Treatment of growth failure in CKD

- Adequate caloric intake for infants and young children
  - Calories; 80-100% of RDA
  - Protein intake 100% of RDA
- Treatment of metabolic acidosis
- Water and electrolyte supplementation in salt-losing nephropathies
- Provide adequate dialysis
- Seek early renal transplantation in ESRD
- Hormonal therapies;
  - Calcitriol; Control of secondary hyperparathyroidism and bone turnover
  - Growth hormone; Efficacy and safety in pediatric CKD has been well established

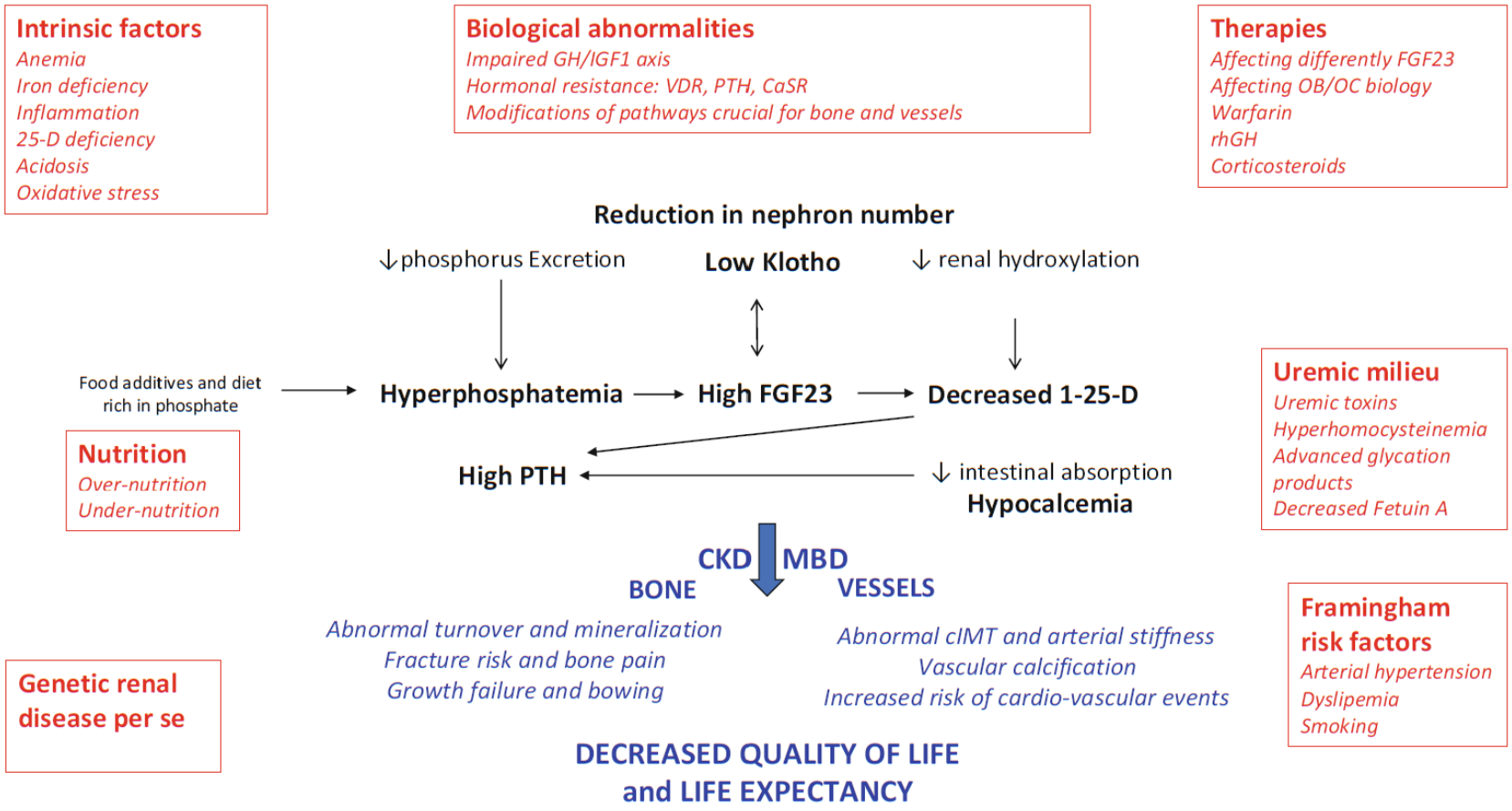
Complications of CKD

CKD- mineral and bone disorder (MBD)

Systemic disorder of mineral and bone metabolism that is manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, linear growth, or strength
- Vascular or other soft tissue calcification

- Metabolic derangements begin as early as in CKD stage II

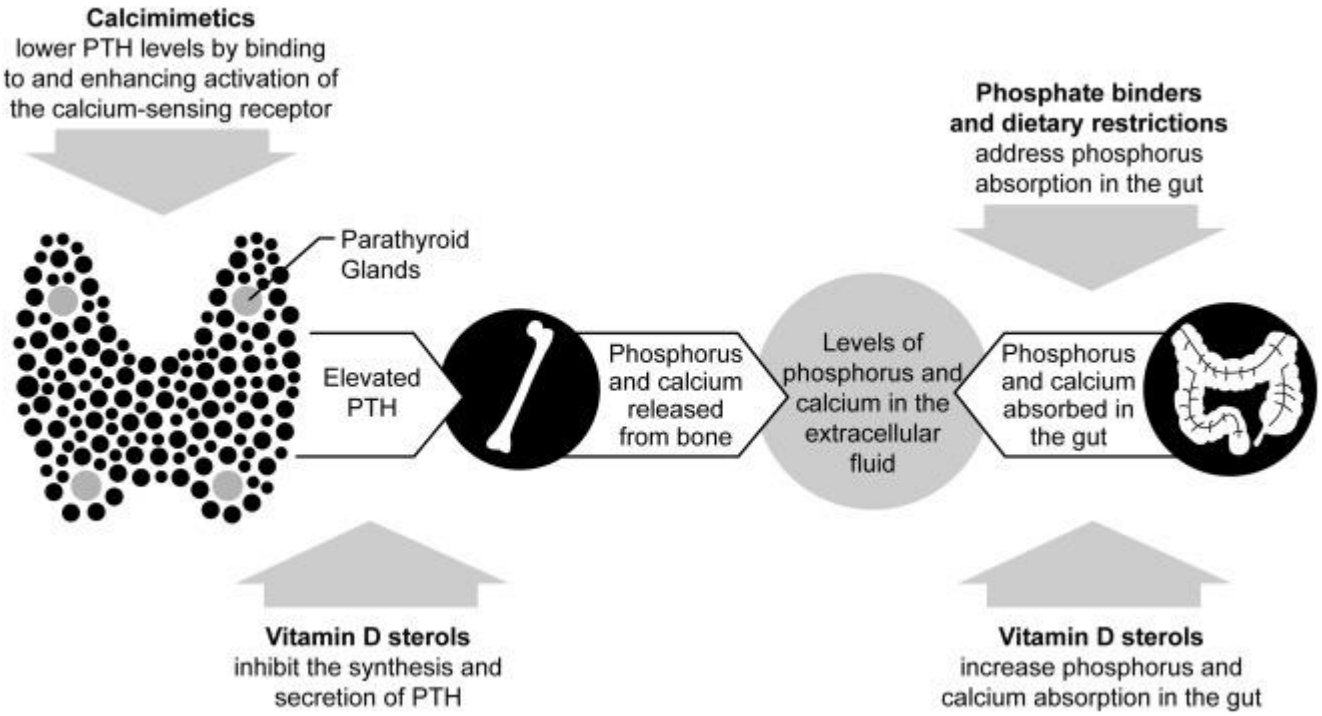


Overview of pediatric CKD-MBD. The reduction in nephron number es both P reabsorption and renal 1-alpha hydroxylation of vitamin D, thus g hyperphosphatemia, decreased 1–25 $(OH)_2$ levels and subsequent hypocalce-l these factors increase PTH levels, with the development of secondary hyper-roidism. Dysregulated mineral metabolism is central to the vasculopathy and bone disease of CKD but additional factors worsen this (already complex) CK setting, as illustrated around the elementary and fundamental factors expla pathophysiology of CKD-MBD. *OB/OC/OCy* osteoblast/osteoclast/osteocy recombinant human growth hormone, *cIMT* carotid intima/media thickness

Assessment of CKD-MBD

- Clinical evaluation;
  - height, growth velocity, blood pressure and a musculoskeletal examination, focusing on bone pain, deformities, and fractures.
- Assessment should be more frequent during periods of rapid growth, such as infancy and adolescence.
- Ca intake from diet, nutritional supplements, and P-binders should also be assessed
- Traditional biochemical markers of mineral metabolism, including Ca, P, PTH, 25-D, and alkaline phosphatase (ALP), should be measured at routine intervals

Bone Mineral Metabolism (CKD-MB)- Treatment



Complications of CKD

Neurologic and Neurocognitive effects

- When compared with healthy controls, children and adolescents with CKD are at higher risk for grade retention, absenteeism, and impairments on measures of intelligence and reading.
- Chronic kidney disease (CKD) is a known risk factor for poor neurocognitive function.
- Compared with their unaffected siblings, children with CKD have poorer performance on tests of intelligence and academic achievement.
- Duration of end-stage renal disease has been shown to be associated with worse neurocognitive outcomes in children
- It is known that after transplantation, school-age children have better neurocognitive function and school performance compared with children receiving chronic dialysis.

Psychological issues

- Depression and ADHD are common comorbidities in patients with CKD.
- Families with a child with CKD experience emotional, physical, and financial stress
- Parental distractions related to the patient's chronic condition can lead to feelings of neglect by siblings and affects the family's financial well-being.
- Financial burdens result from interrupted work schedules, insurance copayments for medical visits or medications, and poor reimbursement for travel costs, meals, or parking.
- In general, parents of a chronically ill child have higher marital distress and decreased marital harmony when compared with parents of healthy children.

Burden of care

- Time and attention by patients and their family.
- The number of medications (mean of 6) patients take once to several times per day, with dialysis and transplant patients requiring the largest number
- The complexity of care also includes procedures
- fluid and dietary restrictions
- Injections (ESA, GH)
- Home peritoneal (daily) or hemodialysis (at least thrice weekly)

Mortality in CKD

- The risk of death in Children with CKD is 30 times higher than peers
- Most common cause of death is cardiovascular- sudden cardiac death (35%) followed by infections
- Risk of mortality is increased with younger age at KRT initiation, female sex, black race and later time of referral to peds neph.

Quality of life

- Compared with healthy children and adolescents, patients with CKD have significantly lower health-related quality of life in the physical, school, emotional, and social domains.

Thank you for your attention

- CKD is a big and complex topic

NOCTURNAL ENURESIS

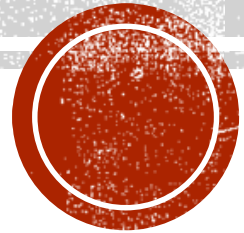
IPNA
International Pediatric Nephrology Association

FIRST IPNA TEACHING COURSE , JORDAN 5/12/5024

NOCTURNAL ENURESIS

- Terminology
- Epidemiology and natural history
- Pathogenesis
- Causes
- Evaluation
- Management

TERMINOLOGY



TERMINOLOGY

- Refers to discrete episodes of urinary incontinence during sleep in children ≥5 years of age.

- Enuresis is divided into monosymptomatic and non-monosymptomatic forms, although the pathogenesis and evaluation of the two forms overlap.

- Monosymptomatic nocturnal enuresis usually is divided into primary and secondary forms.

- Non-monosymptomatic enuresis is defined as enuresis in children with other lower urinary tract symptoms.

MONOSYMPTOMATIC NOCTURNAL ENURESIS

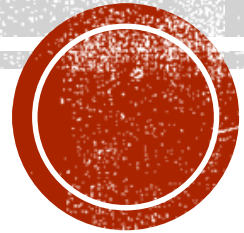
- Primary : in which the child has never achieved a satisfactory nighttime dyness , accounts for about 80% of the cases

- Secondary :in which the child develops enuresis after at least six months of nighttime dryness .

NON-MONOSYMPTOMATIC ENURESIS

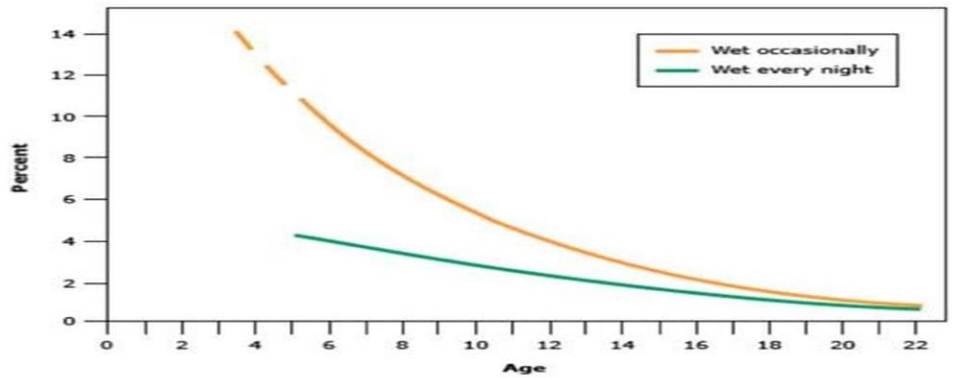
- Consistently increased or decreased frequency of voiding
- Urgency
- Hesitancy
- Daytime incontinence
- Straining
- Weak stream
- Intermittancy
- Holding maneuvers
- Genital or urinary tact pain

EPIDMIOLGY



EPIDEMIOLOGY

Epidemiology and prognosis of monosymptomatic enuresis



Reproduced with permission from: Nevéus T, Eggert P, Evans J, et al. Evaluation and treatment of monosymptomatic enuresis - a standardisation document from the International Children's Continence Society (ICCS). Copyright © 2009 ICCS.

Graphic 58087 Version 3.0

- Monosymptomatic nocturnal enuresis is common in children. The prevalence varies according to age
  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

- Monosymptomatic nocturnal enuresis is twice as common among male compared with female individuals. It resolves spontaneously at a rate of approximately 15 percent per year

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

PATHOGENESIS

PATHOGENESIS

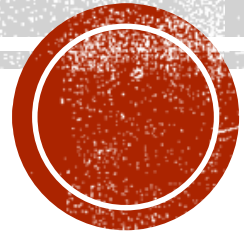
- Maturational delay - In almost all cases, monosymptomatic nocturnal enuresis resolves spontaneously .
- Genetic factors: There is a genetic tendency toward nocturnal enuresis. The concordance among monozygotic twins is almost twice that among dizygotic twins (68 versus 36 percent.When one parent has a history of prolonged nighttime wetting, approximately 50 percent of the offspring are affected; when both parents have a history, approximately 75percent of offspring are affected.

- Nocturnal polyuria and Antidiuretic horomone : Increased nighttime urine output appears to play an important role in nocturnal enuresis.

- Small bladdar capacity :At birth, bladder volume is approximately 60 mL (2 ounces); bladder volume increases with age at a relatively steady rate of approximately 30 mL (1ounce) per year until 10 years of age, Children with NE have been noted to have smaller bladdar capacity .

- Detrusor overactivity:They may have a defect in the circadian rhythm of detrusor inhibtion and pelvic floor activity .

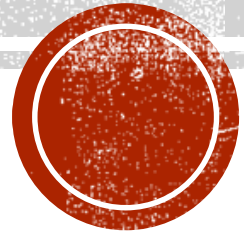
PATHOLOGICAL CAUSES OF NE



CAUSES

- Bladder dysfunction (usually associated with daytime symptoms)
- Urinary tract infection
- Chronic kidney disease associated with poor growth or weight loss, hypertension, abnormal urinalysis.
- Posterior urethral valves (associated with incomplete bladder emptying).
- Obstructive sleep apnea .
- Fecal incontinence and constipation
- Sickle cell disease (may be associated with positive family history, abnormal urinalysis decreased specific gravity, hematuria, proteinuria])
- Seizures (associated with paroxysmal,stereotyped behaviors)
- Diabetes mellitus (associated with polyuria,polydipsia, weight loss, and glucosuria)
- Arginine vasopressin disorders, previous called diabetes insipidus
- Spinal dysraphism (may be associated with abnormal overlying skin)
- Pinworms (associated with perianal excoriation)

EVALUATION



EVALUATION /HISTORY

- Daytime wetting or lower urinary tract symptoms including urgency,holding maneuvers, interrupted micturition,weak stream, and straining. Urologic and neurologic disorders are more common among children with daytime symptoms.

- Whether the child ever had a prolonged period of dryness (ie, six months).

- Frequency and trend of nocturnal enuresis (eg,number of wet nights per week or month, number of episodes per night, time of episodes).

- Fluid intake diary. Consuming the majority of fluids during the late afternoon and evening may be associated with nocturnal polyuria

- Stooling history and history of soiling

- Medical history eg, review of systems for symptoms of sleep apnea, diabetes, sickle cell disease, urinary tract infection [UTI], gait or neurologic abnormalities).

- Family history of nocturnal enuresis.

- Social history (particularly important in secondary enuresis).

- Assessment of how the problem has affected the child and the family

Important aspects of the history for a child with enuresis

Historical feature	Possible significance
Daytime symptoms	Dysfunctional voiding
Lower urinary tract symptoms (voiding ≥8 or ≤3 times per day, hesitancy, straining, weak stream, intermittent stream, incomplete emptying, postmicturition dribble, genital or lower urinary tract pain)	Dysfunctional voiding or anatomic abnormality (eg, posterior urethral valves)
Prolonged period of dryness (>6 months)	Secondary enuresis more often associated with psychologic comorbidities
Frequency of episodes	Nightly enuresis is associated with persistence
Change in frequency of episodes over time	The natural history is of spontaneous resolution
Approximate volume of enuretic void	Estimate of bladder capacity
Fluid intake diary	May suggest etiology of nocturnal polyuria (increased afternoon/evening fluid intake; diabetes mellitus; diabetes insipidus; psychogenic polydipsia)
Stooling history	Constipation may contribute to decreased bladder capacity
Review of systems	May identify previously undiagnosed medical condition that contributes to enuresis
- Snoring	- Obstructive sleep apnea
- Weight loss, fatigue	- Diabetes, kidney disease
- Gait abnormalities	- Spinal dysraphism
- Staring spells	- Seizure disorder
- Perianal itching, vulvovaginitis	- Pinworms
- Excessive thirst, nighttime drinking	- Diabetes, kidney disease, psychogenic polydipsia
Family history of enuresis	Genetic factors may be contributing

Voiding and fluid intake diary

Name: _____ Date of birth: _____

Date: _____

Voiding diary

Time	Urine volume (mL)	Straining/ interrupted stream	Wetting: Damp/wet?	Urge	Comments/observations

Fluid intake diary

Time	Fluid intake (mL)

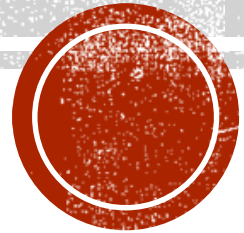
Instructions to caregivers or primary care provider on completing the voiding/drinking diary:

1. Fill out this chart on a day without school or kindergarten (weekend or holiday). This should start on one morning and continue through to the next morning. If possible, fill out the diary two days in a row, as this is even more reliable.
2. Talk to the child beforehand. They should tell you when they want to go to the toilet and should empty the urine into a measuring cup. Please measure the amount of urine and record it with the time of day. You do not have to collect the urine but can

EVALUATION /PHYSICAL EXAMINATION

- The physical examination of the child with primary monosymptomatic nocturnal enuresis usually is normal.
- Poor growth and/or hypertension may indicate renal disease.
- Tonsillar hypertrophy or "adenoid facies may indicate obstructive sleep apnea.
- Detection of wetness in the undergarments is a sign of daytime incontinence.
- Palpation of stool in the abdomen suggests constipation
- Detection of incomplete bladder emptying by percussion and/or palpation or observation of voiding that demonstrates slow urinary stream.
- Perineal excoriation or vulvovaginitis may indicate pinworm infection.
- Abnormalities of the lumbosacral spine may indicate occult spinal cord abnormalities .

MANAGMENT



MANAGEMENT/ BEHAVIORAL AND MOTIVATIONAL COUNSELING

- In primary monosymptomatic enuresis, the mainstay of management is education, and reassurance that no treatment is necessary.
- Void first thing in the morning and immediately before bed. ·
- Frequent voiding (aim for every 2 to 3 h, or 5 to 7 times/ day).
- Wearing a vibrating watch or timer may help decrease daytime LUTS ·
- Optimal posture for girls is to sit upright in the middle of the toilet with feet touching the ground or on a footstool .
- Fluid intake · Drink liquids in the mornings and afternoons, and drink less after dinner. Some studies recommend 80% of total daily fluid intake before 4:00 pm. ·
- Avoid caffeinated drinks .
- Address constipation. Active dietary management, including medication and nutritionist referral, may be needed, with one soft bowel movement per day being the goal.

MANAGEMENT/ ACTIVE THERAPIES/ALARM THERAPY

- Children and families with persistent distress despite education and reassurance, shared decision-making with patients and families should inform the use of active therapies.
- Alarms are used since the 1930s, the enuresis alarm wakes a sleeping child with a moisture sensor at the initial stage of voiding.
- Alarm studies have demonstrated varying success rates (success being defined as 14 consecutive dry nights), typically with an initial response of 60% to 80%, although up to one-half of children may relapse when alarm use is discontinued
- Nightly enuresis is more resistant to alarm therapy, while infrequent enuresis (less than once per week) does not allow sufficient opportunity for appropriate training. At least two episodes per week should be baseline for alarm use to be effective.

MANAGEMENT/ ACTIVE THERAPIES/DESMOPRESSIN

- Desmopressin is a synthetic vasopressin analog that has been used for enuresis since the 1970s.
- Desmopressin works by decreasing both urine volume and intravesical pressure at night.
- Desmopressin is effective for treating enuresis with a range of underlying mechanisms and may be especially useful for nocturnal polyuria with normal (rather than low) daytime bladder capacity (based on history, voiding diary use, and urine measurement).
- Daily use results in a full response in 30% of children, with another 40% experiencing a partial response . The relapse rate when medication is discontinued is up to 70%
- The usual melt dose is 120 mcg administered 30 to 60 min before sleep. The anti-enuretic effect has been observed soon after medication initiation but, if dryness is not achieved, the dose can be doubled to 240 mcg. The maximum dose for desmopressin is 360 mcg.
- Guidelines for continuous use of desmopressin suggest treatment for 3 months at a time, then reassessment with a medication break to determine resolution of enuresis symptoms.

RECOMMENDATIONS FOR CLINICIANS

- Education and reassurance are the mainstays of management for monosymptomatic or ‘simple’ enuresis (MSE).
- Conduct a history and physical exam to determine that enuresis is the correct diagnosis, to distinguish monosymptomatic from non-monosymptomatic enuresis, and to rule out common comorbidities, especially constipation, developmental and psychiatric conditions, and upper airway obstruction.
- lower urinary tract symptoms (LUTS) may not be evident unless clinicians specifically ask about them. When LUTS are present, they should be addressed first or concurrently with treatment for enuresis. Referral to urology is appropriate when symptoms are severe, numerous, or atypical.
- Work with patients and families to determine whether treatment is necessary or desired. Consider the impact of enuresis on the child’s self-esteem, and family factors such as motivation, support, and available resources.
- Patients experiencing distress related to their enuresis may respond well to active treatment, such as an enuresis alarm and/or the intermittent use of desmopressin.


THANK YOU

Approach to hematuria in the outpatient setting

Sermin Saadeh, M.D

Pediatric Nephrology Consultant

King Faisal Specialist Hospital and Research Center

Hematuria comes in different forms

First stop, outpatient…

- 6 year old female referred for asymptomatic microscopic hematuria discovered during a checkup
- 5 year old male with macrosomia and autism. Gross hematuria noted by the mother to have red urine for two days
- 9 year old male with hx of abdominal pain, purpura on the legs and arms a month ago that resolved, continues to have microscopic hematuria

Inpatient …

- 8 yr old male with cola-colored urine for four days, developed renal failure on the fourth day. No history of fever, sore throat, skin rashes or joint complaints!
- 12 yr old female with a crt of 260. She has had fever and fatigue for two weeks and her urine is showing blood, protein and WBCs.
- Now the ICU; 13 year old female admitted to the hospital with a pneumonia, is in respiratory failure now. Her urine is red- brown and her creatinine is rising.

What is hematuria?

- It signifies the presence of blood in urine.
- Could be visible (macroscopic or gross hematuria)
- Or only under the microscope (microscopic hematuria)

- Definition: the presence of more than 3- 5 RBCs per high power field collected in an un-centrifuged freshly voided midstream urine collection and confirmed in 2 out of 3 appropriately collected urine samples.

Urine discoloration by blood

- Urine turns red in color in presence of as little as 1 ml of blood in a liter of urine.
- The intensity of redness can vary based on the amount of blood and location of bleeding
  - bright red or pink usually originates from the lower tract
  - brown or dark color results from oxidation of the heme pigment and is usually of a glomerular origin.

Urine discoloration

- Conditions that cause red or dark discoloration, other than gross hematuria, can be ruled out by the absence of increased RBCs on urine microscopy.

Food/ Dye:
Food coloring
Beetroot
Blackberries
Rhubarb
Medications:
Rifampin
Nitrofurantoin
Metronidazole
Presence of pigment:
Hemoglobin
Myoglobin
Urate crystals
Porphyrins

Prevalence of hematuria

- Our knowledge of the prevalence of hematuria in children is based on large screening studies done in the 1970's and it is estimated to be about 1-4%.
- There are no recent large population-based study because a routine screening by urinalysis is not encouraged in most countries.
- The American Academy of Pediatrics no longer recommends a routine screening of healthy children with urinalysis during routine health surveillance visits.
- Because of a high rate of false positive results or transient abnormalities that lead to a low yield in detecting kidney problems in healthy asymptomatic children.

Screening urinalysis

- It is advisable to limit screening urinalysis to selected few patients who have a high risk for CKD;

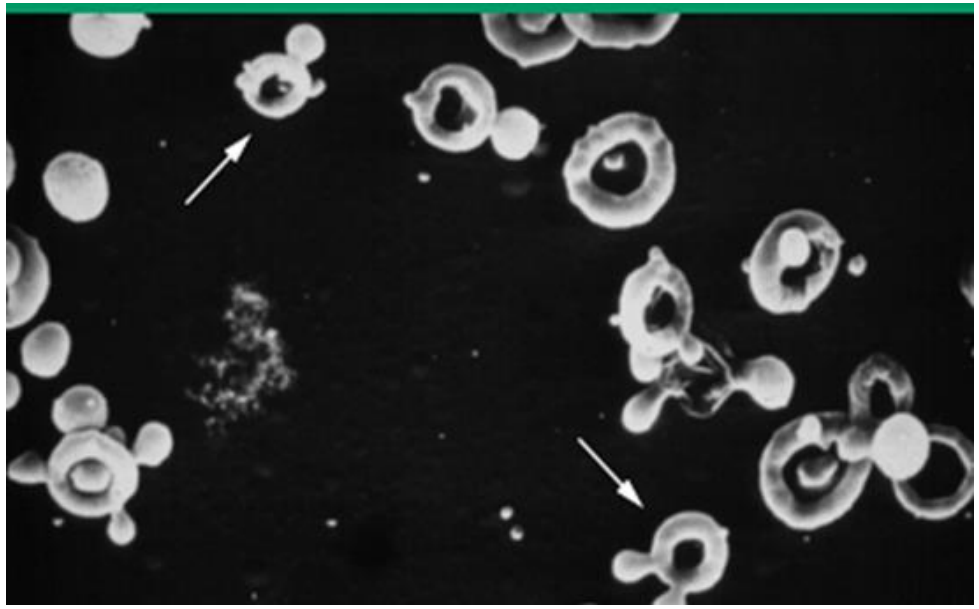
Previous Acute Kidney Injury (AKI)
Congenital anomalies of the kidneys and urinary tract (CAKUT)
Previous acute glomerulonephritis
Hypertension
Active systemic disease
Prematurity and/ or Intrauterine growth retardation
Family history of kidney disease

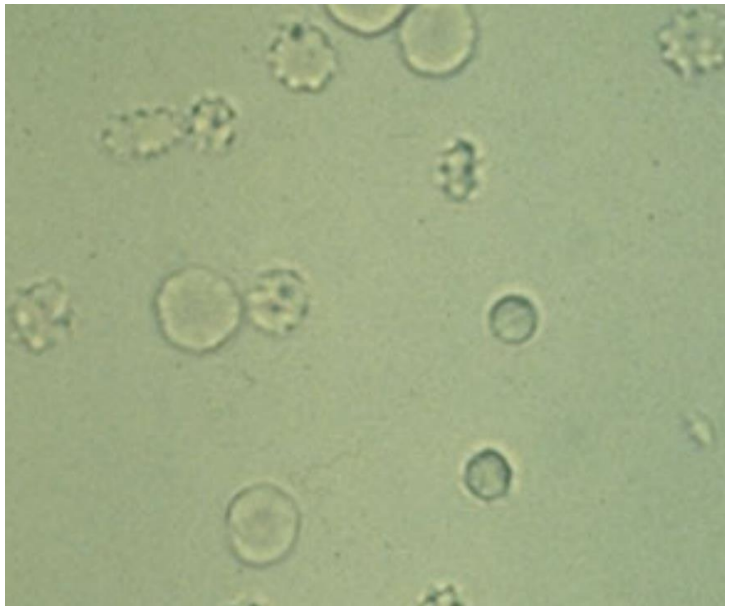
Diagnosis- Urine dipstick

- Urine dipstick is very sensitive for the presence of blood and detects as little as 150 microgram/L of hemoglobin.
- False positive can result from the presence of free hemoglobin following intravascular hemolysis, myoglobin following rhabdomyolysis, urine contamination with oxidizing agents, or concentrated urine.
- False negative tests can result from very dilute urine, very acidic specimen (pH <5), and the presence of reducing substances (ascorbic acid).

Diagnosis- Urine microscopy

- The presence of hematuria by dipstick should be confirmed by microscopy of a fresh urine sample.
- RBCs from a lower urinary tract bleeding are generally intact in shape (isomorphic).
- RBCs that have undergone the sheer stress of passing through the glomerular basement membrane are mostly denatured (dysmorphic; blebs and segments). A glomerular pathology should be suspected if more than 30% of RBCs are dysmorphic.

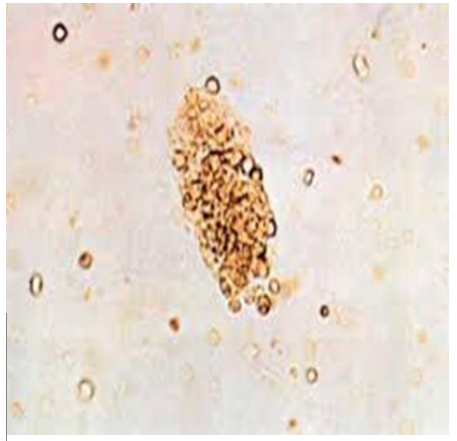


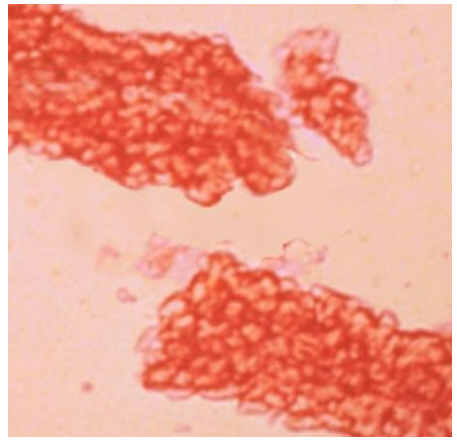


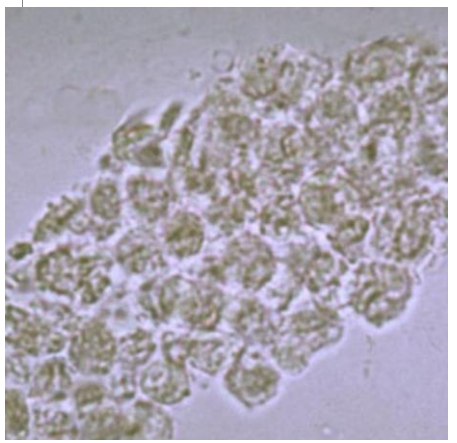
UpToDate

Diagnosis- Urine microscopy

- Presence of RBC with granular casts is suggestive of glomerular disease
- Presence of RBCs with white blood cells is suggestive of infection or interstitial or glomerular inflammation
- Presence of eosinophils makes interstitial nephritis more likely.
- Neutrophils can be seen with infections and acute nephritis such as poststreptococcal glomerulonephritis.

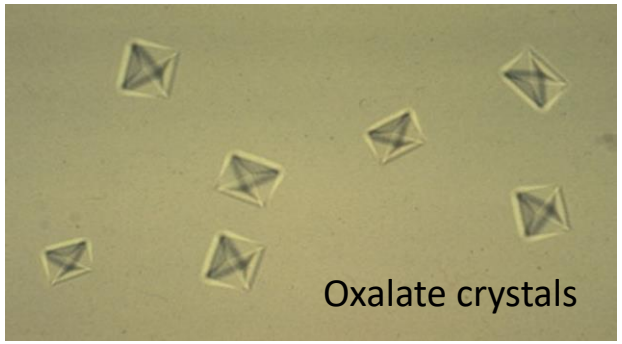


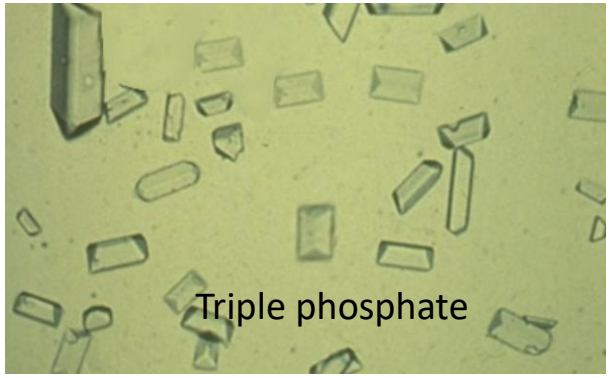


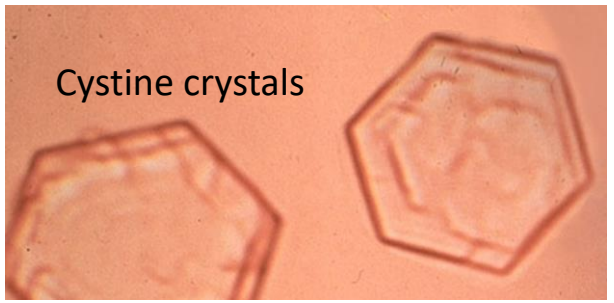


Diagnosis- Urine microscopy

- The presence of crystals in urine can be indicative of nephrolithiasis as the underlying etiology for hematuria, shape of crystals may also give some insight into the possible chemical composition of kidney stone.







Urine dipstick vs. microscopy

- Dipstick is a good starting point…
- Dipstick alone is not enough!
- Use dipstick and microscopy together to make a diagnosis of hematuria

Talking about hematuria

Glomerular vs. Non-glomerular

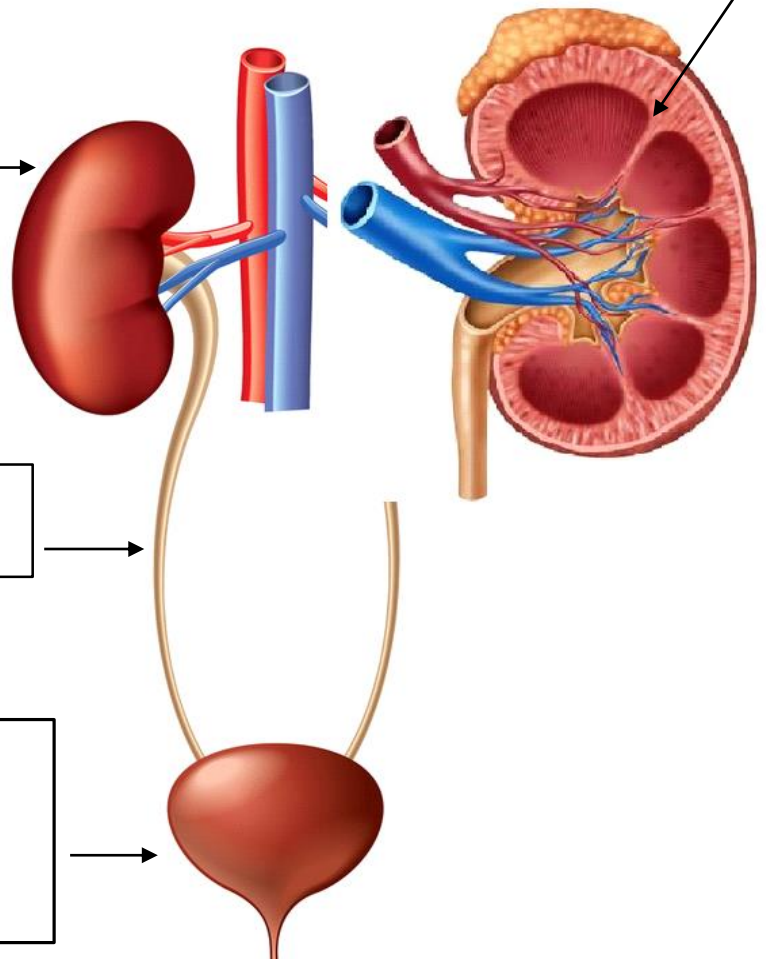
Microscopic vs. Macroscopic (gross)

Kidneys:

- RENAL MASSES
- TRAUMA
- RENAL VEIN THROMBOSIS
- NUTCRACKER

Glomerular/ Tubulointerstitial

- Glomerulonephritis
- Familial hematuria
- Hemolytic- uremic syndrome
- Polycystic kidney disease
- Pyelonephritis
- Hypercalciuria
- Papillary necrosis (Sickle – cell)



Ureters:

- RENAL CALCULI
- MALIGNANCY

Bladder and Urethra:

- Cystitis
- TUMORS
- CALCULI
- TRAUMA

Causes of hematuria by anatomical location

- In children, the causes are more often glomerular rather than from the urinary tract.

- Isolated persistent microscopic hematuria in pediatrics is most often caused by familial hematuria, IgA nephropathy or idiopathic hypercalciuria.

Glomerular		Non- Glomerular
Familial Hematuria syndromes - **Autosomal dominant thin basement membrane (TBMN)** - **X-linked Alport (Male)** - **X-linked Alport (female)** - **Autosomal recessive Alport**	Glomerulonephritis (GN) Primary GN - Post-infectious GN - Membranoproliferative GN - Membranous nephropathy - Rapidly progressive GN - IgA Nephropathy Secondary GN - Systemic lupus erythematosus - Henoch Schonlein purpura - Polyarteritis nodosa - ANCA positive systemic vasculitis	Urinary Tract Infection Hypercalciuria Kidney Calculi Trauma Exercise- induced Chemical cystitis (cyclophosphamide) Coagulopathy Vascular malformation Nutcracker syndrome Urinary Schistosomiasis Malignancy Menarche Factitious
	Hemolytic Uremic Syndrome	
	Renal Vein Thrombosis	
	Interstitial Nephritis	
	Cystic kidney disease	

Glomerular Hematuria

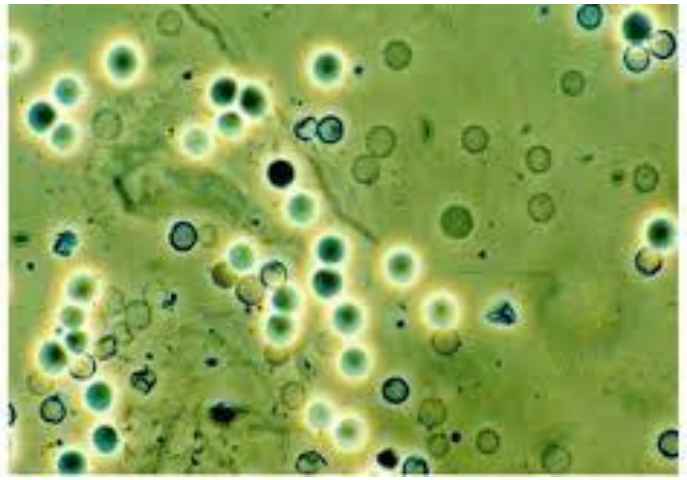
- Tea or cola-colored
- Casts
- Proteinuria
- Dysmorphic appearing red blood cells
- No blood clots
- Systemic signs: hypertension, edema, oliguria, impaired renal function
- Recurring/persisting pattern

Hematuria: a simple method for identifying glomerular bleeding
Kidney Int 1982;21:105

	Urinary erythrocytes		
	Dysmorphic	Isomorphic	Mixed
Glomerulonephritis	55/58	0/58	3/58
Urological disorders	0/30	30/30	0/30

Non-Glomerular Hematuria

- Clots
- Red-colored
- No casts
- Little protein
- Non-dysmorphic appearing red blood cells
- GU symptoms: flank pain, dysuria, fever, urinary frequency
- Recurring/resolving pattern



Lower tract vs. Upper tract

- Terminal hematuria
- Hesitancy, incomplete bladder emptying, frequency
- Irregular or interrupted stream

- Normal voiding
- Hematuria throughout micturition
- Painful?

Clinical Approach

The goal is to…

- Rule out serious conditions
- Avoid unnecessary investigations
- And provide guidelines for future follow-up and further studies

History

Ask about:

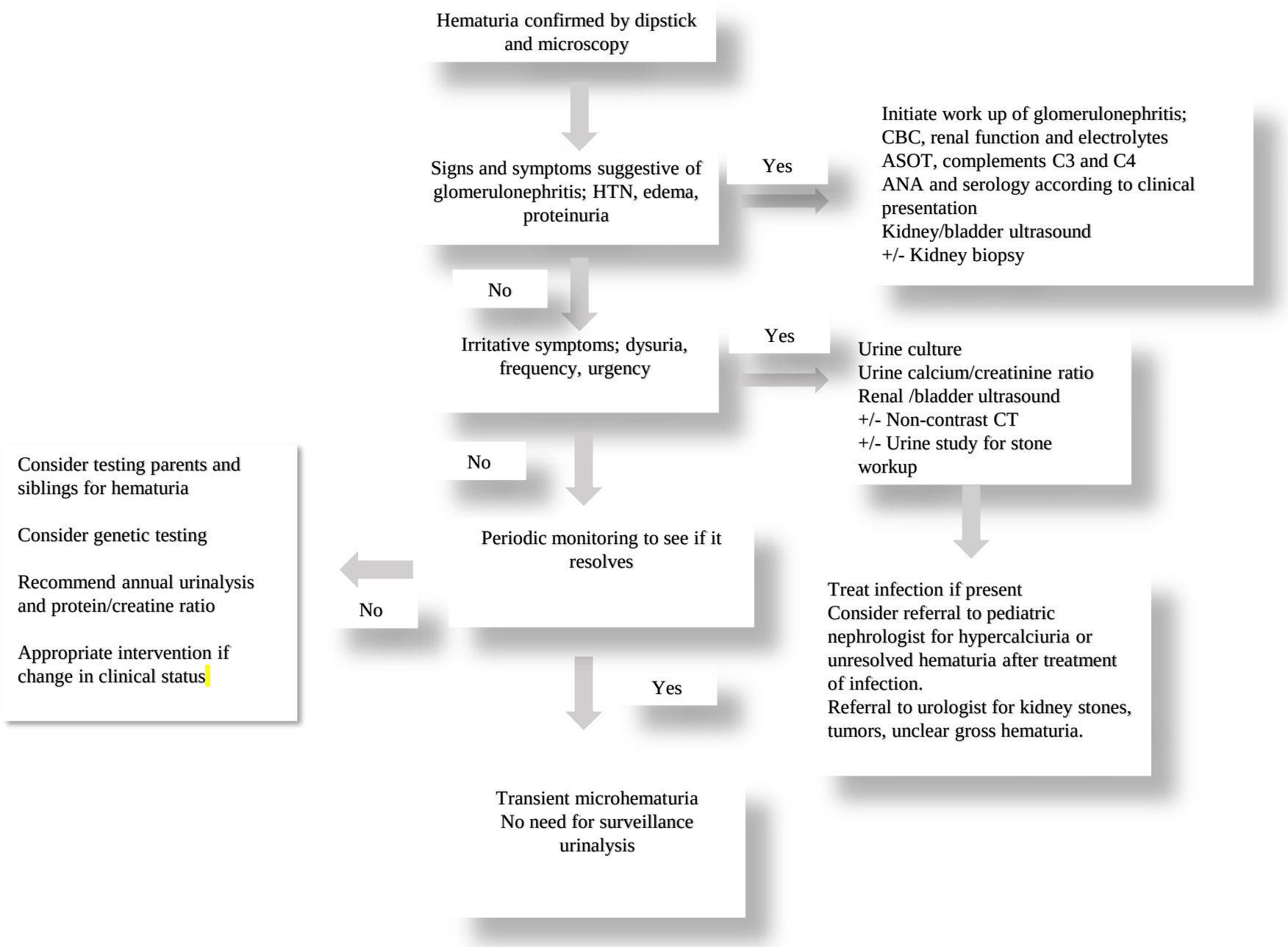
- Timeline of symptoms; at the onset or end of urination vs. throughout the stream
- Associated symptoms: fever, back pain, dysuria, urinary frequency and urgency
- Systemic symptoms; skin rashes, joint symptoms, face and leg swelling
- Preceding events; trauma, exercise, recent respiratory or skin infections
- Intake of medications (including OTC) and herbal
- Predisposing conditions: sickle cell disease or trait, coagulopathy
- Family history: chronic kidney disease, hematuria, hypertension, stones, deafness and coagulopathy.

Some clues…

- Persistent microhematuria with episodes of gross hematuria precipitated by URI is suggestive of a glomerular disease such as IgA nephropathy.
- Hematuria in the neonatal period is suspicious for renal vein thrombosis and factors increasing the risk of this condition include maternal diabetes, dehydration, polycythemia, and umbilical catheters.
- Gross hematuria in a child with nephrotic syndrome is worrisome for renal vein thrombosis.
- Menarche and the possibility of menstrual bleeding at the time of testing should be checked.

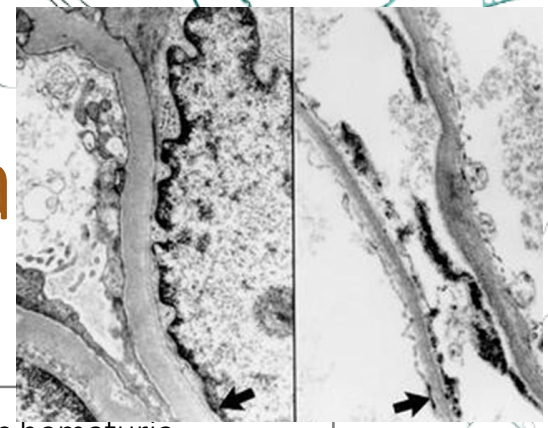
Physical Examination

- Vital signs (temperature, heart rate, and blood pressure)
- Systemic examination;
- Edema
- Skin rashes
- Joint inflammation
- CVA tenderness
- Palpable kidneys



Clinical approach to the child with confirmed hematuria in ambulatory Setting

Asymptomatic microscopic hematuria

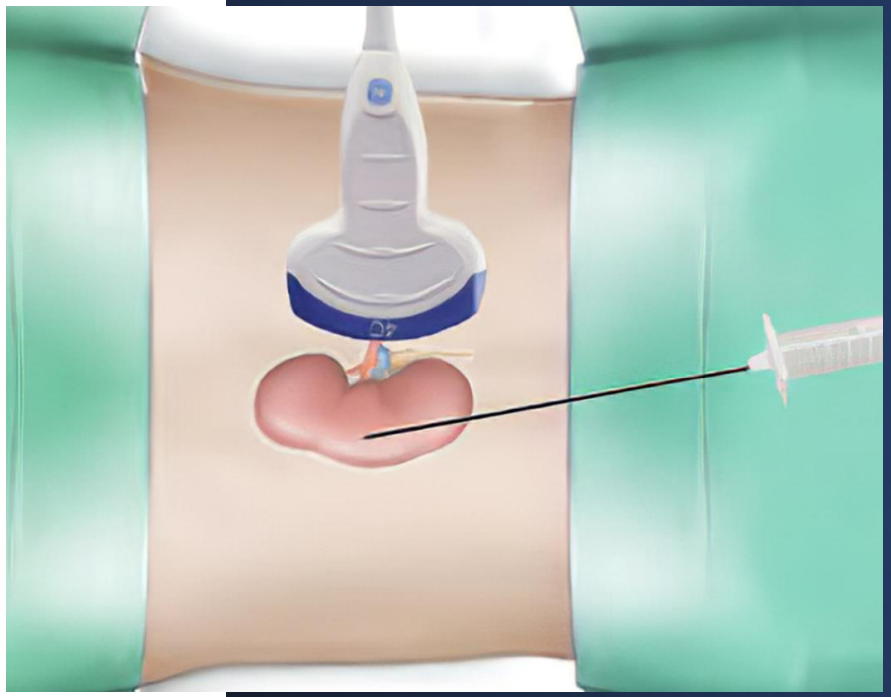


- Urinalysis with urine microscopy should be repeated three times to confirm the presence of persistent microscopic hematuria.
- The presence of febrile illness, vigorous activity and menses can cause transient microscopic hematuria.
- The presence of proteinuria, hypertension and significant history or physical examination findings; a glomerular etiology is likely and would require further work up
- Patients with family history of hematuria of impaired kidney function should be worked up further.
- Patients with family history of isolated hematuria and normal kidney function can be given the tentative diagnosis of thin basement membranes disease.
- Generally, don’t require extensive investigations or biopsy for diagnosis.
- A reasonable approach would be annual screening with urinalysis and blood pressure measurement.

Role of kidney biopsy

Considered in cases suspicious for glomerulopathy that requires therapy or could lead to CKD.

- This may include the following
  - Significant proteinuria, except in poststreptococcal glomerulonephritis
  - Persistent low serum complement C3
  - Unexplained change in kidney function
  - Systemic diseases such as systemic lupus erythematosus or ANCA-positive vasculitis
  - Family history of significant kidney disease suggestive of progressive forms of familial hematuria
-

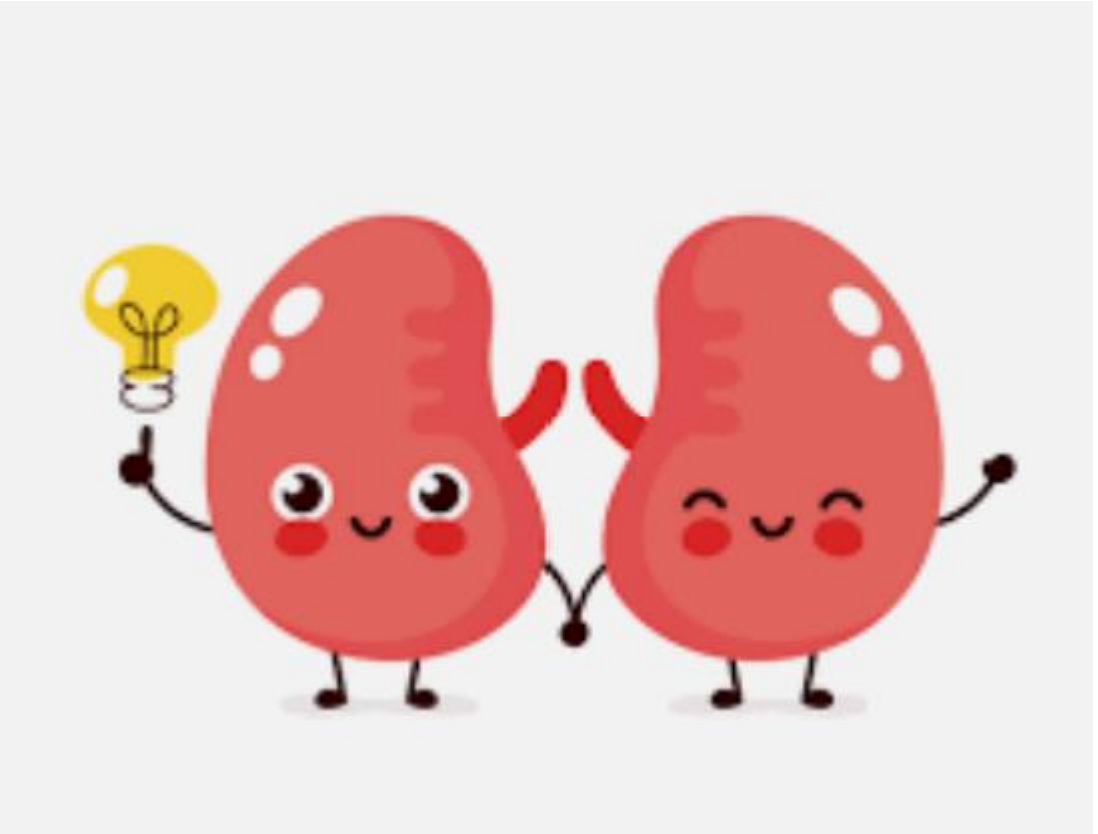


Role of genetic testing

- Can be used to establish the diagnosis without the need for kidney biopsy, in some cases.
- Genetic testing for pathogenic COL4A3–5 variants is advised for patients with persistent hematuria, especially with a family history of hematuria or kidney function impairment.
- It is also suggested that first-degree family members are tested because of their risk of impaired kidney function.
- Family members with COL4A3 or COL4A4 heterozygotes are advised against donating.
- Recent recommendations have also extended the scope of testing to include persistent proteinuria and steroid-resistant nephrotic syndrome due to suspected inherited FSGS and for familial IgA glomerulonephritis and kidney failure of unknown cause.

Conclusion

- The presence of hematuria with/ without proteinuria in the ambulatory setting requires individualized workup.
- History, initial clinical findings and laboratory work up guide the way.
- The differential diagnosis is wide and a step wise approach on multiple occasions is suggested to identify the cause.
- The availability of genetic testing to identify diseases associated with hematuria with or without proteinuria has decreased the need for kidney biopsy in many cases.



Thank you

Genetics In Pediatric Nephrology

Dr. Samah Al-Jbour

Pediatric Nephrology Consultant

IPNA

International Pediatric Nephrology Association

THE AMERICAN SOCIETY OF HUMAN GENETICS

Genetic Testing in Children

Testing purpose and method

Types of information

Predictive
Risk assessment
Screening
Prevention

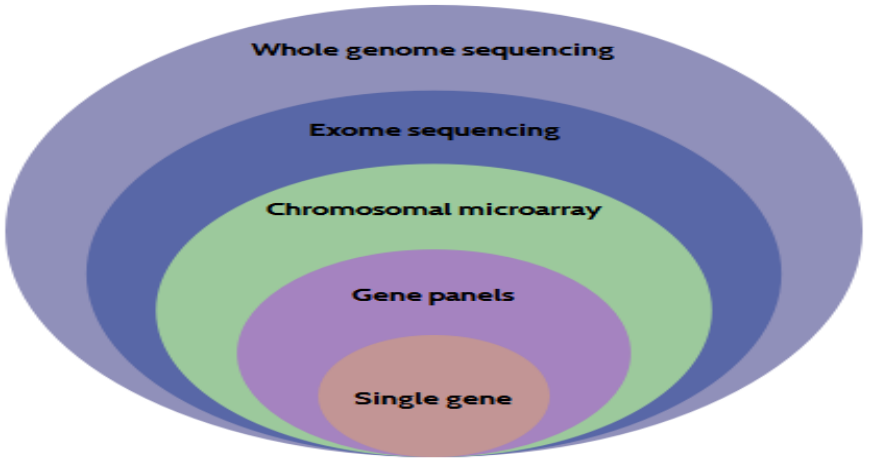
Diagnostic
Disease identification
Prognosis
Management

Carrier
Reproductive planning

Pharmacogenetic
Drug efficacy

Direct-to-Consumer
Education
Research

Amount of information by method



Common principles

Testing in children

- Autonomy
- Benefit to child
- Parental decision making on behalf of the child
- Uncertainty
- Communication

Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Position Statement. American Journal of Human Genetics; 97:1, 6-21. 2015

Ethical and policy issues in genetic testing and screening of children. American Academy of Pediatrics Policy Statement. Pediatrics 131;3. 620-22. 2013

THE AMERICAN SOCIETY OF HUMAN GENETICS

Genetic Testing in Children

Ethical, legal and social issues

Incidental or secondary findings

1. Findings unrelated to the condition for which testing was ordered
2. Variants of uncertain significance
3. Discovery of false paternity or consanguinity

INFORMED CONSENT

- Report with parental consent and if clinically important to child and family
- Decide how to handle before testing
- Do not report unless safety of the child is an issue

Genetic testing in adoption

Treat adopted child like biological child - test only if in the child's best interest

Public health issues

- Storage and communication of genetic information throughout the lifetime
- Capabilities of electronic health records
- Genetics education for health professionals

Common principles

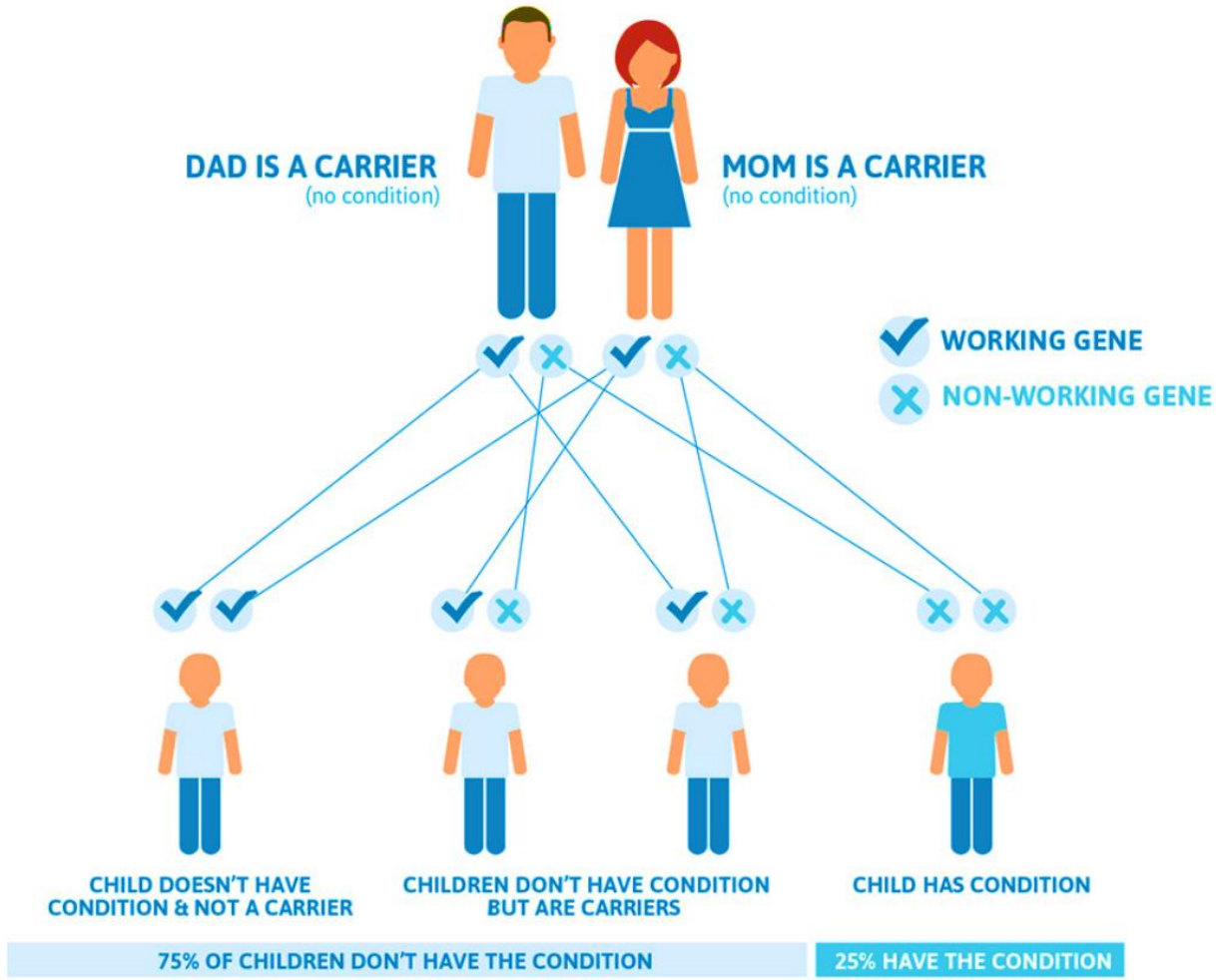
Testing in children

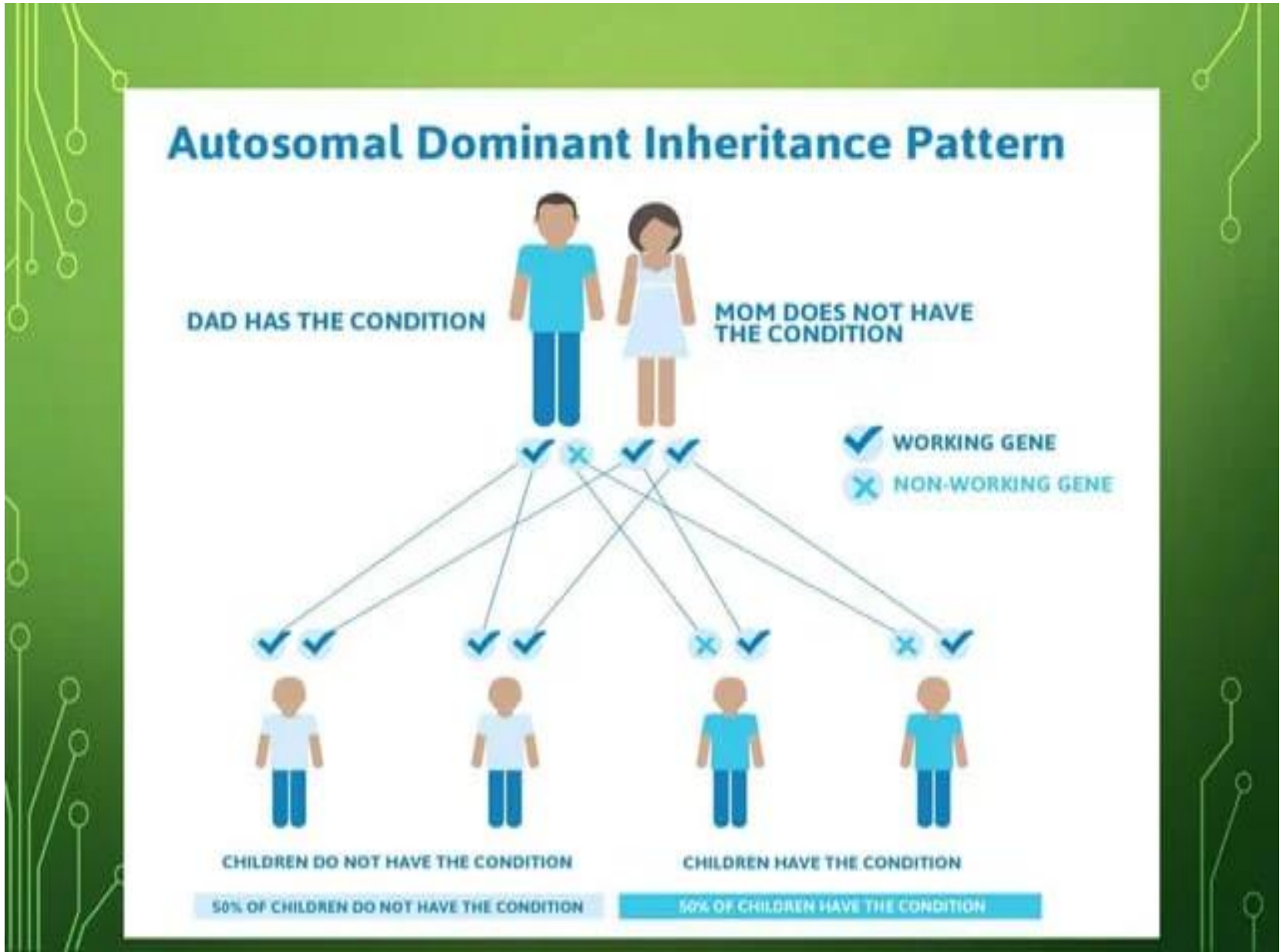
- Autonomy
- Benefit to child
- Parental decision making on behalf of the child
- Uncertainty
- Communication

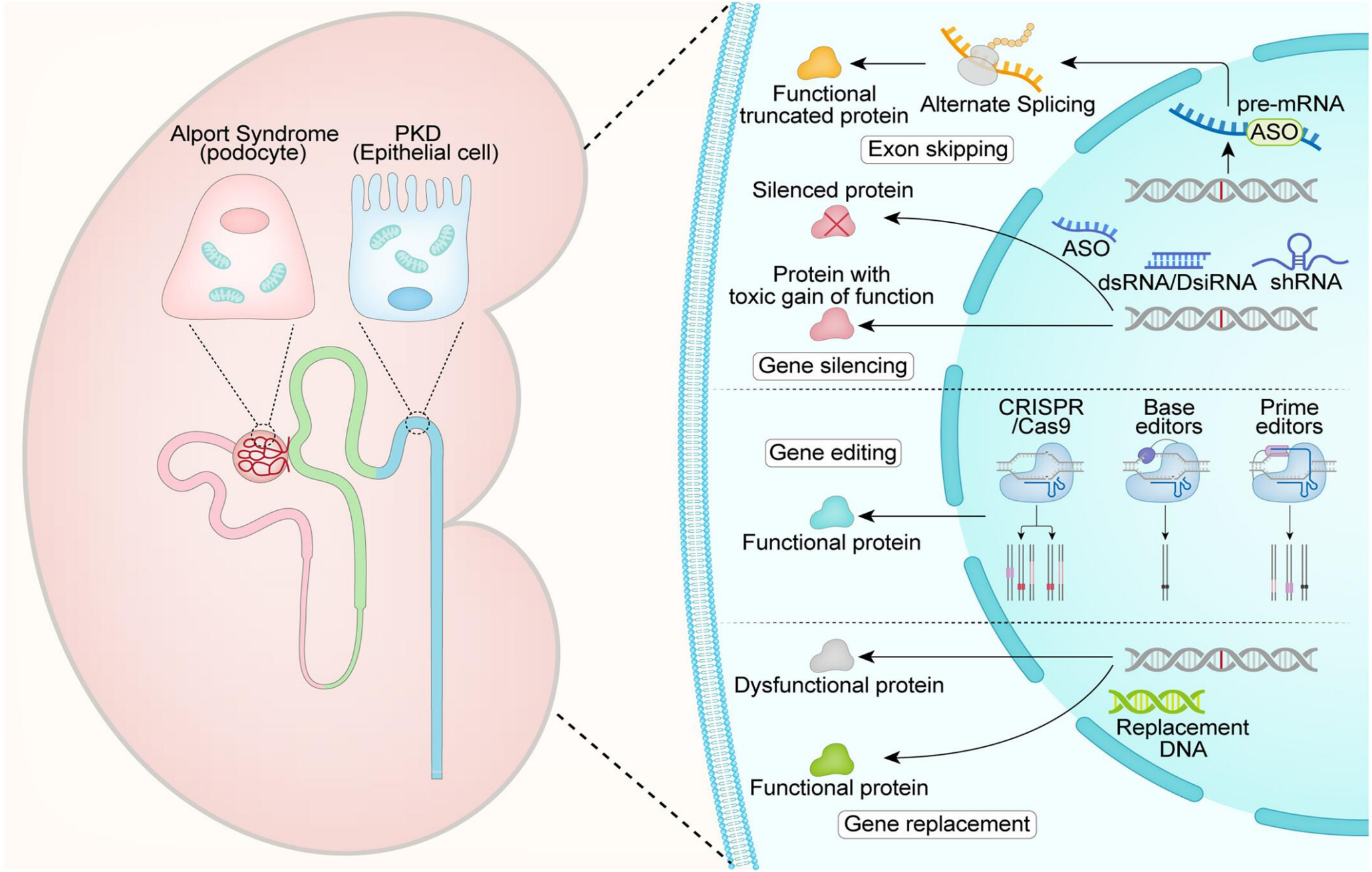
Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Position Statement. American Journal of Human Genetics; 97:1, 6-21. 2015

Ethical and policy issues in genetic testing and screening of children. American Academy of Pediatrics Policy Statement. Pediatrics 131;3. 620-22. 2013

Autosomal Recessive Inheritance Pattern




Autosomal Dominant Inheritance Pattern
DAD HAS THE CONDITION
MOM DOES NOT HAVE THE CONDITION
WORKING GENE
NON-WORKING GENE
CHILDREN DO NOT HAVE THE CONDITION
CHILDREN HAVE THE CONDITION
50% OF CHILDREN DO NOT HAVE THE CONDITION
50% OF CHILDREN HAVE THE CONDITION


Alport Syndrome
(podocyte)
PKD
(Epithelial cell)
Functional
truncated protein
Alternate Splicing
pre-mRNA
ASO
Exon skipping
Silenced protein
ASO
dsRNA/DsiRNA
shRNA
Protein with
toxic gain of function
Gene silencing
CRISPR
/Cas9
Base
editors
Prime
editors
Gene editing
Functional protein
Dysfunctional protein
Replacement
DNA
Functional protein
Gene replacement

CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE GmbH • Am Strande 7 • 18055 Rostock • Germany

Dr. Samah Jbour
Dr Samah Jbour Clinic
.
Jordan

Order no.: 63266027
Order received: 15 Oct. 2024
Sample type / Sample collection date:
blood, EDTA / 12 Oct. 2024
Report date: 22 Nov. 2024
Report type: Final report

[redacted]

Test(s) requested: CentoXome® Solo

CLINICAL INFORMATION

Abnormal stomach morphology; Autistic behavior; Chronic gastritis; Decreased serum zinc; Duodenitis; Enuresis; Gastritis; Global developmental delay; Hypoalbuminemia; Increased circulating copper concentration
(Clinical information indicated above follows HPO nomenclature.)
Diagnosed Condition(s): hyperemic stomach, diffuse gastropathy.
EEG normal.
MRI normal.
Family history: Unknown.
Consanguineous parents: Yes.

POSITIVE RESULT
Pathogenic variant with partial clinical overlap identified
Potentially relevant findings identified

INTERPRETATION

A homozygous pathogenic variant was identified in the *ALB* gene.**The result is consistent with a genetic diagnosis of autosomal recessive analbuminemia.**

Please also note the variants in the potentially relevant findings section.

No further clinically relevant variants related to the described phenotype were detected.

INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

[redacted]

Gender:
Patient ID (MRN):

Sample type: Blood
Sample collection date: 08-AUG-2022
Sample accession date: 15-AUG-2022

Report date: 10-SEP-2022
Invitae #: RQ3926290
Clinical team: Fadi Qiqieh

Reason for testing
Family history

Test performed
Sequence analysis and deletion/duplication testing of the gene listed in the Genes Analyzed section.

REQUESTED VARIANTS

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION	RESULT
NPHS1	Deletion (Exons 12-20)	heterozygous	PATHOGENIC	Detected

The table above reflects the information for the requested variant(s) as of the date that this report was issued. Please see the result box for a summary of any reportable findings.

RESULT: CARRIER

One Pathogenic variant identified in NPHS1. NPHS1 is associated with autosomal recessive nephrotic syndrome.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
NPHS1	Deletion (Exons 12-20)	heterozygous	PATHOGENIC

About this test
This diagnostic test evaluates 1 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Clinical comments

- Please note, familial variant analysis includes full gene sequencing and deletion/duplication testing unless otherwise indicated. The presence or absence of the requested variant(s) as well as any clinically informative variants in the gene(s) analyzed will be reported. Variants of Uncertain Significance elsewhere in these gene(s), if present, would not be reported.

GPDx
Genomic Precision Diagnostic
by Igenomix

Igenomix®
PART OF VITROLIFE GROUP

MOLECULAR GENETIC TESTING REPORT

Primary Hyperoxaluria Precision Panel

Patient Information

[redacted]

Gender: Male

Lab Code: GPU-24G0206

Sample Information

Sample Type: Blood

Date of Collection: 14/08/2024

Date of Receipt: 19/08/2024

Report Date: 18/09/2024

Referral Information

Patient ID/MRN: DUBJR-00515887_RMS240850

Referral Center: Royal Medical services

Applicant: Dr. SAMAH ALJBOOR

Clinical Indication:

The index presented with the symptoms of hyperoxaluria.

POSITIVE RESULT
Genetic findings are compatible with the clinical indication.

Conclusion:

[redacted] is homozygous for the Pathogenic variant [NM_000030.2:c.358+1G>A, p.(?)] in the *AGXT* gene. Pathogenic variants in the *AGXT* gene are associated with Hyperoxaluria, primary, type 1 (#259900) with an Autosomal recessive mode of inheritance.

This result is compatible with the clinical indication.

Familial segregation of this variant is strongly recommended.

These results must be interpreted in the patient's clinic and family history context and according to the technical limitation and current scientific knowledge.

- Pediatric renal diseases vary widely and are linked to high morbidity and mortality; hence, early diagnosis is vital.

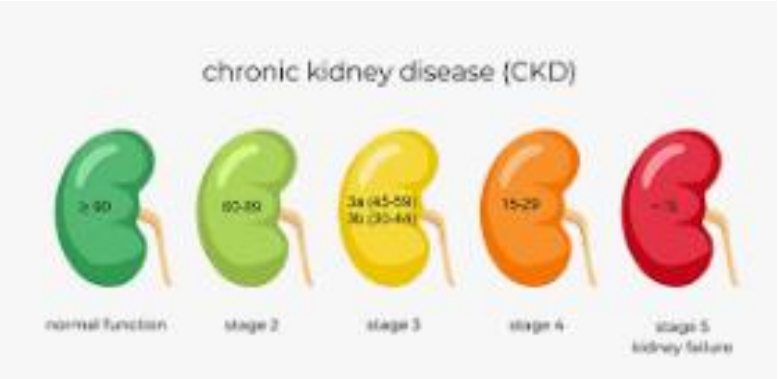
- Presently, genetic testing is being incorporated into the standard of care for children and their families.

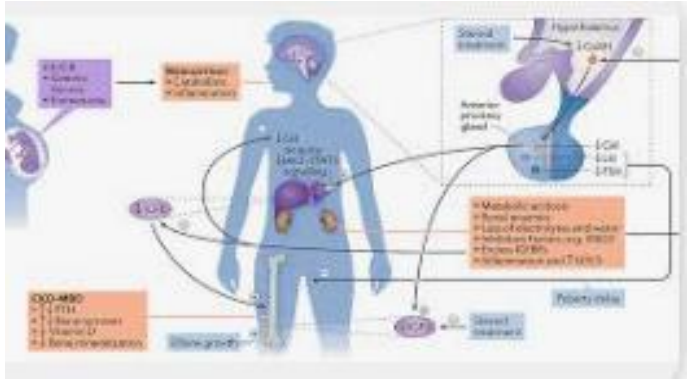
- The importance of both clinical and social support emerged as a strong theme.

- Literature findings suggest that compassionate family–clinician partnerships were important to parents throughout the genetic testing process and contributed to easing emotional distress.

- Pediatric kidney diseases include a wide range of disease entities with varying clinical manifestations, courses of development, and treatment choices.

- Children with end-stage renal disease constitute a greater portion of the monogenic condition population, accounting for almost 30% of children with chronic kidney disease (CKD).





- The spectrum of renal diseases varies significantly, and even within the same nation, there are regional variations in the pattern of childhood renal disease.

- Genetic predisposition, environmental background, and, to a significant extent, level of consciousness all have an impact on this diversity.

- In addition to approximately 50% of children and 10% of adults who enroll in end-stage renal failure programs, it is predicted that 20% of children with renal disease may have an underlying genetic malformation.

- Gene identification for a range of renal disorders is made possible by massively parallel sequencing, which has become an essential part of renal research.

- More recently, the creation of approved diagnostic testing platforms has made it possible to integrate sequencing technology into routine clinical practice.

- The families of children with renal disease can benefit from information provided by genetic testing, such as the opportunity for an earlier diagnosis, the identification of relatives who are at risk, and possibly a decrease in morbidity and mortality.

- Over the past two decades, revolutionary advancements in genetic knowledge and technology have radically changed the understanding of pediatric renal disorders.
- The main causes of CKD in children are CAKUT and genetic conditions that affect specific nephron components.
- More than 160 genes, including those involved in nephrogenesis, primary cilia development and function, podocyte and tubular cell activities, complement regulation, and more, have been linked to hereditary nephropathies to date.

- A genetic diagnosis can be made in 15%-20% of cases of severe kidney malformations, up to 30% of cases of steroid-resistant nephrotic syndrome, 60%-70% of cases of complement-mediated atypical hemolytic uremic syndrome, and 50-80% of cases of hereditary tubulopathy following a systematic screening of all known genes within each disease group by next generation sequencing.

- Nephrolithiasis and nephrocalcinosis have a complex etiology that includes heredity, systemic illnesses such as inflammatory bowel disease, parathyroid dysfunction, metabolic variables, anatomical abnormalities of the kidneys, and recurrent urinary tract infections, although the primary causes of nephrolithiasis and nephrocalcinosis are hereditary factors.
- There have been reports of more than 30 genes being connected to the monogenic types of nephrolithiasis and nephrocalcinosis.

- In monogenic disease, the ability to identify the underlying mutations in a monogenic disease gene is of significant diagnostic and maybe therapeutic relevance.

- The relevance of genetic diagnosis in children cannot be overstated for various reasons.

- The first is that it might be significant in terms of how the disease is treated clinically; a typical example of this is with nephrotic syndromes, where the identification of structural variants in genes related to podocytes provides evidence against immunosuppressive treatments that would otherwise be regularly administered over a period of several months.

- Secondly, it might be very important for the family of the child and for identifying other family members who have the mutation that might be passed on to future generations. Cascade testing of family members and genetic counseling for variant carriers are routine procedures in clinical genetics if a harmful variant is discovered in a proband.

- Thirdly, in the scenario of transplantation, where the donor may be a relative, understanding the harmful variation is crucial. It is crucial to identify all family members who might require a transplant as well as rule out the possibility that the organ donor carries the same variants.

- Furthermore, some disorders, such as focal segmental glomerulosclerosis, have a significant chance of relapsing after organ transplantation, or a more specialized selection of the transplant to be carried out may enhance their prognosis, like in the case of primary hyperoxaluria, where a combined kidney-liver transplant may produce a better prognosis.

- It's reported that more than 450 monogenic diseases have been identified as the cause of chronic kidney disease to date; these disorders account for 5-30% of cases in adult cohorts and over 30% of cases in pediatric cohorts.

- Whole-exome sequencing was utilized to find novel genes. About 33,000 exons from all 22,000 genes, or about 1-2% of the protein-coding regions, were able to be studied with the assistance of whole exome sequencing.

- This technique of analysis continues to be the basis for the identification of novel genes involved in a variety of renal illnesses.

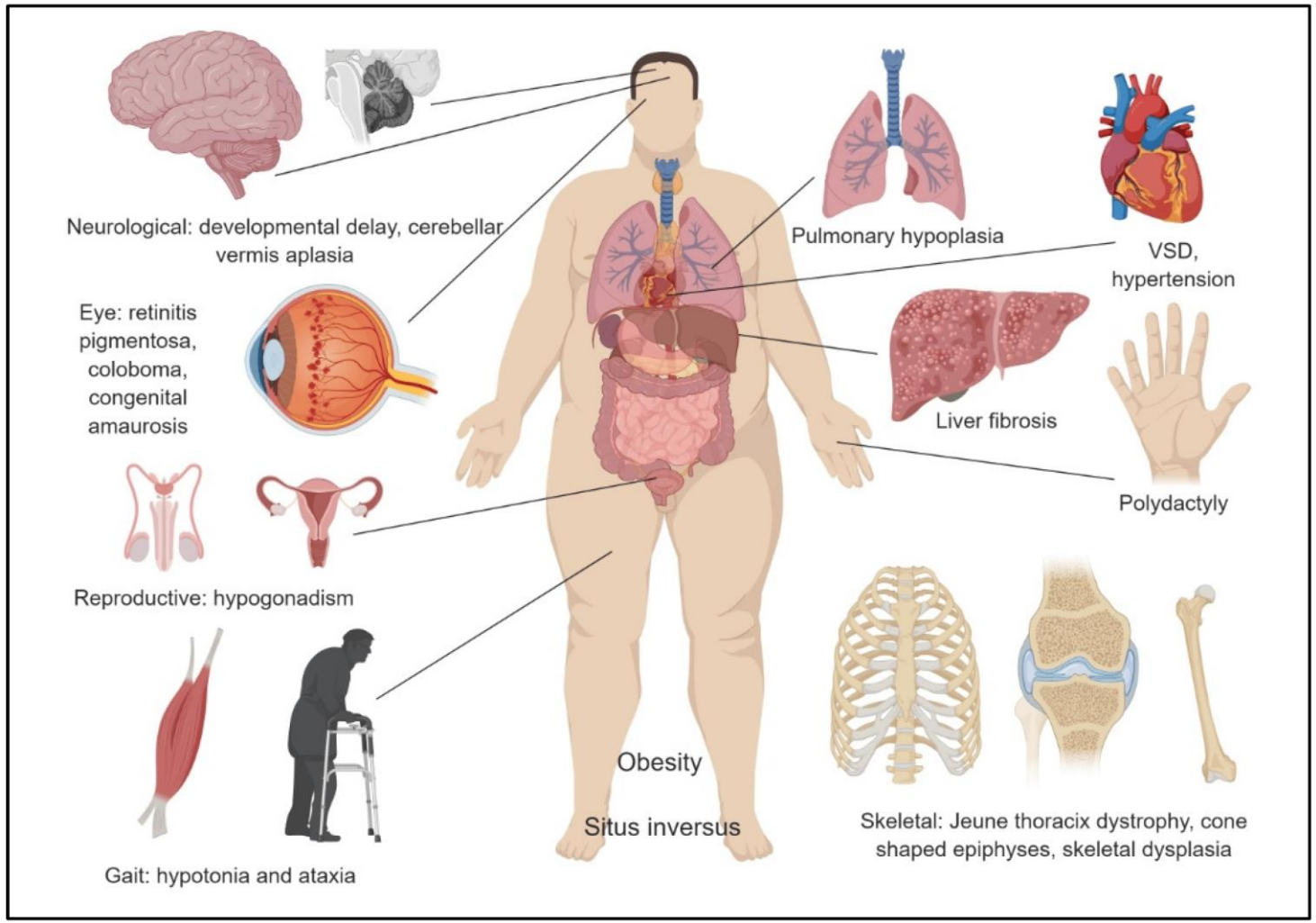
- Since 1995, when a mutation in PAX2 was originally identified as the cause of optic nerve coloboma, renal hypoplasia, and vesicoureteral reflux, genetic causes of CAKUT have been identified. More than 40 genetic abnormalities have been found in earlier research, and more than 50 genes have been linked to CAKUT.

- Currently, monogenic causes, the majority of which have a dominant pattern of inheritance, can account for up to 18% of CAKUT patients.

- Further research utilising chromosomal microarrays revealed that 4.5-16.6% of CAKUT patients have genetic abnormalities, particularly those with renal hypodysplasia.

- Furthermore, understanding the genetic, epigenetic, and environmental roots of kidney and urinary tract abnormalities is crucial from a therapeutic standpoint because CAKUT is the leading cause of kidney failure in children.

- This area of the genomic landscape of CAKUT has been extensively delineated by the advent of next-generation sequencing. Currently, more than 50 genes linked to the etiology of CAKUT have been discovered. Although the development of next-generation sequencing and bioinformatic methods has enhanced knowledge of the molecular landscape of CAKUT, the majority of the patients' etiologies are still unknown.


Neurological: developmental delay, cerebellar vermis aplasia
Eye: retinitis pigmentosa, coloboma, congenital amaurosis
Reproductive: hypogonadism
Gait: hypotonia and ataxia
Pulmonary hypoplasia
VSD, hypertension
Liver fibrosis
Polydactyly
Obesity
Situs inversus
Skeletal: Jeune thoracix dystrophy, cone shaped epiphyses, skeletal dysplasia

Genetic Characterization of Kidney Failure of Unknown Etiology in Spain

Setting & Participants

Case series

51 centers in Spain

N = 818 patients in Gensen study

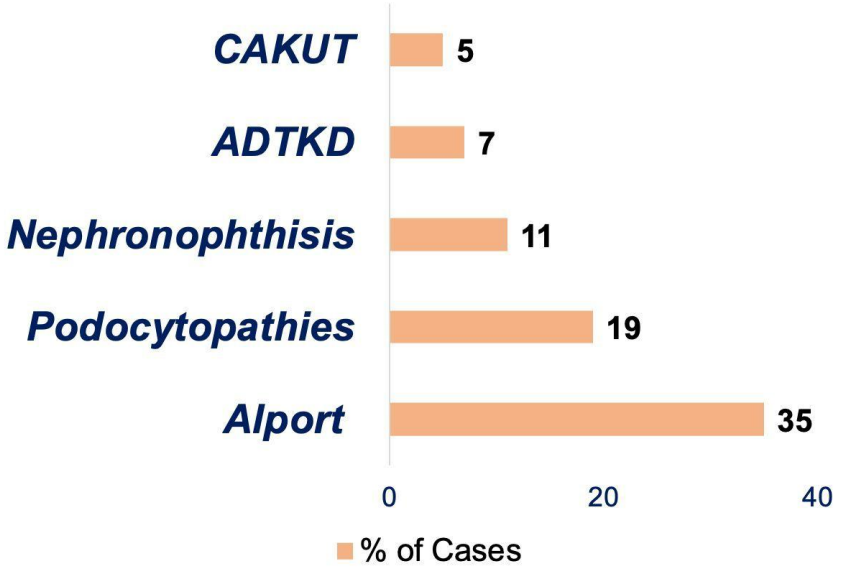
- Aged ≤45 years
- With CKD of unknown etiology (CKDUE)
- eGFR <15 mL/min/1.73 m^2 or treated with dialysis/transplantation
- 191 (23.3 %) reported family history of kidney disease

Results

High-throughput sequencing (HTS) directed at 529 genes

- 203 (25%) patients had pathogenic and/or likely pathogenic (P/LP) gene variants
- 87 novel variants classified as P/LP were identified
- Variants in type IV collagen genes were the most frequent (35% of total gene variants)

Top 5 Most Common Previously Undiagnosed Diseases

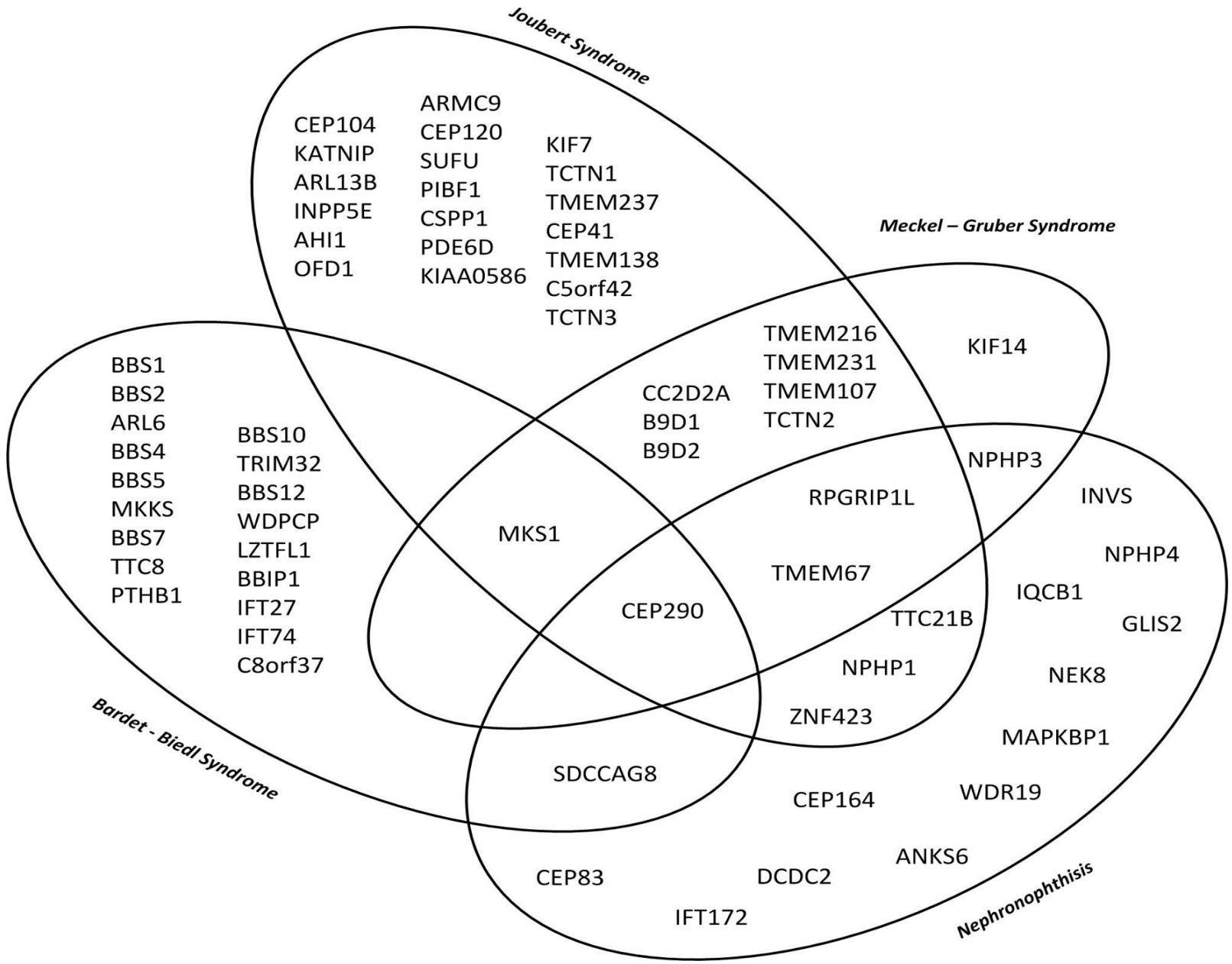


CONCLUSION: Genomic testing with HTS identified a genetic cause of kidney disease in approximately one quarter of young patients with CKDUE and advanced kidney disease.

Miquel Blasco, Borja Quiroga, José M. García-Aznar, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2024.04.021

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES


Joubert Syndrome
CEP104
KATNIP
ARL13B
INPP5E
AHI1
OFD1
ARMC9
CEP120
SUFU
PIBF1
CSPP1
PDE6D
KIAA0586
KIF7
TCTN1
TMEM237
CEP41
TMEM138
C5orf42
TCTN3
Meckel – Gruber Syndrome
TMEM216
TMEM231
TMEM107
TCTN2
KIF14
CC2D2A
B9D1
B9D2
NPHP3
RPGRIP1L
INVS
MKS1
NPHP4
TMEM67
IQCB1
CEP290
TTC21B
GLIS2
NPHP1
NEK8
ZNF423
MAPKBP1
SDCCAG8
CEP164
WDR19
ANKS6
CEP83
DCDC2
IFT172
Nephronophthisis
Bardet - Biedl Syndrome
BBS1
BBS2
ARL6
BBS4
BBS5
MKKS
BBS7
TTC8
PTHB1
BBS10
TRIM32
BBS12
WDPCP
LZTFL1
BBIP1
IFT27
IFT74
C8orf37

Nephropathy	Pooled Diagnostic Yield	Commonly linked mutated genes
Nephrolithiasis	47.45%	CLCN5, OCRL
Nephrocalcinosis	62.3%	
Cystic kidney Disease	70.2%	HNF1B,COL4A4,PKHD1,WT1
CAKUT	26.53%	

Nephropathy	Pooled Diagnostic Yield	Commonly linked mutated genes
Glomerular diseases	26.65%	COL4A4, COL4A5, NPHS1, SMARCAL1
Tubulopathies	53.65%	
Hematuria, Proteinuria	44.45%	COL4A3, COL4A4, COL4A5, CLCN5, NPHS1, PKD1, PKHD1, SMARCAL1, OCRL
Rare diseases	41.8%(X-linked inherited) 29.1%(autosomal)	

Conclusions

- Genetic testing validates clinical diagnosis and aids in tailoring management strategies; hence, a more precise treatment plan is developed and unnecessary investigations are avoided, which is crucial in the case of children.

- These findings have further highlighted the role of genetic testing for the diagnosis of kidney diseases among children, especially during routine nephrology clinic visits. However, during routine nephrology clinic visits, genetic counseling is of utmost importance, so all ethical and social concerns are catered for in addition to patient satisfaction.

Social Implications

- Undergoing genetic testing can be an additional stressor for parents caring for a child with chronic illness, and both diagnostic and prognostic ambiguity can cause significant psychological distress and contribute to long-lasting emotion.

- Studies show that most parents report experiencing anxiety while awaiting the test results and after receiving the results.

Social Implications

- Considering that some parents reported social isolation, health care providers could encourage the development of local genetic support and advocacy groups to increase opportunity to connect with other families in similar circumstances.

Social Implications

- As renal-specific genetic testing becomes routine, understanding patient/family experiences and perspectives affords greater insight into the practical utility of the testing process.

- Expanding support mechanisms for families living with rare renal diseases by providing greater access to genetic counseling, peer support, and multimodal information resources may be important to reduce feelings of isolation and improve psychosocial outcome.


THANK YOU

Evaluation and overview of hydronephrosis/CAKUT

- The first IPNA teaching course in collaporation with the Hashemite university
- Knowledge for safe practice

IPNA
International Pediatric Nephrology Association

- 5/12/2024
- Amman ,Jordan

Evaluation and overview of hydronephrosis/CAKUT

Dr. Jumana Albaramki, MRCPCH
Pediatric nephrology consultant/professor of pediatrics
University of Jordan/Jordan University Hospital

Antenatal hydronephrosis/Urinary tract dilatation

Incidence: 1-5% of pregnancies,more in males,bilateral 20-40%

Postnatal ultrasound will be normal in 21-28% of patients

More than half of the cases of AHN resolve spontaneously by the end of gestation or during the first year of life

Associated with other non renal anomlies,sydnrome.

In children with AHN, a second postnatal US at 4-6 wk should be performed even if the first one is normal

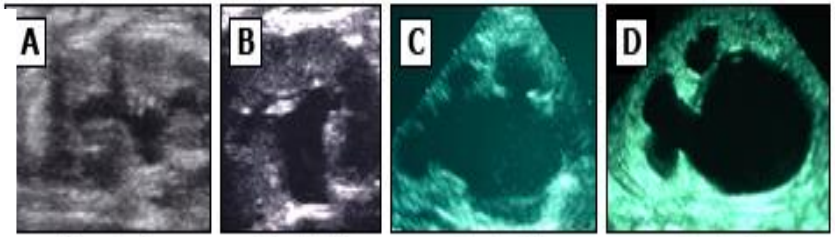
Measure hydronephrosis by measurement of AP diameter of renal pelvis in transverse plane

Table 2 SFU classification system [7]

Classification of AHN	Second trimester APRPD (mm)	Third trimester APRPD (mm)
Mild	4–7	7–9
Moderate	7–10	9–15
Severe	>10	>15

SFU, Society of Fetal Urology; *AHN*, antenatal hydronephrosis; *APRPD*, anteroposterior renal pelvic diameter

Society for Fetal Urology grading system for hydronephrosis



Grade 0 – No dilation (not shown)
Grade 1 – Renal pelvis is only visualized
Grade 2 – Renal pelvis as well as a few, but not all, calyces are visualized
Grade 3 – Virtually all calyces are visualized
Grade 4 – Similar to grade 3, but when compared with the normal contralateral kidney, there is parenchymal thinning

Antenatal hydronephrosis

Mild : < 10 mm APRPD ,grade 1-2 SFU

80% of cases ,benign , 70–98% of this group resolve, or improve during follow up.

Risk of VUR and UTI is 3%

Repeat ultrasound at 4-6 months

SFU recommends at least follow-up for 1 year

Moderate :10-15 mm APRPD ,grade 3 SFU

Severe > 15 mm APRPD ,grade 4 SFU

MCUG if bilateral and ureteral dilation

MAG3/DTPA with Lasix: non dilated ureter

Urinary tract dilatation classification

Table 1 Grading of UTD according to the UTD classification system

Old nomenclature	New nomenclature	Before birth		New nomenclature	After birth
		Second trimester	Third trimester		> 48 h
Mild	UTD A1	APD 4 to < 7 mm	APD 7 to < 10 mm	UTD P1	APD 10 to < 15 mm or central calyx dilatation
Moderate	UTD A2–3	APD ≥ 7 mm or abnormal kidney parenchyma, calyces, ureters, bladder, or amniotic fluid	APD ≥ 10 mm or abnormal kidney parenchyma, calyces, ureters, bladder, or amniotic fluid	UTD P2	APD ≥ 15 mm or peripheral calyx dilatation or ureter > 4 mm (with APD ≥ 10 mm or calyx dilatation)
Severe				UTD P3	Parenchymal abnormality, bladder abnormality and APD ≥ 10 mm or calyx dilatation

UTD, urinary tract dilatation; *APD*, anterior posterior diameter; *mm*, millimeters

Timing of ultrasound

U/S in first 24 h:bilateral with distended bladder,solitary kidney,oligohydraminos

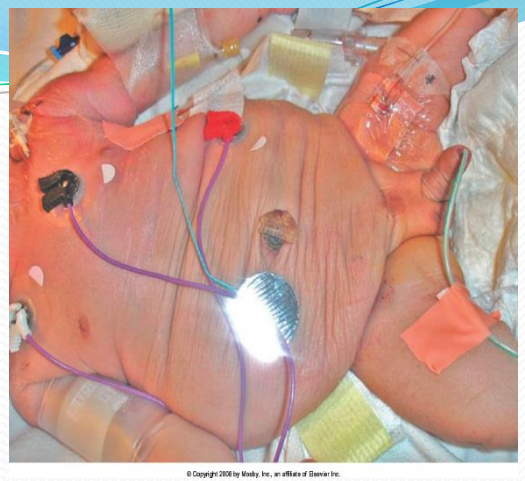
To ensure volume repletion and increase uop :U/S performed between 2-7 days

Table 2 Additional US findings relevant for the diagnosis of ANH

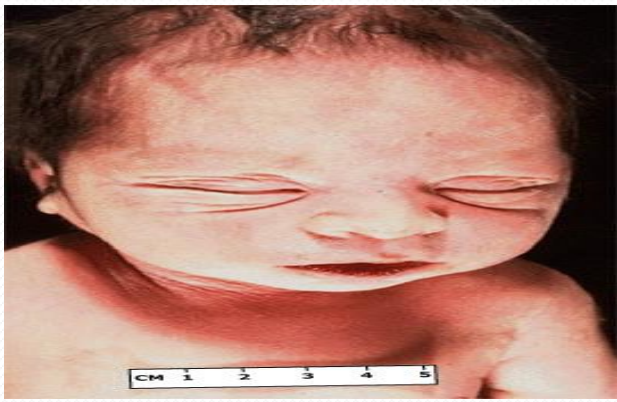
Structure	Parameters
Kidney:	Renal parenchyma
	Echogenicity
	Thickness
	Unilateral vs. Bilateral
	Variation in the degree of hydronephrosis
Ureter	Ureteral dilation
Bladder	Size and emptying
Urethra	Posterior urethral dilation (Keyhole sign)
Other	Amniotic fluid volume
	Extra renal fluid (ascites)
	Other anomalies (Neurological and cardiac)
	Gender
	Overall growth and development

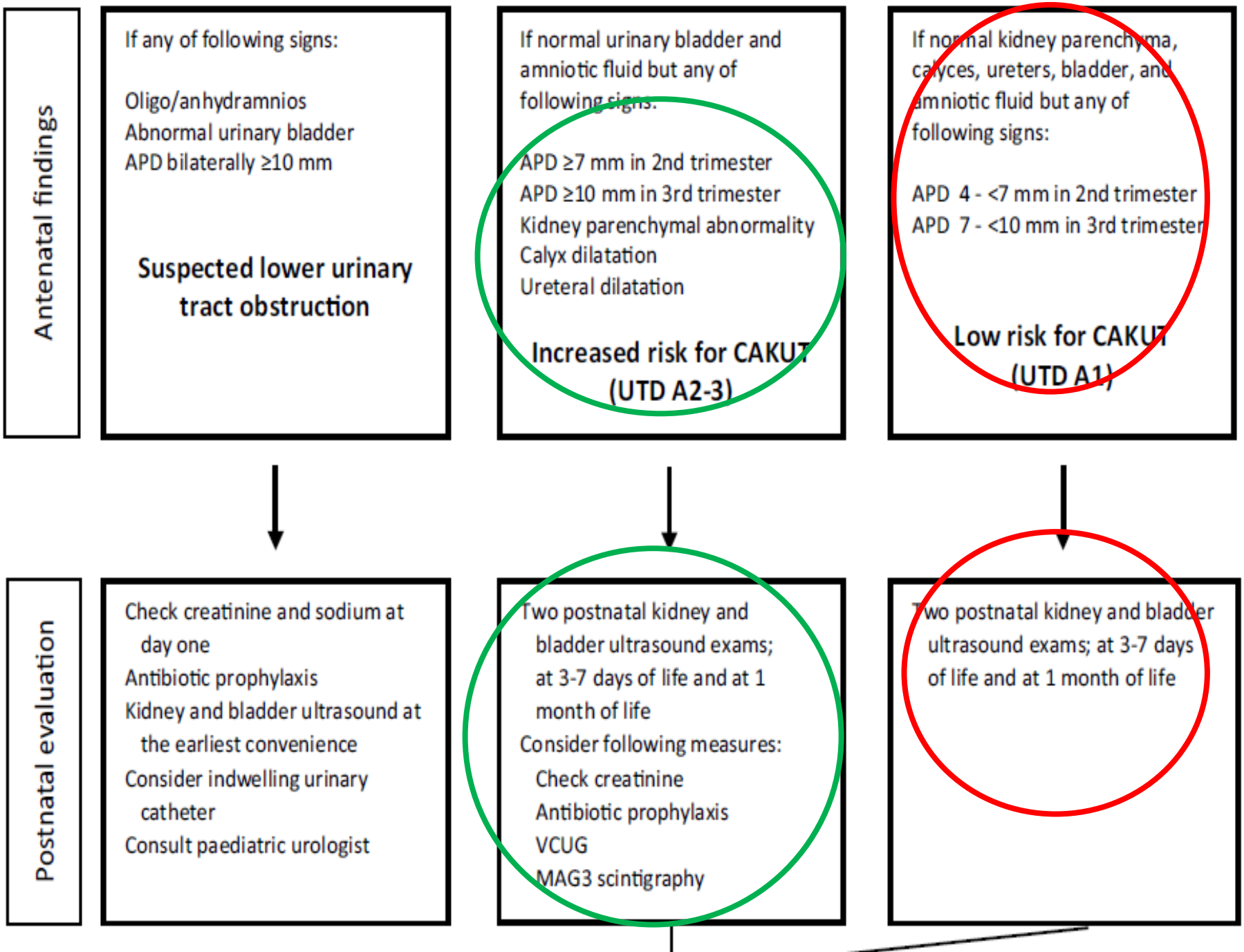
Pediatr Nephrol
DOI 10.1007/s00467-012-2240-7

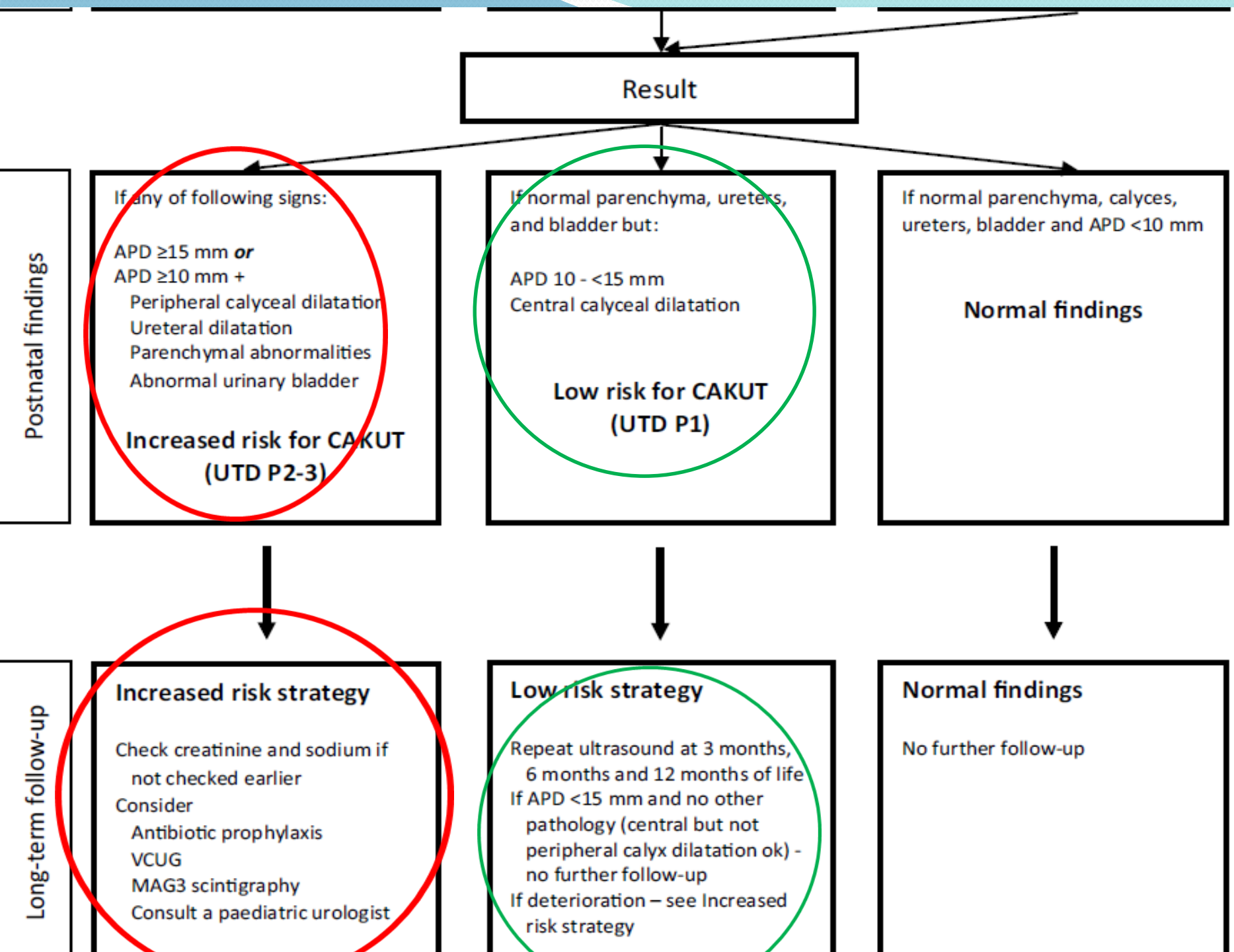
Postnatal evaluation



- Pulmonary:
- Abdomen masses,palpable bladder
- Deficient abdomen muscles
- Single Umbilical artery
- Outer ear anomalies
- Genital exam: undesecended testes
- Spinal and lower extremity abnormality




Antenatal findings
If any of following signs:
Oligo/anhydramnios
Abnormal urinary bladder
APD bilaterally ≥10 mm
Suspected lower urinary tract obstruction
If normal urinary bladder and amniotic fluid but any of following signs:
APD ≥7 mm in 2nd trimester
APD ≥10 mm in 3rd trimester
Kidney parenchymal abnormality
Calyx dilatation
Ureteral dilatation
Increased risk for CAKUT (UTD A2-3)
If normal kidney parenchyma, calyces, ureters, bladder, and amniotic fluid but any of following signs:
APD 4 - <7 mm in 2nd trimester
APD 7 - <10 mm in 3rd trimester
Low risk for CAKUT (UTD A1)
Postnatal evaluation
Check creatinine and sodium at day one
Antibiotic prophylaxis
Kidney and bladder ultrasound at the earliest convenience
Consider indwelling urinary catheter
Consult paediatric urologist
Two postnatal kidney and bladder ultrasound exams; at 3-7 days of life and at 1 month of life
Consider following measures:
Check creatinine
Antibiotic prophylaxis
VCUG
MAG3 scintigraphy
Two postnatal kidney and bladder ultrasound exams; at 3-7 days of life and at 1 month of life


Result
Postnatal findings
If any of following signs:
APD ≥15 mm or
APD ≥10 mm +
Peripheral calyceal dilatation
Ureteral dilatation
Parenchymal abnormalities
Abnormal urinary bladder
Increased risk for CAKUT (UTD P2-3)
If normal parenchyma, ureters, and bladder but:
APD 10 - <15 mm
Central calyceal dilatation
Low risk for CAKUT (UTD P1)
If normal parenchyma, calyces, ureters, bladder and APD <10 mm
Normal findings
Long-term follow-up
Increased risk strategy
Check creatinine and sodium if not checked earlier
Consider
Antibiotic prophylaxis
VCUG
MAG3 scintigraphy
Consult a paediatric urologist
Low risk strategy
Repeat ultrasound at 3 months, 6 months and 12 months of life
If APD <15 mm and no other pathology (central but not peripheral calyx dilatation ok) - no further follow-up
If deterioration – see Increased risk strategy
Normal findings
No further follow-up

Antenatal hydronephrosis

One-third of prenatally detected ANH will resolve before birth, another third will persist into the neonatal period but resolve spontaneously within the first 2 to 3 years of life, and the remaining third will end up with a CAKUT

Etiology:

Transient hydronephrosis : most common in 41-88%

CAKUT with PUJ most common

Causes of Hydronephrosis

Table 1 Differential diagnosis of AHN

Transient AHN (resolves prenatally)
Isolated AHN (no renal abnormality)
Ureteropelvic junction obstruction
Vesicoureteric reflux
Ureterovesical junction obstruction
Multicystic dysplastic kidney
Duplex kidneys (± ureterocele)
Posterior urethral valves
Others: Ectopic ureter, megaureter, urethral atresia, urogenital sinus malformations, prune-belly syndrome, tumors

AHN antenatal hydronephrosis

Pediatric Nephrology (2020) 35:2231–2239

Antenatal Hydronephrosis as a Predictor of Postnatal Outcome: A Meta-analysis

Richard S. Lee, MD[a], Marc Cendron, MD[a], Daniel D. Kinnamon, MS[b], Hiep T. Nguyen, MD[a]

[a]Department of Urology, Children's Hospital Boston, Boston, Massachusetts; [b]Department of Pediatrics, Division of Pediatric Clinical Research, University of Miami Miller School of Medicine, Miami, Florida

Pediatrics 2006;118;586-593

The risk of a postnatal CAKUT diagnosis increases with the degree of prenatal and postnatal dilatation, except for vesicoureteral reflux (VUR)

1678 infants diagnosed with fetal hydronephrosis, postnatal evaluation identified CAKUT in one-third .

PUJ was the most common followed by VUR

RESULTS. We screened 1645 citations, of which 17 studies met inclusion criteria. We created a data set of 1308 subjects. The risk of any postnatal pathology per degree of antenatal hydronephrosis was 11.9% for mild, 45.1% for moderate, and 88.3% for severe. There was a significant increase in risk per increasing degree of hydronephrosis. The risk of vesicoureteral reflux was similar for all degrees of antenatal hydronephrosis.

Antibiotic prophylaxis for urinary tract infections in antenatal .hydronephrosis

Braga .Pediatrics 2013

In a systematic review and meta-analysis that included 21 studies

In low-grade hydronephrosis (SFU grades 1 and 2), rates of UTI were similar between patients treated with or without antibiotic prophylaxis (2.2 versus 2.8 percent).

patients with high-grade hydronephrosis (SFU grades 3 and 4;) who received antibiotic prophylaxis had a lower rate of UTI compared with those who were not treated with antibiotics (15 versus 29 percent).

Antibiotic prophylaxis for prevention of urinary tract infections in the first year of life in children with vesicoureteral reflux diagnosed in the workup of antenatal hydronephrosis: a systematic review

Pediatric Nephrology (2020) 35:1639–1646

Jennifer Leigh[1] · Mandy Rickard[2] · Stephanie Sanger[5] · Joanne Petropoulos[5] · Luis H. Braga[4] · Rahul Chanchlani[3,6]

PREDICT Trial
'Antibiotic Prophylaxis and REnal Damage In Congenital Abnormalities of the Kidney and Urinary Tract'

CONCLUSIONS

In infants with III, IV, or V vesicoureteral reflux and no previous UTI, continuous antibiotic prophylaxis for 24 months was associated with a small but significant benefit with respect to the occurrence of a first symptomatic UTI, as compared with no prophylaxis.

Dilated ureters (ectopic or refluxing)

- An enlarged bladder (suggestive of PUV)
- Bilateral UPJ obstruction
- Giant hydronephrosis (massively enlarged kidney with RPD >30 mm)

Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux

Morello W et al. DOI: 10.1056/NEJMoa2300161

CLINICAL PROBLEM

Infants with grade III, IV, or V vesicoureteral reflux often receive continuous antibiotic prophylaxis in an attempt to prevent urinary tract infection (UTI) and long-term adverse effects from related kidney scarring. However, this strategy is controversial, owing in part to research suggesting that it has no effect on kidney scarring and to the potential emergence of multidrug-resistant organisms.

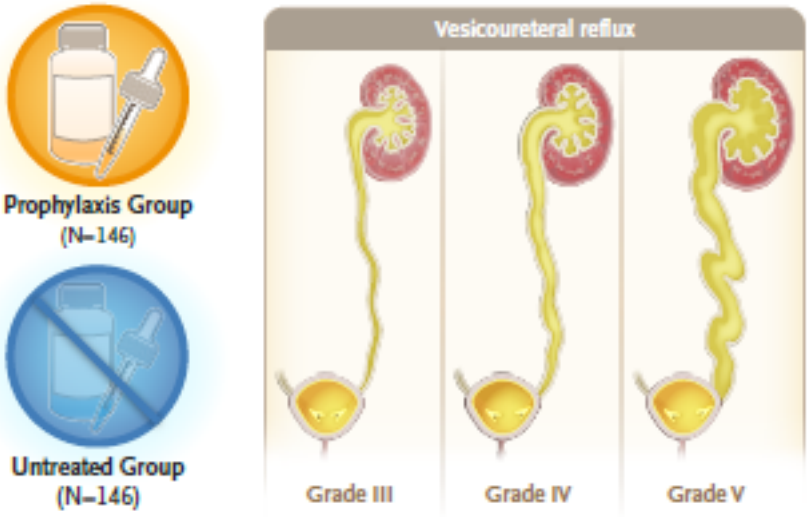
CLINICAL TRIAL

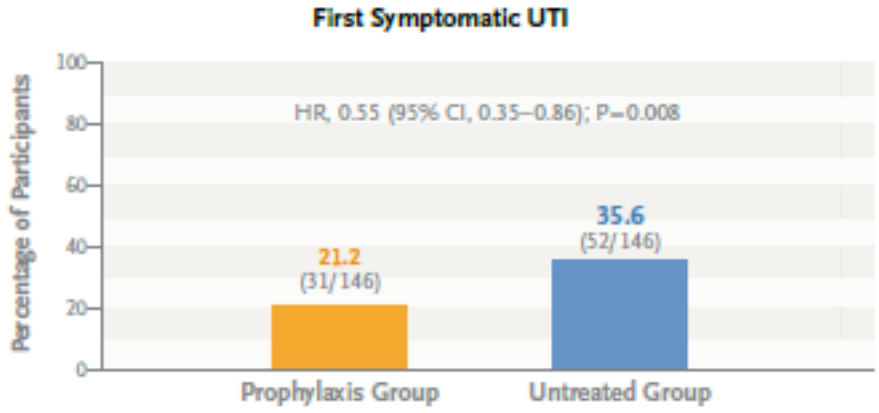
Design: An investigator-initiated, phase 3, multicenter, open-label, randomized trial in Europe assessed whether continuous antibiotic prophylaxis would prevent a first symptomatic UTI and secondary kidney damage in infants with grade III, IV, or V vesicoureteral reflux.

Intervention: 292 infants 1 to 5 months of age with grade III, IV, or V vesicoureteral reflux and no previous UTI were assigned to receive or not receive continuous antibiotic prophylaxis for 24 months. The primary outcome was the occurrence of a first symptomatic UTI.

RESULTS

Efficacy: Continuous antibiotic prophylaxis had a small but significant benefit with respect to the occurrence of a first symptomatic UTI, as compared with no treatment. The incidence of new kidney scarring and the mean estimated glomerular filtration rate were similar in the two groups.





Kidney embryology

Pronephros : nonfunctioning
3 wk

Mesonephros :intermediate mesoderm,5 wk, fuses with cloaca

Metanephros : metanephric mesencyhme and ureteric bud epithelium ,6-9 wk

Migrate from pelvis to lumbar region and rotate 90,so hilum medially

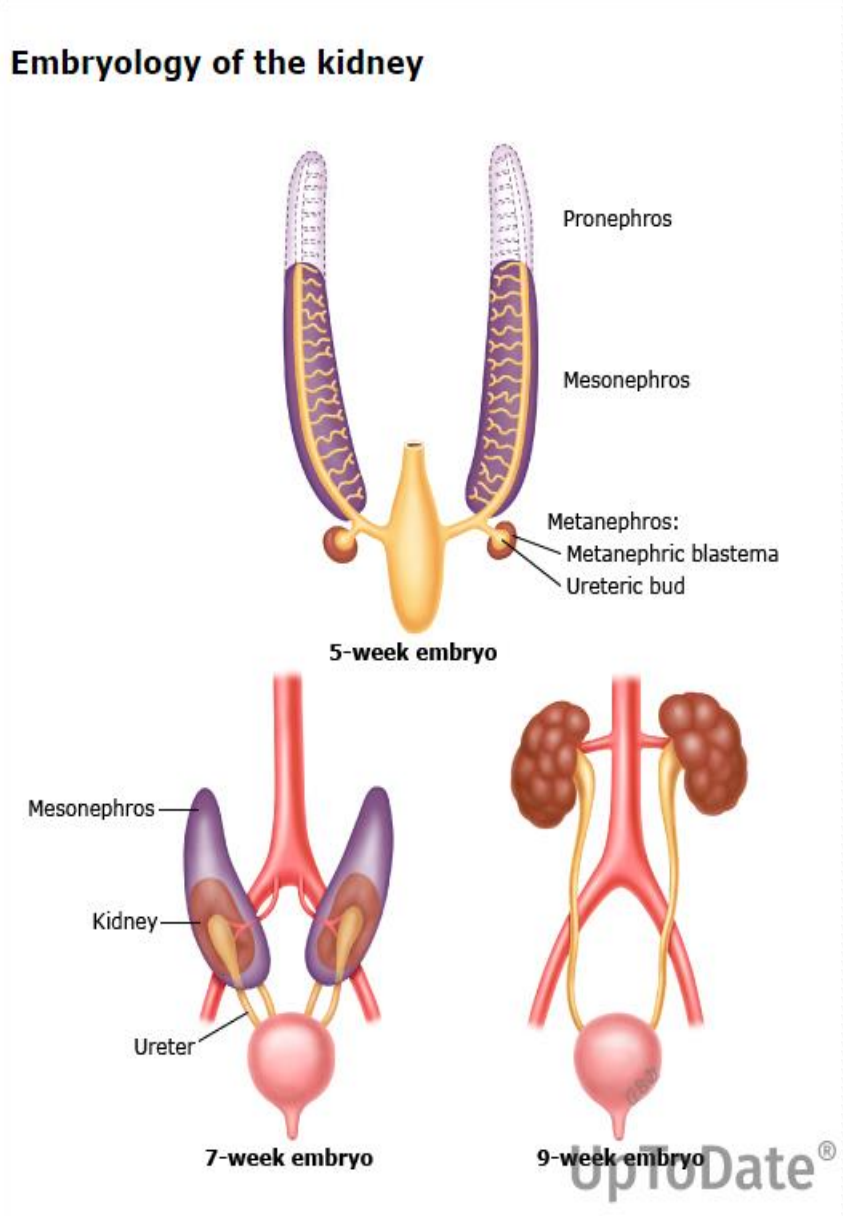


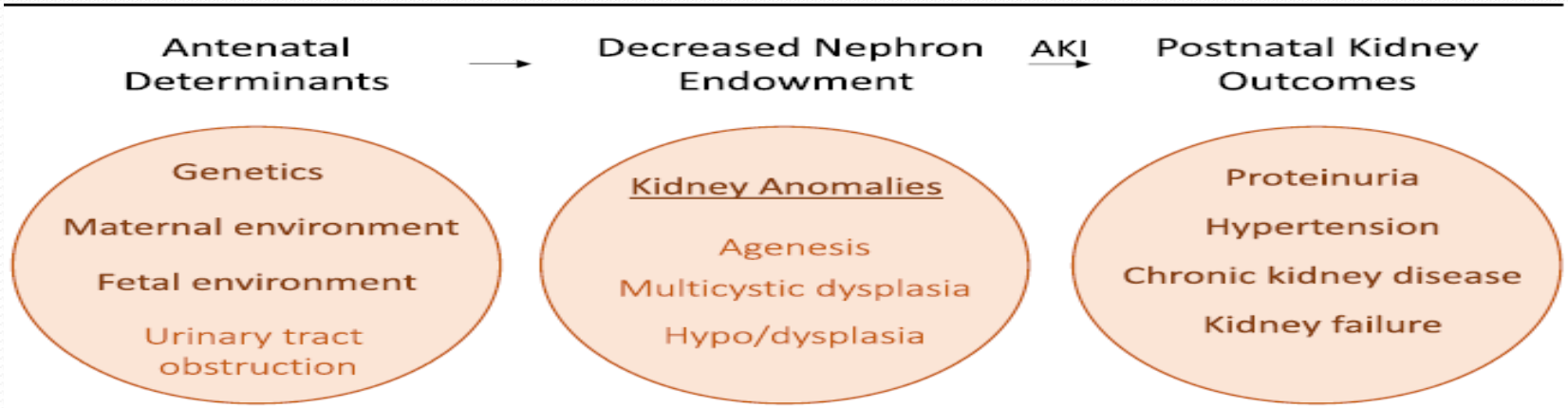
Table 2 Overview of environmental risk factors in the etiology of CAKUT

Maternal health factors	Strength of association
Obesity	++
Increased age	+/−
Ethnicity	?
Gravidity	?
Diabetes	++
Gestational diabetes	+/−
Subfertility	+
Infections	+
Maternal exposures during pregnancy	
Smoking	+/−
Alcohol	+/−
Folic acid use	+/−
Medication use (ACEi, retinol)	?

CAKUT :20-30% of all anomalies

CAKUT associated with non kidney anomalies in 30%

30-50% of CKD

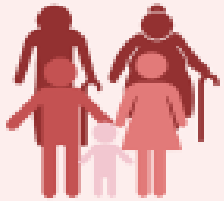
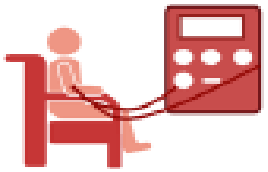
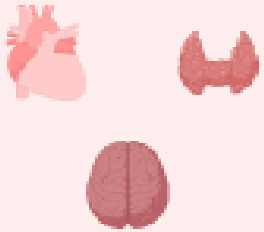
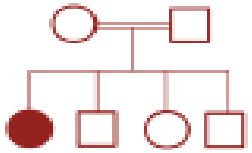


Genetic and CAKUT

Genetic conditions causing CAKUT are individually rare, and contribute to disease etiology in 16-20%

Genes (transcription factors)play a role during embryonal kidney development

Clinical clues for monogenic CAKUT

Family history of kidney anomalies or kidney impairment	Early onset kidney disease or CAKUT causing kidney failure	Extra-kidney manifestation	Consanguinity	Syndromic features
				

Consider referring to genetic counseling if any of the following co-exist with CAKUT phenotype: (1) family history

Genetic and CAKUT

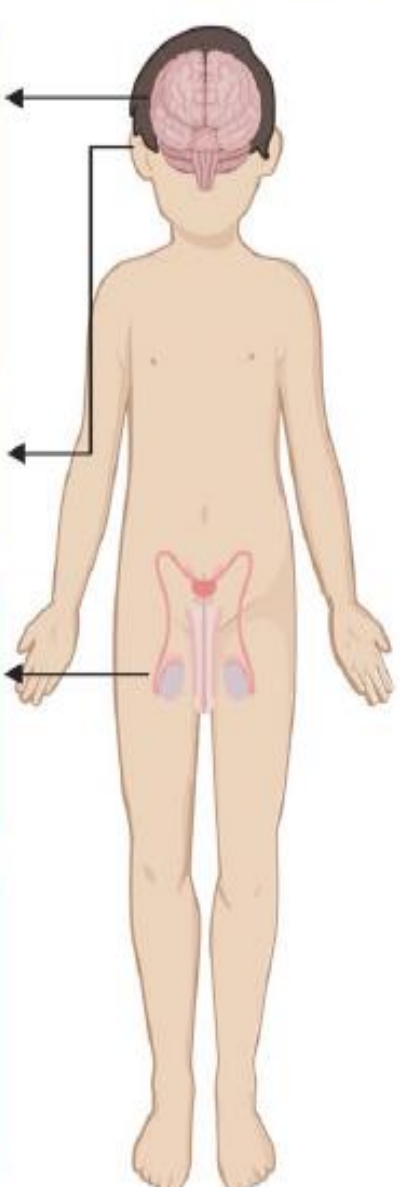
Single-gene causes of isolated/ oligosyndromic CAKUT	
HNF1B (hepatocyte nuclear factor-1B)	Renal cysts diabetes syndrome (MODY5)
PAX2 (paired box gene 2)	Renal coloboma syndrome
EYA1 (eyes absent homolog 1)	Brachio oto renal syndrome

Human gene variants associated with defects in kidney morphogenesis

Primary disease	Gene	Kidney phenotype
Alagille syndrome	*JAGGED1, NOTCH2*	Cystic dysplasia
Apert syndrome	*FGFR2*	Hydronephrosis
Bardet-Biedl syndrome	*BBS1*	Cystic dysplasia
Beckwith-Wiedemann syndrome	Dysregulation of imprinting in chromosome 11p15.5	Medullary dysplasia
Branchio-oto-renal syndrome	*EYA1, SIX1, SIX5*	Unilateral/bilateral agenesis/dysplasia, hypoplasia, collecting system anomalies
Campomelic dysplasia	*SOX9*	Dysplasia, hydronephrosis
Cenani-Lenz syndrome	*LRP4*	Agenesis, UPJO
DiGeorge syndrome	22q11.2 deletions	Agenesis, dysplasia
Fraser syndrome	*FRAS1, FREM2, GRIP1*	Agenesis, dysplasia
Hypoparathyroidism, sensorineural deafness, and renal anomalies	*GATA3*	Dysplasia
Kallmann syndrome	*KAL1, SEMA3A*	Agenesis
Mammary-Ulnar syndrome	*TBX3*	Dysplasia
Meckel Gruber syndrome	*MKS1, MKS3, NPHP6, NPHP8*	Cystic dysplasia
Nephronophthisis	*CEP290, GLIS2, RPGRIP1L, NEK8, SDCCAG8, TMEM 67, TTC21B*	Cystic dysplasia
Okihiro syndrome	*SALL4*	Unilateral agenesis, VUR, malrotation, cross-fused ectopia
Pallister-Hall syndrome	*GLI3*	Agenesis, dysplasia, hydronephrosis
Renal-coloboma (papillorenal) syndrome	*PAX2*	Hypoplasia, VUR
Renal cysts and diabetes syndrome	*HNF1b, TCF2*	Dysplasia, hypoplasia
Renal dysplasia, isolated (cystic or noncystic)	*DACH1, BICC1, CDC5L, NRIP1*	Dysplasia
Renal hypoplasia, isolated	*BMP4, RET, DSTYK*	Hypoplasia, VUR; *DSTYK* variants also associated with UPJO
Renal tubular dysgenesis	Renin, angiotensinogen, ACE, AT1 receptor	Tubular dysgenesis
Rubinstein-Taybi syndrome	*CREBBP*	Agenesis, hypoplasia
Simpson-Golabi Behmel syndrome	*GPC3*	Medullary dysplasia
Townes-Brock syndrome	*SALL1*	Hypoplasia, dysplasia, VUR
Zellweger syndrome	*PEX1*	Cystic dysplasia
Smith-Lemli-Opitz syndrome	*DHCR7*	Renal hypoplasia, cysts, and aplasia

ACE: angiotensin-converting enzyme; AT1: angiotensin II receptor type 1; VUR: vesicoureteral reflux; UPJO: ureteropelvic junction obstruction.

Main extra-renal manifestations associated with monogenic CAKUT

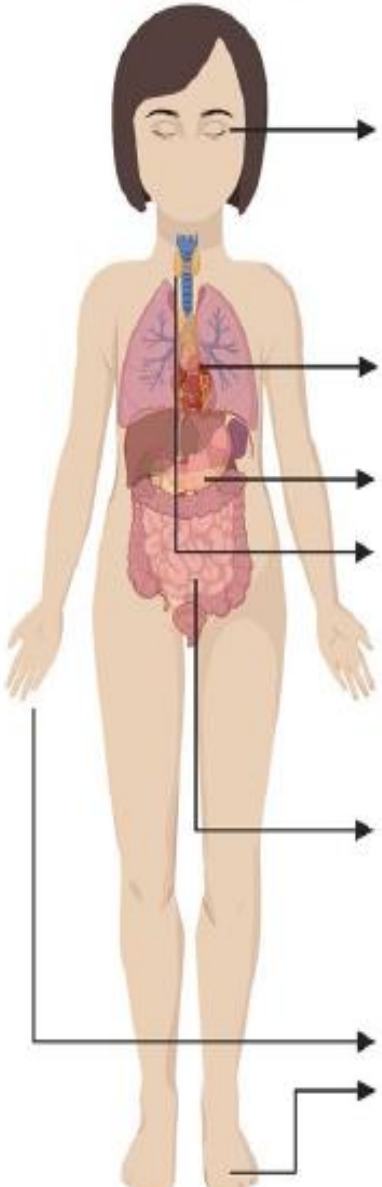


CNS
Autism, Schizophrenia- 17q12 del, *GATA3*
Developmental delay- *PAX2, PBX1*
CNS malformations- *PAX2, SALL1, PBX1*
Cerebral infarction- *GATA3*
Basal ganglia calcifications- *GATA3*

Ears
Hearing loss- *PAX2, EYA1, SALL1, PBX1*
Dysplastic ear- *EYA1, SALL1, PBX1*

Genitourinary
Polycystic ovaries - *GATA3*
Urogenital anomalies- *HNF1B, SALL1, GATA3*
Cryptorchidism- *PBX1*
Hypomagnesemia- *HNF1B*

Others
Branchial fistula or cysts- *EYA1*
IUGR- *HNF1B, PBX1*
Palate abnormalities- *EYA1*
Skeletal defects- *PBX1, PAX2*
Diaphragm malformations, lung hypoplasia- *PBX1*



Eyes
Coloboma- *PAX2, SALL1*
Optic nerve dysplasia- *PAX2*
Retinitis pigmentosa- *GATA3*

Cardiac
Congenital heart disease- *SALL1, GATA3, PBX1*

Endocrine
MODY- *HNF1B*
Hypoparathyroidism- *GATA3*
Hyperparathyroidism- *HNF1B*
Hypothyroidism- *SALL1*
Thyroiditis- *GATA3*

Gastrointestinal
Elevated pancreatic enzymes- *PAX2*
Pancreatic hypoplasia- *HNF1B*
Abnormal liver function- *HNF1B*
Anal malformation- *SALL1*

Limbs
Gout- *UMOD, PAX2, HNF1B*
Thumb malformation- *SALL1*
Foot malformation- *SALL1*

Congenital anomalies of the kidney and urinary tract: defining risk factors of disease progression and determinants of outcomes

Pediatric Nephrology (2023) 38:3963–3973

Laura Walawender[1,2] · Brian Becknell[1,2] · Douglas G. Matsell[3]

Table 2 CAKUT outcomes and risk factors for decline in kidney function

CAKUT category	↑BP (%)	↑UProt (%)	CKD (%)	CKD Stage 5 (%)	FU (yrs)	Risk factors	I
Multicystic dysplastic kidney[a]	5	15	7	–	5.9	genetic syndrome, kidney size, associated CAKUT, baseline eGFR	
Unilateral renal agenesis[b]	16	21	10	–	9.1	genetic syndrome, kidney size, associated CAKUT, baseline eGFR	
Renal hypodysplasia[c]	17–39	18–25	37–38	9–12	6.4–10.2	kidney size, hypertension, baseline eGFR	
Posterior urethral valves[d]	21–35	32–45	6–22[d]	15–37[d]	2–31[d]	oligohydramnios, nadir eGFR, kidney size, VUR	
Prune Belly syndrome	–	–	53	40–50	14.2	kidney size, nadir eGFR, pyelonephritis	
Non-glomerular disease[e]	26	40	15	19	5.2	proteinuria, hypertension, CKD stage	

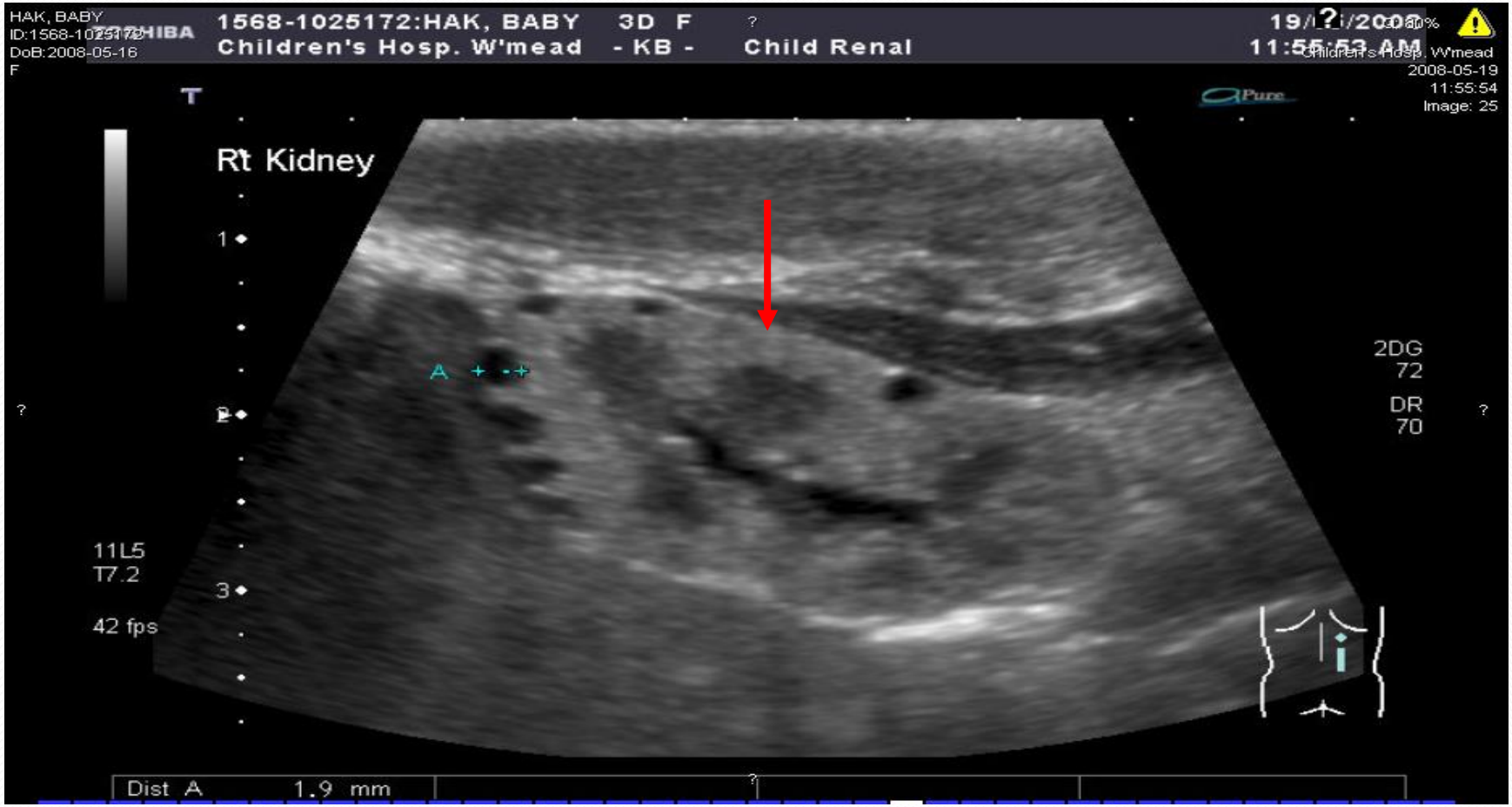
Renal Hypodysplasia

Malformed kidney tissue elements associated with reflux,small cysts and lead to CKD

Appears as increased echogenicity or ‘bright’ kidneys, poorly defined corticomedullary differentiation with with or cystic parenchymal changes

Outcome depends if compensatory hypertrophy

Hypoplasia : nephron mass less,kidney lenghth 2 SD below mean


HAK, BABY
ID:1568-1025172
DoB:2008-05-16
F
1568-1025172:HAK, BABY 3D F
Children's Hosp. W'mead - KB - Child Renal
Children's Hosp. W'mead
2008-05-19
11:55:54
Image: 25
Rt Kidney
2DG
72
DR
70
11L5
T7.2
42 fps
Dist A 1.9 mm

Multicystic dysplastic kidney

Non communicating cysts seperated by dysplastic tissue

Asymptomatic or as abdomenal mass

Associated with extrarenal malformation

Course: majority involutes within 5 -10 years

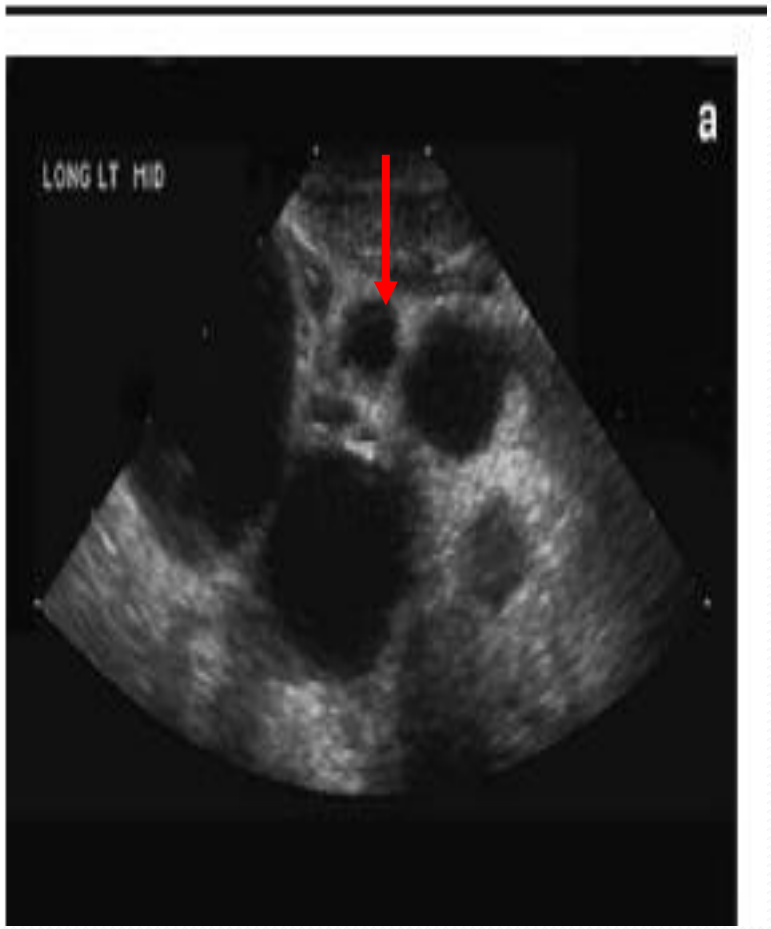
Low risk of HTN,malignancy comparable to general population

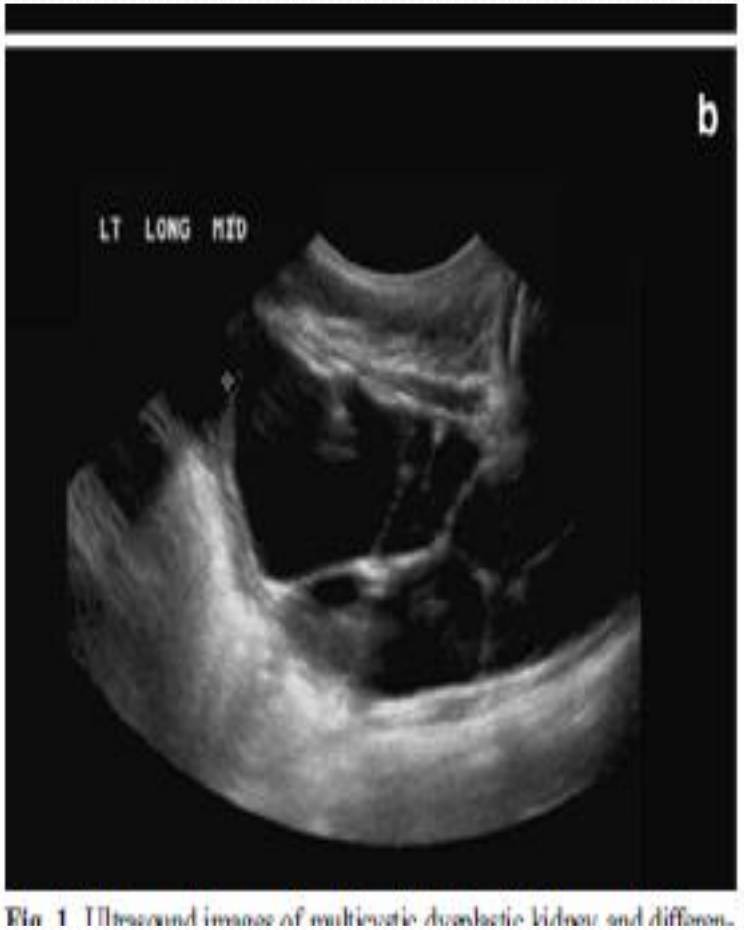
VUR in 21 % of contralateral kidney

Serial ultrasound at 6 m,2,5,10 year

Evaluate BP,creatinine,UA for proteinuira

Differentiate between UPJ,MCDK





Management and etiology of the unilateral multicystic dysplastic kidney: a review

Pediatr Nephrol

David S. Hains · Carlton M. Bates · Susan Ingraham · Andrew L. Schwaderer

tural and functional in nature. A review of the literature reveals that involution rates are reported to be 19–73%, compensatory hypertrophy of the contralateral kidney occurs from 24–81% of the time, and estimated glomerular filtration rates (GFRs) (by the Schwartz formula) range from 86–122 ml/min per 1.73 m^2 body surface area. Most authors suggest serial ultrasonography to monitor contralateral growth, routine blood pressure monitoring, and a serum creatinine monitoring algorithm. The risk of hypertension in those with MCDKs does not appear to be greater than that of the general population, and the rates of malignant transformation of MCDK are small, if at all increased, in comparison with those in the general population. If the patient develops a urinary

Solitary Kidney

Isolated unilateral kidney agenesis occurs in 1 in 1000 to 2000 births

Unilateral renal agenesis: a systematic review on associated anomalies and renal injury

Nephrol Dial Transplant (2013) 28: 1844–1855

43 studies with 2684 patients, associated CAKUT anomalies were observed in one-third of patients with solitary kidneys, other anomalies in 31%

Evidence of kidney injury :

Microalbuminuria (21 %)

Hypertension (16 %)

Reduced kidney function (10 %)

Table 3 Most reported syndromes in association with congenital solitary kidney

Syndrome	Extrarenal manifestations	Genes	Possible inheritance
Branchio-oto-renal	Sensorineural hearing loss, preauricular pits, branchial cysts, and microtia	*EYA1, SIX1, SIX5*	Autosomal dominant
DiGeorge	Congenital heart disease, hypocalcaemia, immunodeficiency, and neurocognitive disorders	22q11 deletion	Autosomal dominant
Fraser	Cryptophthalmos, cutaneous syndactyly, occasionally malformations of the larynx, ambiguous genitalia, and mental retardation	*FRAS1, FREM2*	Autosomal recessive
Herlyn-Werner-Wunderlich or OHVIRA (obstructed hemivagina and ipsilateral renal agenesis)	Obstructed hemivagina and uterus didelphys	Unknown	Autosomal dominant
Kallmann 1	Micropenis, bilateral cryptorchidism, and anosmia	*KAL1*	X-linked
Klinefelter	Small, firm testis, gynaecomastia, azoospermia, and hypergonadotropic hypogonadism	47, XXY	Sporadic
MURCS (Mayer-Rokitansky-Kuster–Hauser type 2)	Müllerian duct aplasia-hypoplasia and cervicothoracic somite dysplasia	Unknown	Autosomal dominant
Renal coloboma	Retinal and optic nerve coloboma	*PAX2*	Autosomal dominant
Renal cysts and diabetes	Maturity-onset diabetes of the young type 5, hyperuricaemia, hypomagnesemia, and uterine malformations	*HNF1B*	Autosomal dominant
Townes–Brocks	Thumb anomalies, imperforate anus, and sensorineural hearing loss	*SALL1*	Autosomal dominant
VACTERL association	Vertebral anomalies, anorectal malformations, cardiovascular disease, tracheoesophageal fistula, esophageal atresia, and limb defects	*TRAP1*	Autosomal recessive
Williams–Beuren	Developmental delay, cardiovascular anomalies,	7q11.23 deletion	Autosomal dominant

Pediatric Nephrology (2022) 37:2185–2207
https://doi.org/10.1007/s00467-022-05528-y

GUIDELINES

Management of the congenital solitary kidney: consensus recommendations of the Italian Society of Pediatric Nephrology

Claudio La Scola[1] · Anita Ammenti[2] · Cristina Bertulli[1] · Monica Bodria[3] · Milena Brugnara[4] · Roberta Camilla[5] · Valentina Capone[6] · Luca Casadio[7] · Roberto Chimenz[8] · Maria L. Conte[9] · Ester Conversano[10] · Ciro Corrado[11] · Stefano Guarino[12] · Ilaria Luongo[13] · Martino Marsciani[14] · Pierluigi Marzuillo[12] · Davide Meneghesso[15] · Marco Pennesi[10] · Fabrizio Pugliese[16] · Sara Pusceddu[17] · Elisa Ravaioli[9] · Francesca Taroni[6] · Gianluca Vergine[9] · Licia Peruzzi[5] · Giovanni Montini[6,18]

Received: 12 August 2021 / Revised: 3 March 2022 / Accepted: 4 March 2022 / Published online: 17 June 2022

How should a CSK be confirmed postnatally?

1. For the definitive diagnosis of CSK, a neonatal US performed by an experienced pediatric radiologist is sufficient in most cases (grade B).
2. We do not recommend the routine use of scintigraphy to confirm the anatomical or functional absence of a kidney (grade B).

b) Should imaging to detect VUR be performed routinely?

Statements/recommendations:

1. In children with a normal CSK and urinary tract on US (Box 1), routine imaging to rule out the presence of VUR is not recommended (grade B).
2. We believe that VCUG should be performed when abnormalities of the CSK or urinary tract are reported on US (see Box 1) (Grade C).

a) Is a child with CSK at risk of decreasing glomerular filtration rate?

1. Children without compensatory enlargement of the CSK and/or additional ipsilateral CAKUT are at risk of GFR reduction and CKD progression (grade B).

   Children showing a CSK with compensatory enlargement and the absence of ipsilateral CAKUT are at a lesser risk of GFR reduction and CKD progression (grade B).

b) Is a child with CSK at risk of proteinuria?

1. The prevalence of proteinuria in children with a CSK is higher than in the normal pediatric population (Grade B). Evaluation of proteinuria is warranted in every child with a CSK (grade B).

c) Is a child with CSK at risk of developing hypertension?

Statements/Recommendations:

1. We recommend that office BP be measured in every child with a CSK (grade B).
2. At present, no clear risk factors for hypertension in children with a CSK have been demonstrated (grade C).

Table 8 Opinion-based recommendations for follow-up in children and adolescents with congenital solitary kidney

	Low risk*	Medium risk*		High risk*
		Without CAKUT	With ipsilateral CAKUT	
Setting	Primary pediatric care[1]	Pediatric nephrologist[1]/pediatric nephrology unit		Pediatric nephrology unit
Ultrasound[2]	Yearly until 3 years of age, then every 5 years	Yearly until 3 years of age, then every 3 to 5 years	Further work-up depending on additional ipsilateral CAKUT finding	According to kidney function and clinical data
Proteinuria by urinalysis[3]	Yearly until 3 years of age, then every 5 years	Yearly		
Office Blood pressure	Yearly ≥ 3 years	Yearly		
Serum creatinine/eGFR	Not necessary	Yearly		
Abdominopelvic ultrasound in girls	Between thelarche and menarche	Between thelarche and menarche		Between thelarche and menarche

*Risk stratification:

- low risk: kidney length > 50th pct in the first 2 years of life and ≥ 95th pct thereafter, and absence of ipsilateral CAKUT
- medium risk: CSK without compensatory enlargement, and/or with an ipsilateral CAKUT
- high risk: decreased eGFR (i.e., mean eGFR for age -1 SD in children younger than 2 years, < 90 ml/min per 1.73 m^2 in children older than 2 years) and/or proteinuria, and/or hypertension

Case

A one day old baby, oligohydraminos ,who remained anuric after birth and has rise in creatinine.

Renal ultrasound was normal

The baby died at two week of age

WES showed renal tubular dysgenesis

ANOMALIES OF EMBRYONIC KIDNEY MIGRATION

Ectopic and fusion anomaly

Hoarse shoe kidney

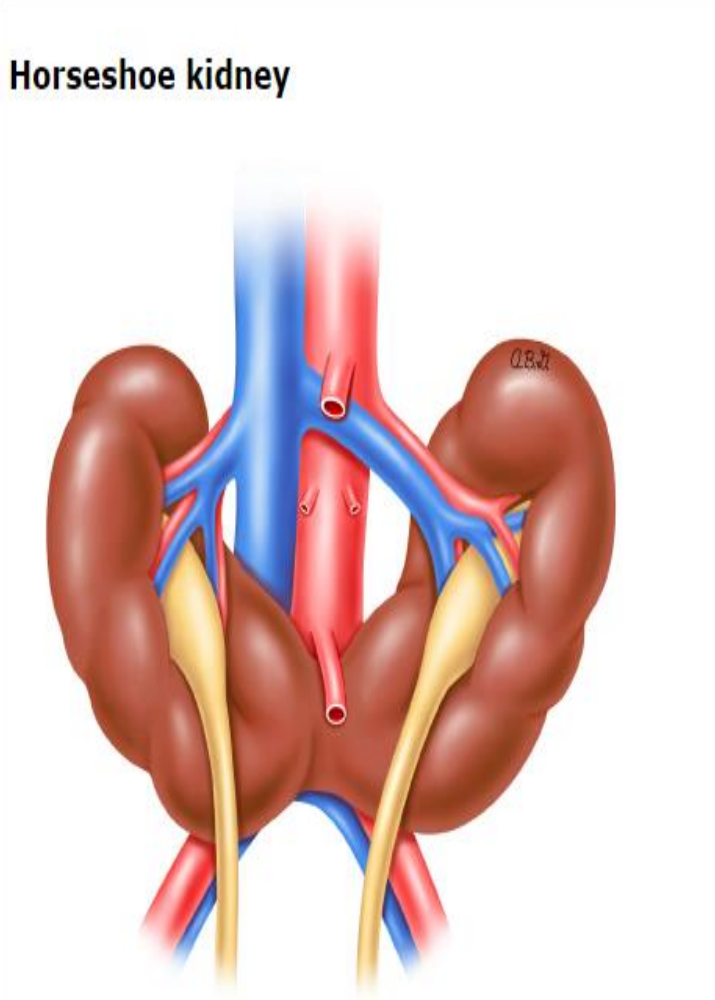
1.present as asymptomatic,UTI,stones

2,associated with VUR and PUJ

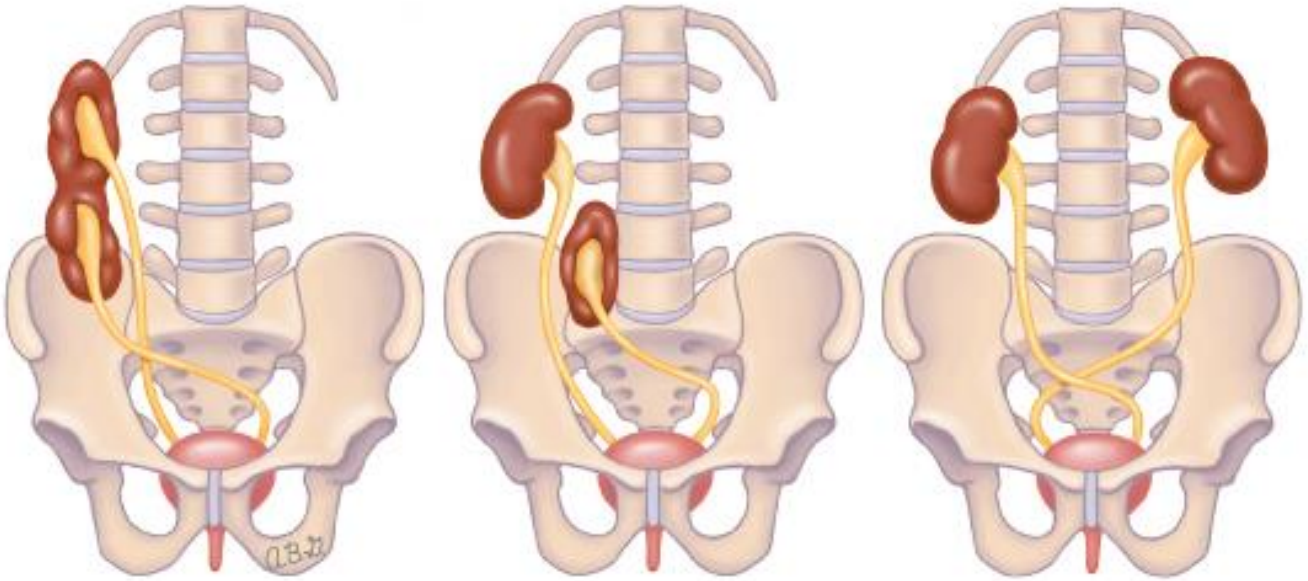
3.Turner and triosmy 13,18,21

4.Genital anomalies

Monitor by ultrasound,BP,creat,UA



Crossed renal ectopia



Different forms of crossed renal ectopia.

- **Fused** – Ectopic kidney moves across the midline and fuses to the lower pole of the normally positioned contralateral kidney.
- **Nonfused** – Ectopic kidney moves across the midline without fusion and is positioned at the rim of the pelvis (pelvic kidney).
- **Bilateral** – Both kidneys are ectopic and cross the midline with the ureters maintaining their normal bladder insertion.

ANOMALIES OF THE COLLECTING SYSTEM

- Renal pelvis (eg, ureteropelvic junction obstruction)
- Ureter (eg, megaureter, ectopic ureter, ureterocele, or vesicoureteral reflux [VUR]
- Urethra (eg, posterior urethral valve)

Ureteropelvic junction obstruction

Caused by intrinsic narrowing/crossing vessel

Present ; antenatal screen,UTI,flank pain during diuresis

Diagnosis: diuretic renogram/MRU

Ureteropelvic junction obstruction

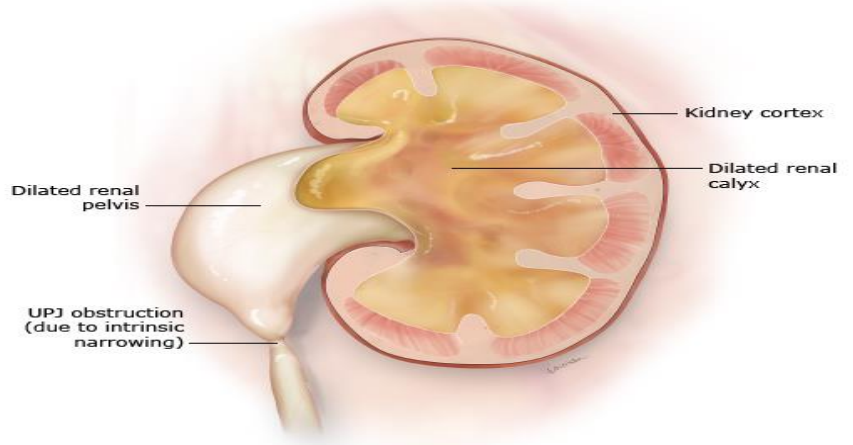


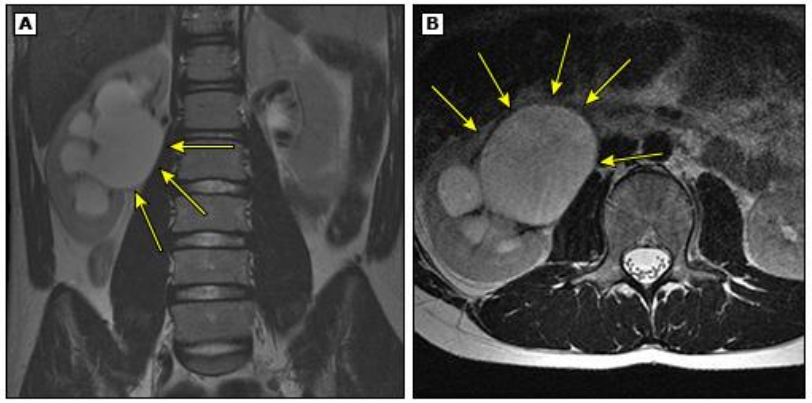
Illustration of a kidney with a UPJ obstruction, causing dilation of the renal pelvis and calices. In this case, the obstruction is caused by intrinsic narrowing, which is the most common cause of UPJ obstruction.

UPJ: ureteropelvic junction.

Modified from: Baskin LS, Kogan BA. Handbook of Pediatric Urology, 2nd ed, Lippincott Williams & Wilkins 2005.

UpToDate®

MRI demonstrating right ureteropelvic junction obstruction



MRI (magnetic resonance imaging) showing ureteropelvic junction obstruction of the right kidney demonstrated by dilation of the renal collecting system (arrows).

(A) Coronal view.

(B) Transverse view.

UPJ: ureteropelvic junction

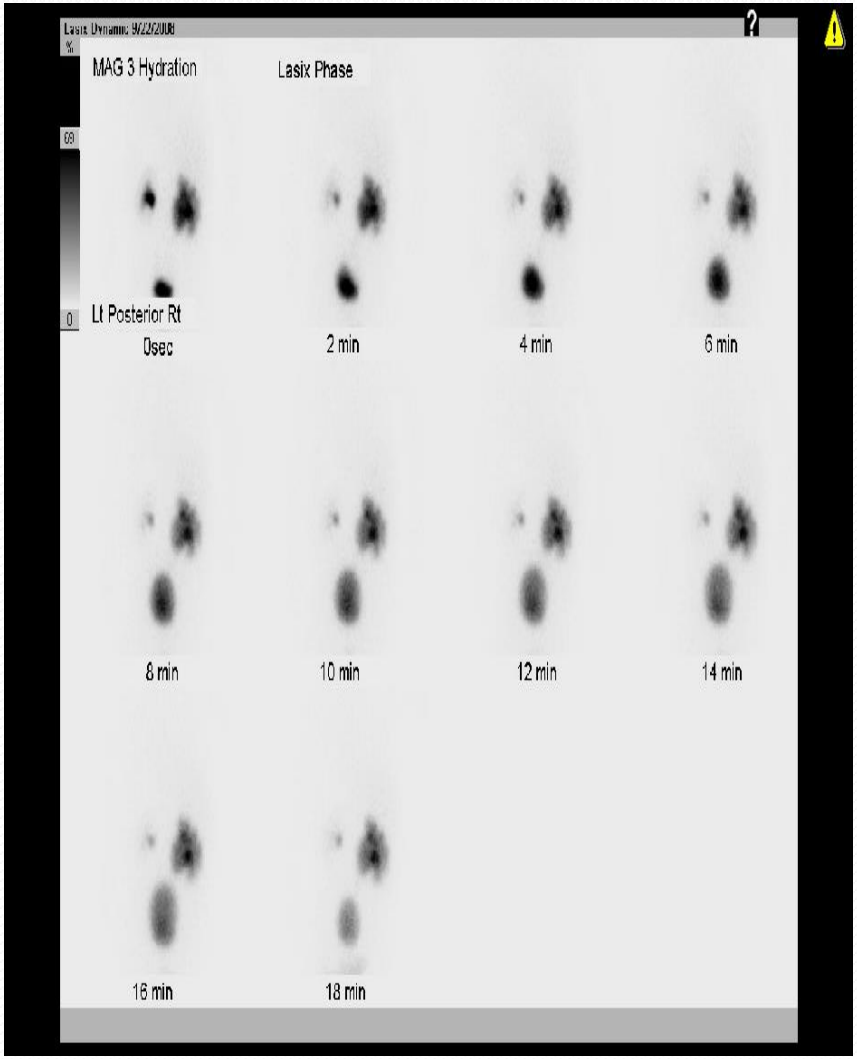
clinically significant obstruction on diuretic renogram :

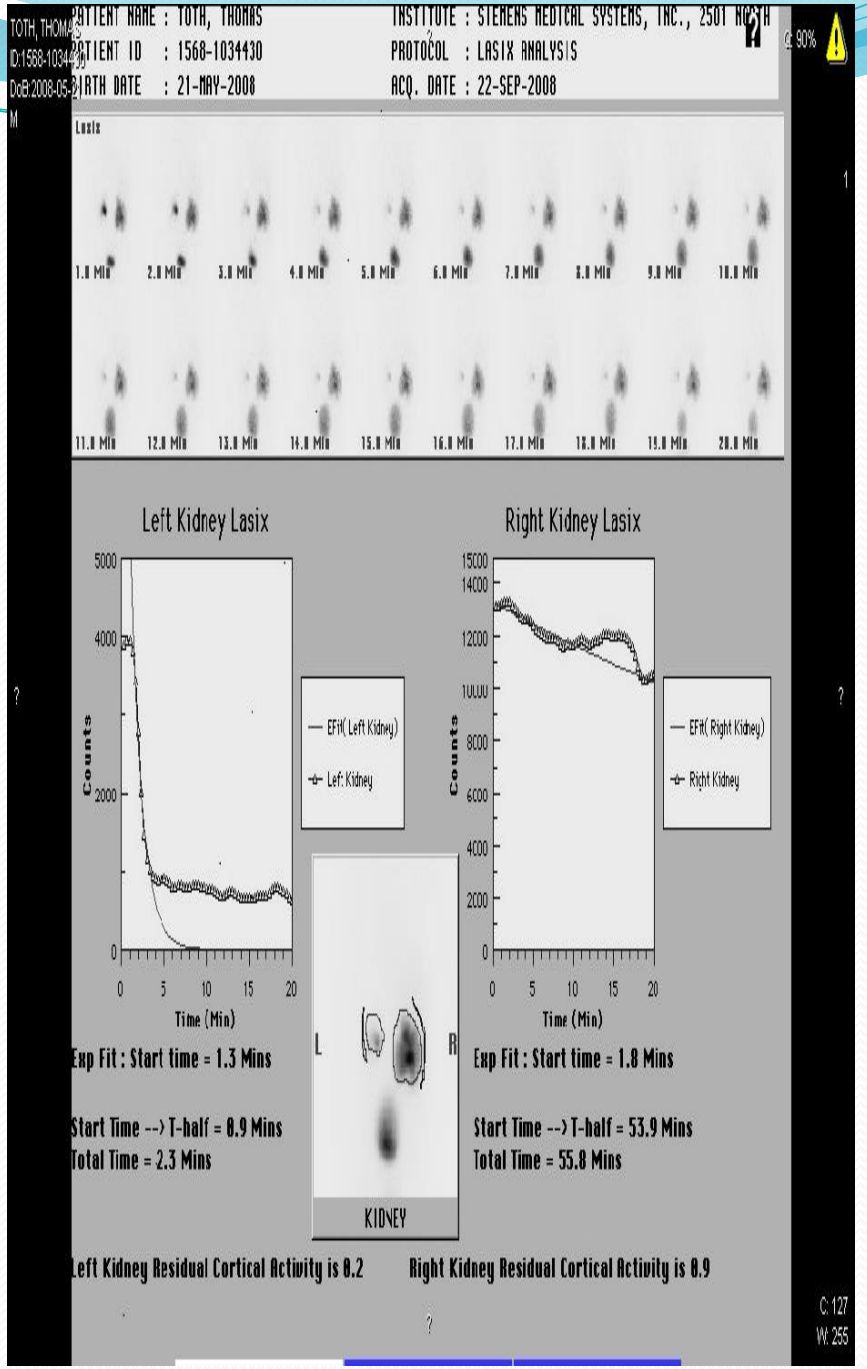
- Prolonged washout – A half-life >20 minutes,.
- Impaired kidney function – Affected kidney with <40% of total kidney function or >10 % decline in function of the affected kidney from baseline on).

25-52 percent of patients underwent surgical correction

Conservative :Follow up by ultrasound,renogram 3-6 months

Right PUJ mag3





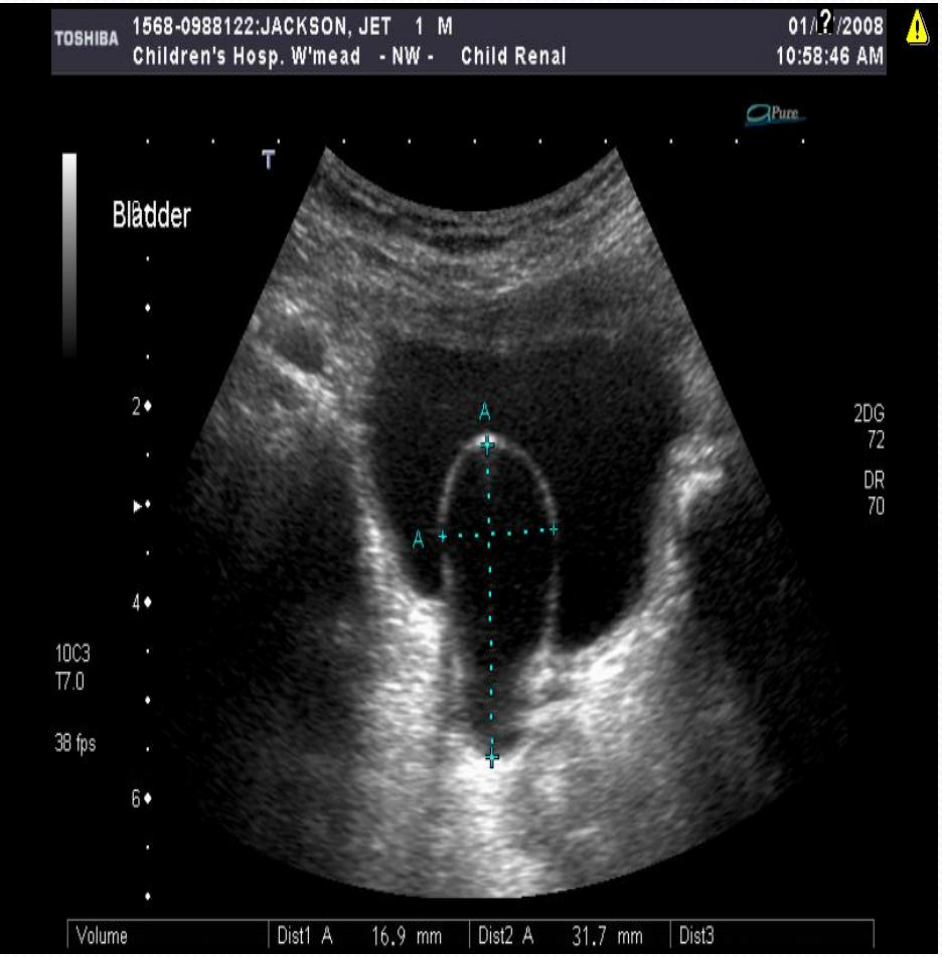
Case 2

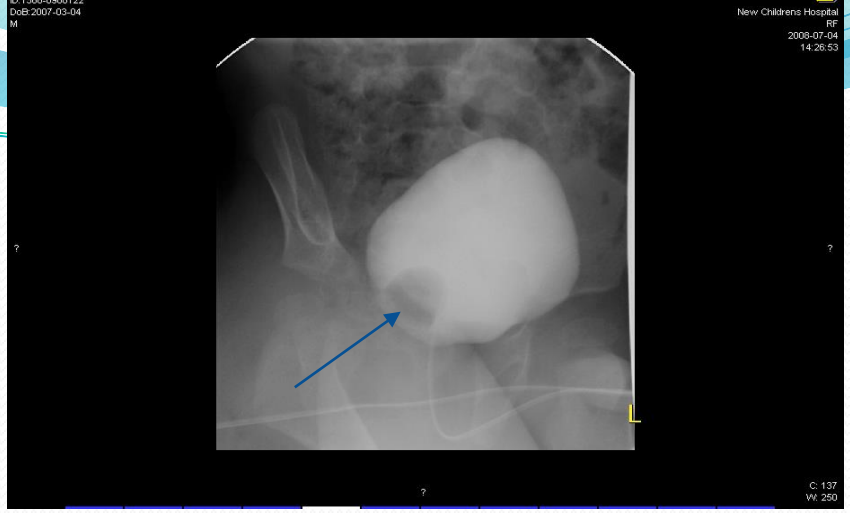
A one month baby was admitted with two episodes of urine retention complicated by UTI

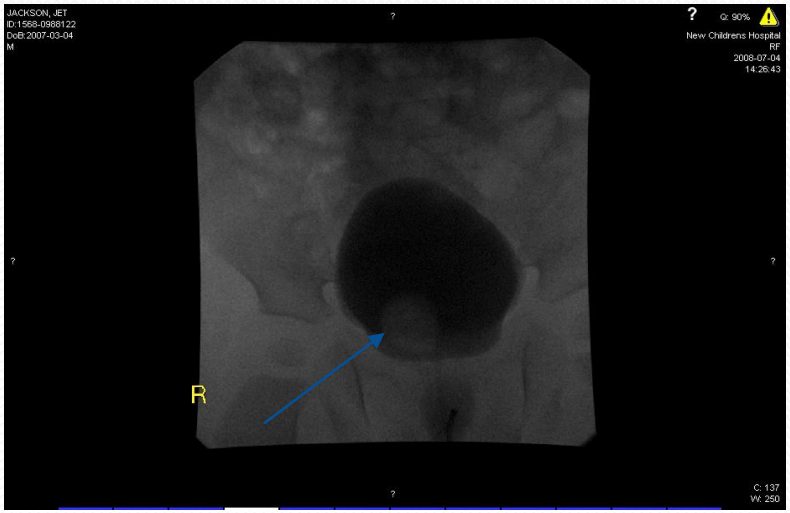
Ultrasound shows unilateral moderate dilatation duplex kidney

Associated

ureterocele







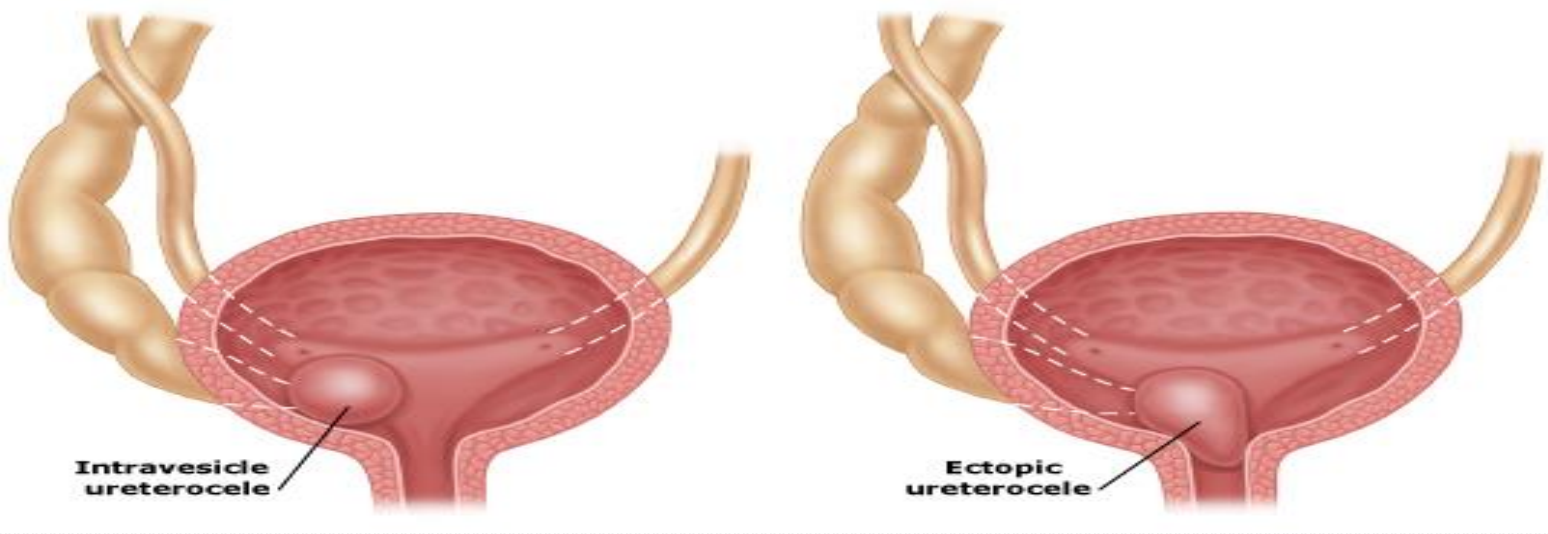
ureterocele

Cystic dilatation of submucosal or intravesical portion of ureter

Associated with upper pole of duplex kidney

Cause obstruction of ureter or bladder neck

Treated by transurethral puncture



Posterior Urethrel valve

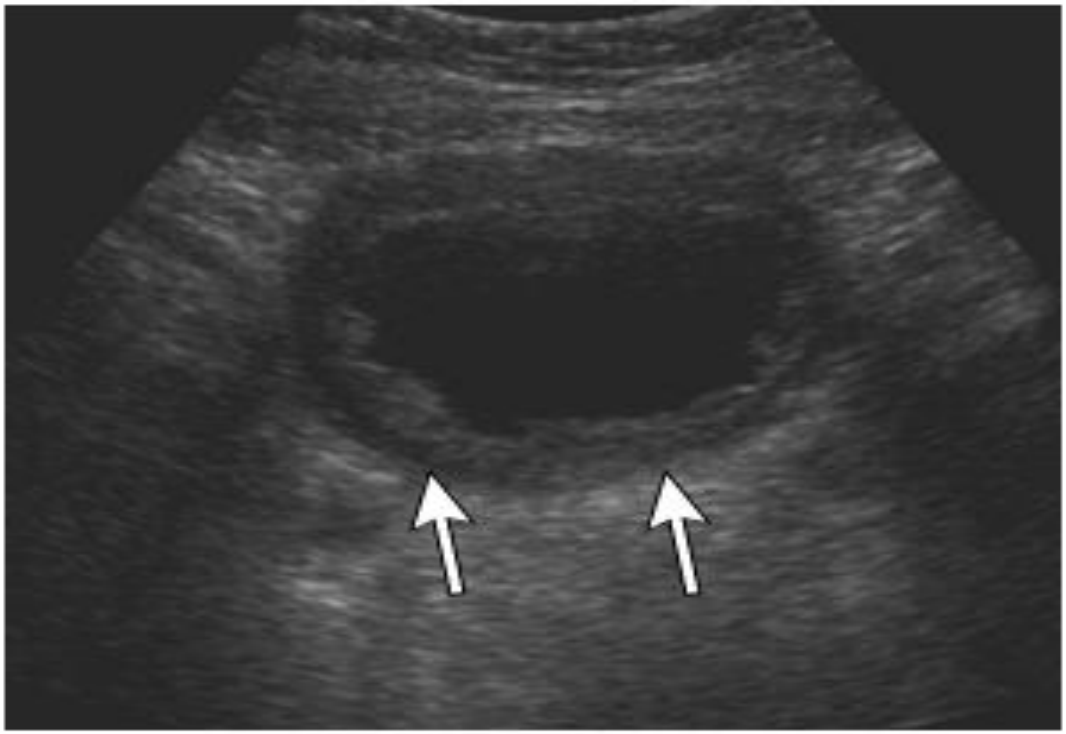
Persistance of urogenital membrane,abnormal canalization of urethrea

Diagnosis : antenatal (keyhole sign),urinoma,distended bladder ,poor stream,UTI ,wetting,straining to void

Outcome : CKD, VUR, bladder dysfunction

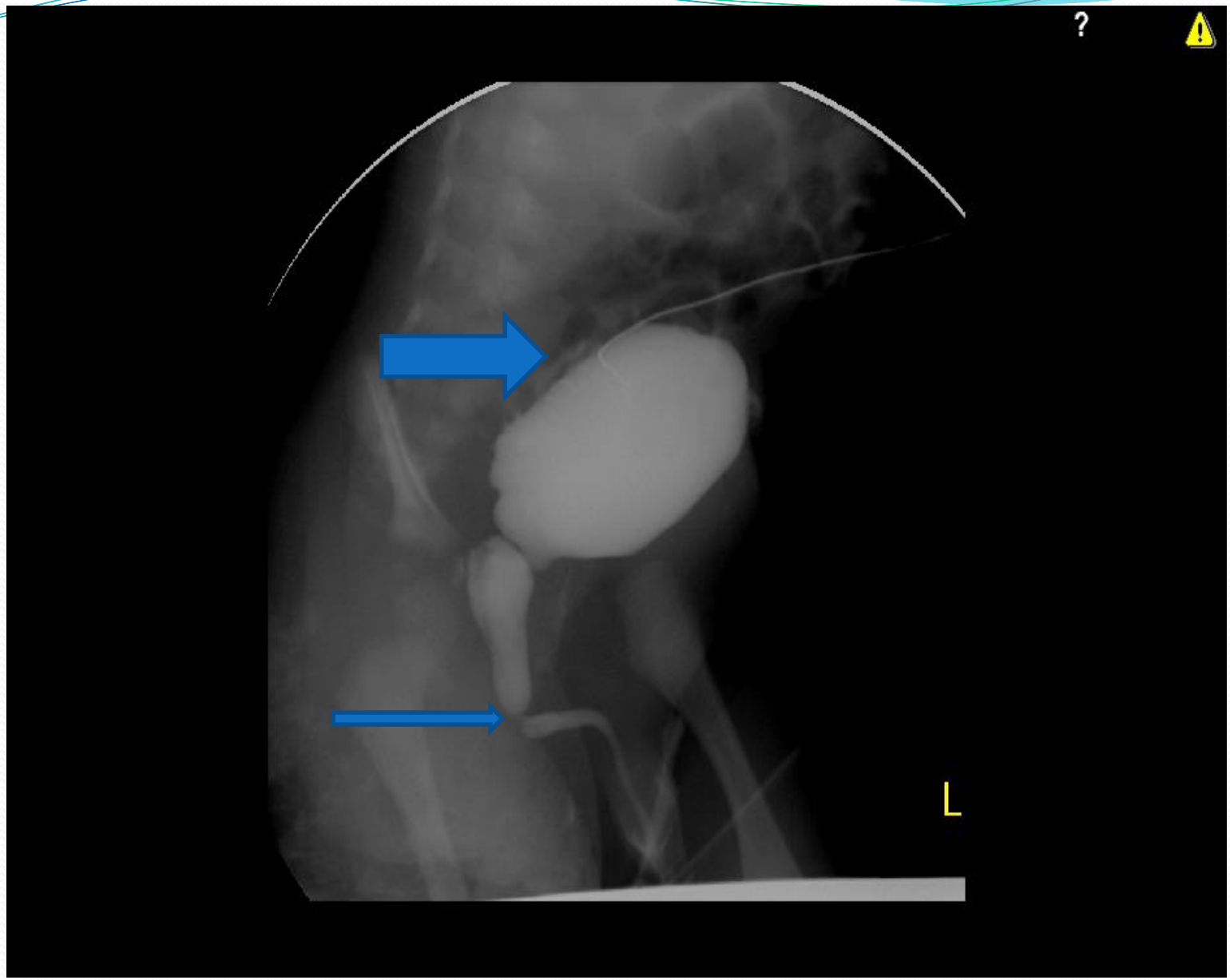
Management :valve ablation, folley, vesicotomy,

Ultrasound image of thickened bladder wall in patient with posterior urethral valves



Ultrasound demonstrating a thickened bladder wall (arrows) in a male infant with posterior urethral valves.

Courtesy of Nicholas Holmes, MD.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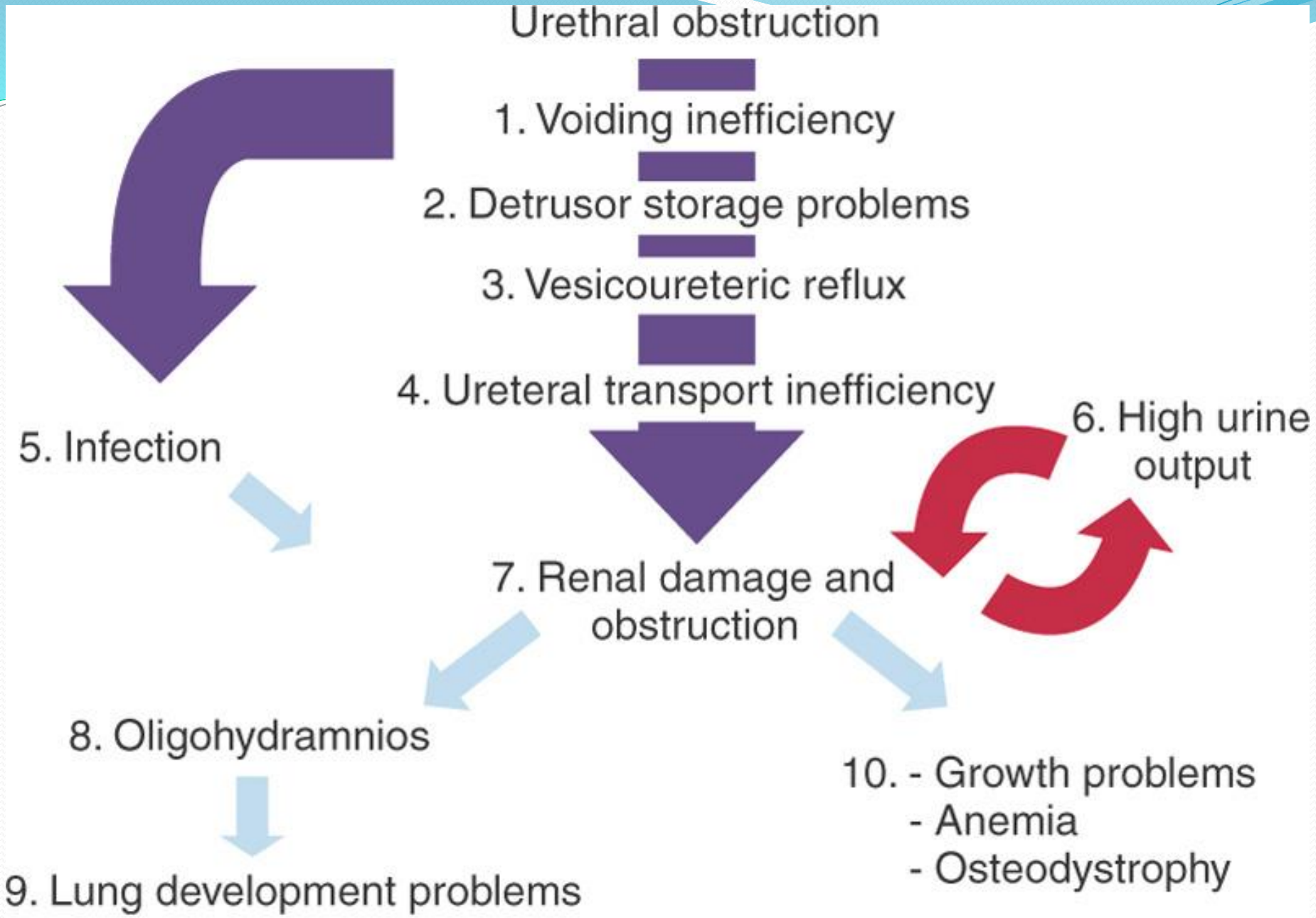
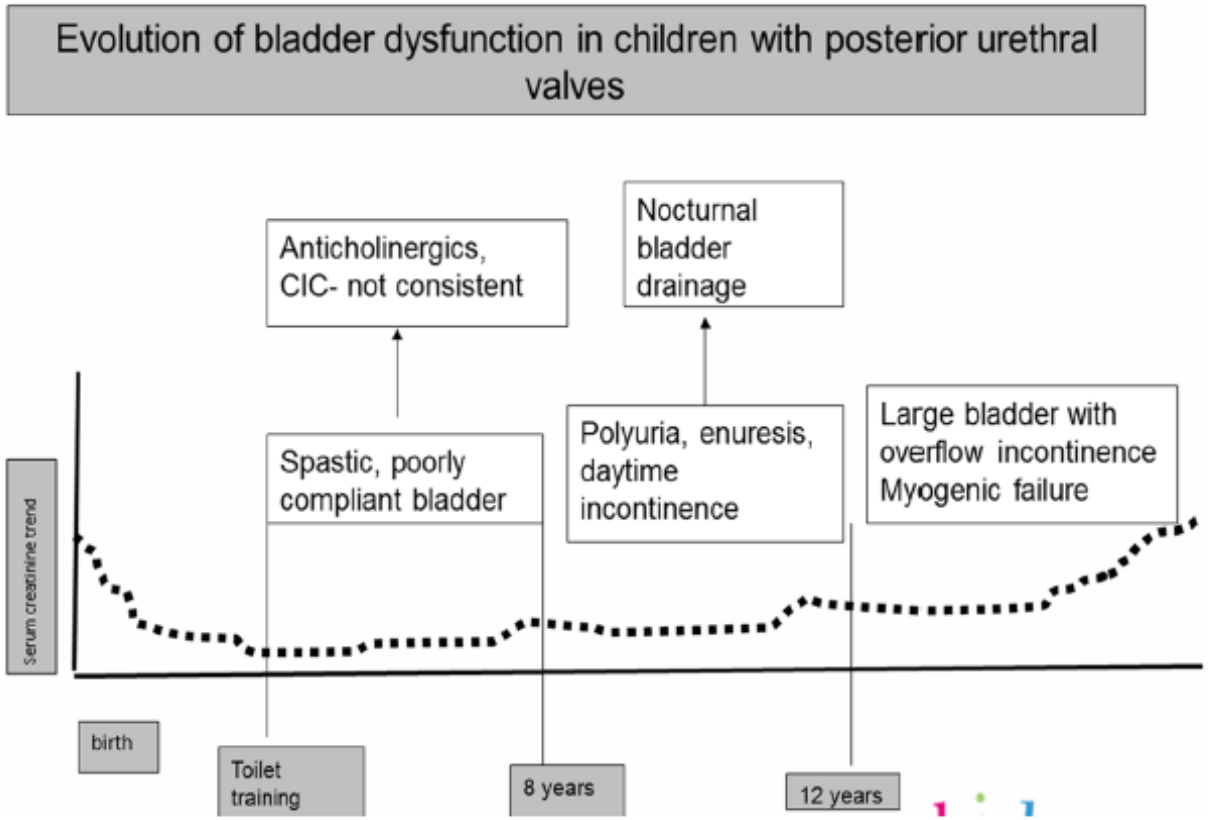


Current strategies to predict and manage sequelae of posterior urethral valves in children

Pediatr Nephrol (2018) 33:1651–1661



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- www.uptodate.com

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- Primary non-surgical management of unilateral ureteropelvic junction obstruction in children: a systematic review. Pediatr Nephrol (2017) 32:2203–221
- Unilateral renal agenesis: a systematic review on associated anomalies and renal injury. Nephrol Dial Transplant (2013) 28: 1844–1855


THANK YOU

Minimal Change Nephrotic Syndrome in Children

Management update

The 1st IBNA Teaching Course in Pediatric Nephrology

5/12/2024

Issa Alkhatatbeh MD,FRCP

Consultant Pediatric Nephrologist

Minimal Change Nephrotic Syndrome

- Most common cause of the nephrotic syndrome in children
- ~10-15% of nephrotic syndrome in adults,
  - More common in Hispanics, Asians, Arabs and Caucasians
- clinical and pathological entity defined by selective proteinuria and hypoalbuminemia that occurs in the absence of
  - cellular glomerular infiltrates or immunoglobulin deposits

Primary nephrotic syndrome in Arab children in Kuwait. The annual incidence was 7.2 and 6.0 per 100,000 children below 10 and 12 years of age, respectively.

Zaki etal, 1989, Volume 3, Number 2, Pages 218-220.

Primary nephrotic syndrome in Arab children. The annual incidence was 11.6/100 000

Elzouki Arch Dis Child.1984 Mar;59(3):253-5.

incidence of Nephrotic Syndrome range from 2-7 per 100,000 children, and the prevalence from 12-16 per 100,000

Eddy AA, Symons JM. Nephrotic syndrome in childhood.

Lancet 2003; *362* : 629-39.

IPNA 2023 clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome

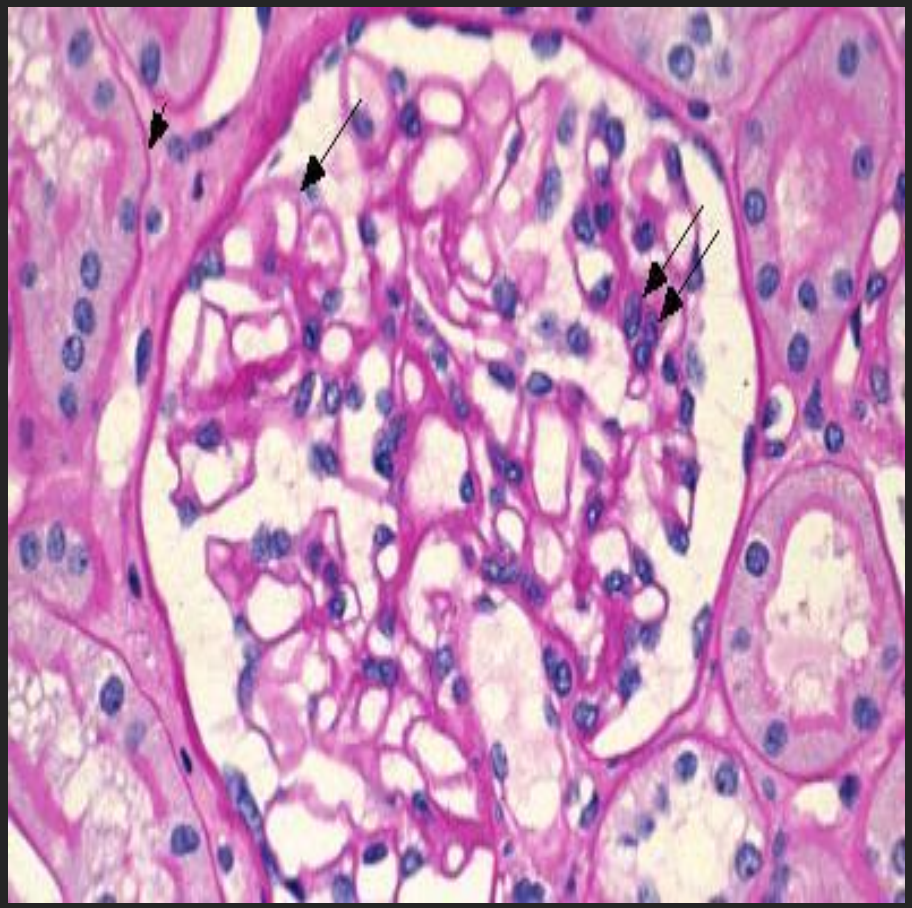
- Nephrotic-range proteinuria UPCR ≥ 200 mg/mmol (2 mg/mg) in first morning void or 24 h urine sample ≥ 1000 mg/m2/day corresponding to 3+ or 4+ by urine dipstick
- Nephrotic syndrome Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/l) or edema when serum albumin level is not available
- SSNS Complete remission within 4 weeks of prednisone or prednisolone (PDN) at standard dos(60 mg/m2/day or 2 mg/kg/day, maximum 60 mg/day).

IPNA 2023 clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome

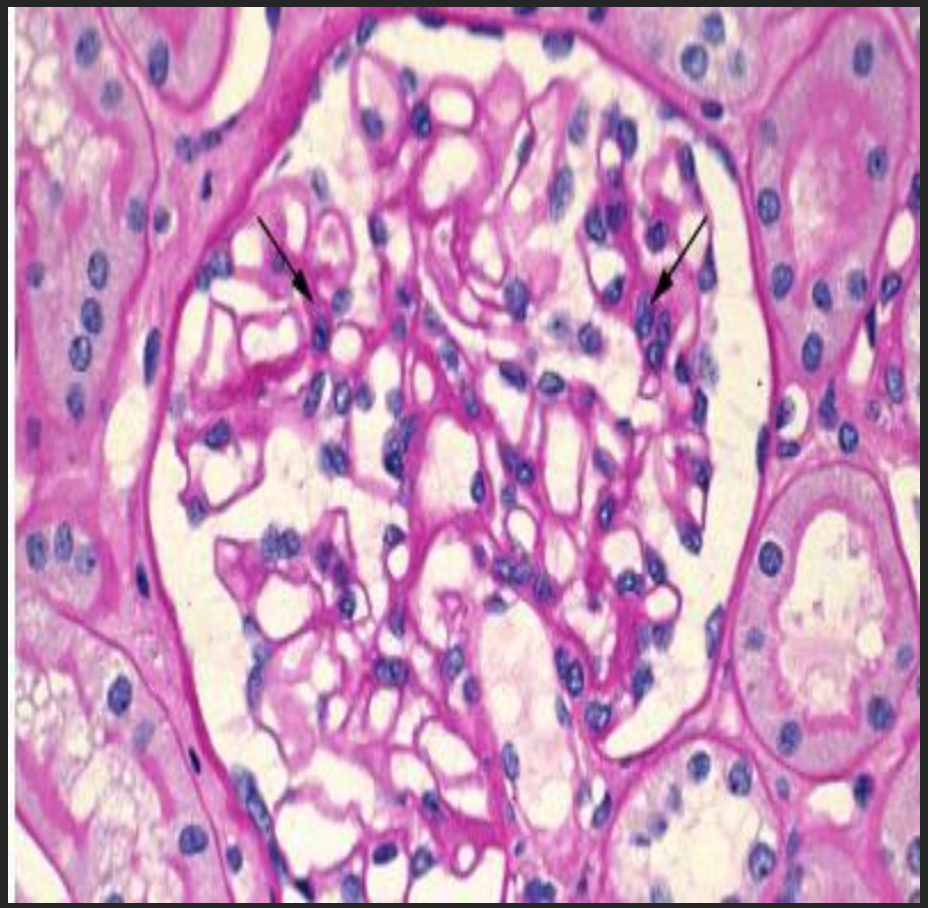
- SRNS Lack of complete remission within 4 weeks of treatment with PDN at standard dose
- Confirmation period Time period between 4 and 6 weeks from PDN initiation during which response to further oral PDN and/or pulses of iv MPDN and RAASi are ascertained in patients achieving only partial remission at 4 weeks.

- A patient achieving complete remission at 6 weeks is defined as a late responder.
  A patient not achieving complete remission at 6 weeks although he had achieved partial remission at 4 weeks is defined as SRNS.
- Complete remission UPCR (based on first morning void or 24 h urine sample) ≤ 20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on three or more consecutive occasions.

Minimal Change Nephrotic Syndrome

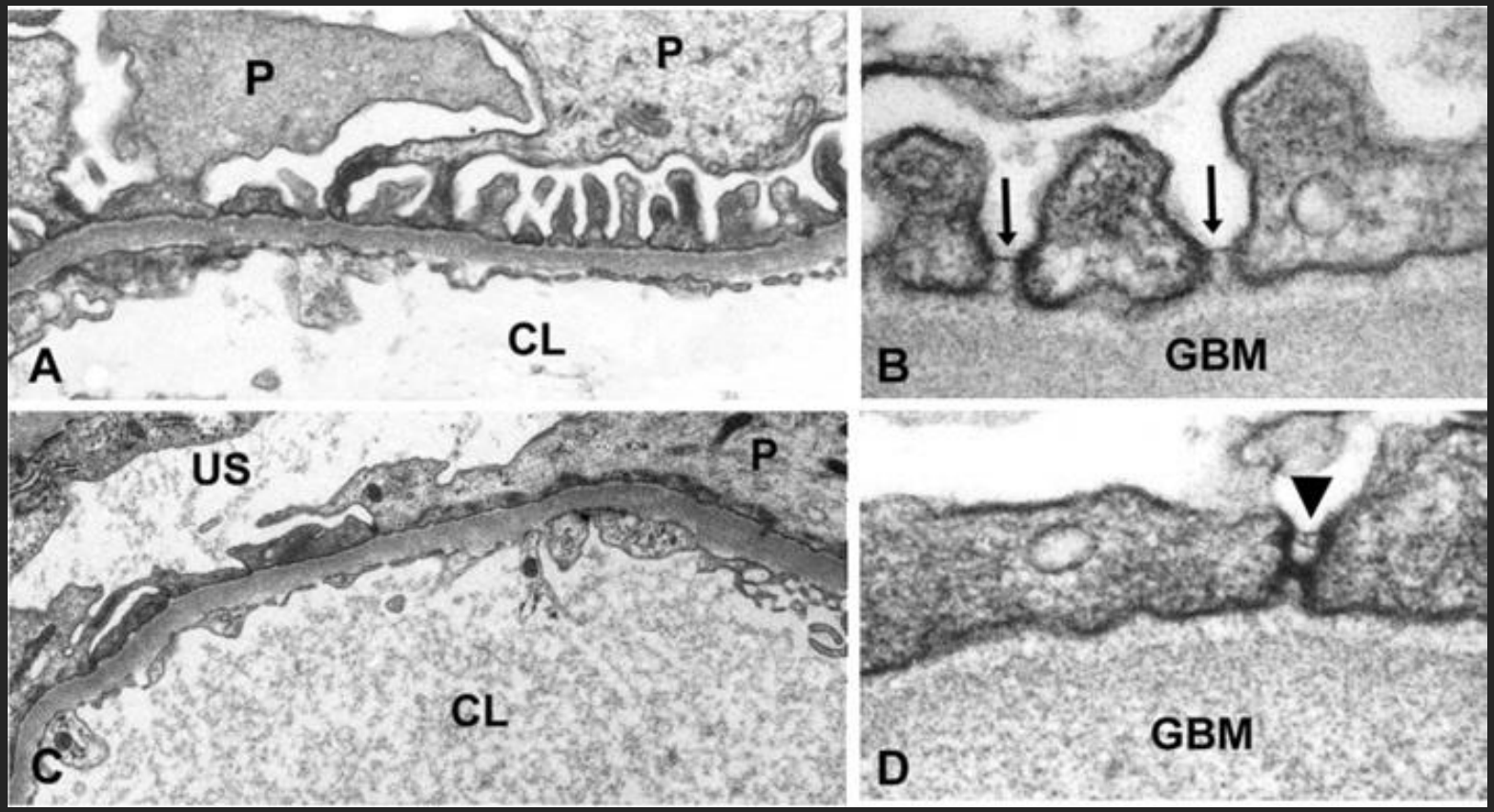


NORMAL GLOMERULUS



MINIMAL CHANGE

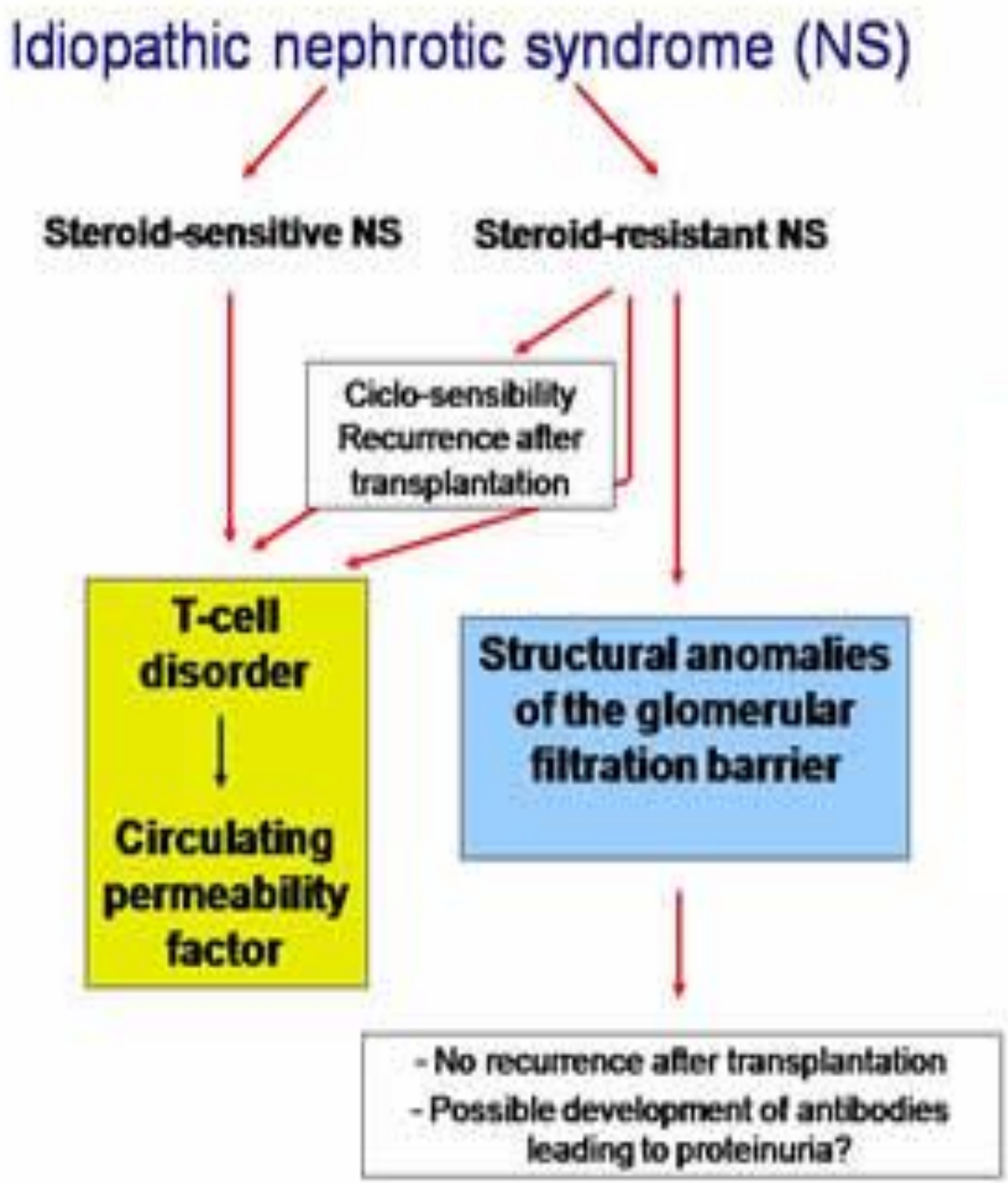
The glomerular capillary wall



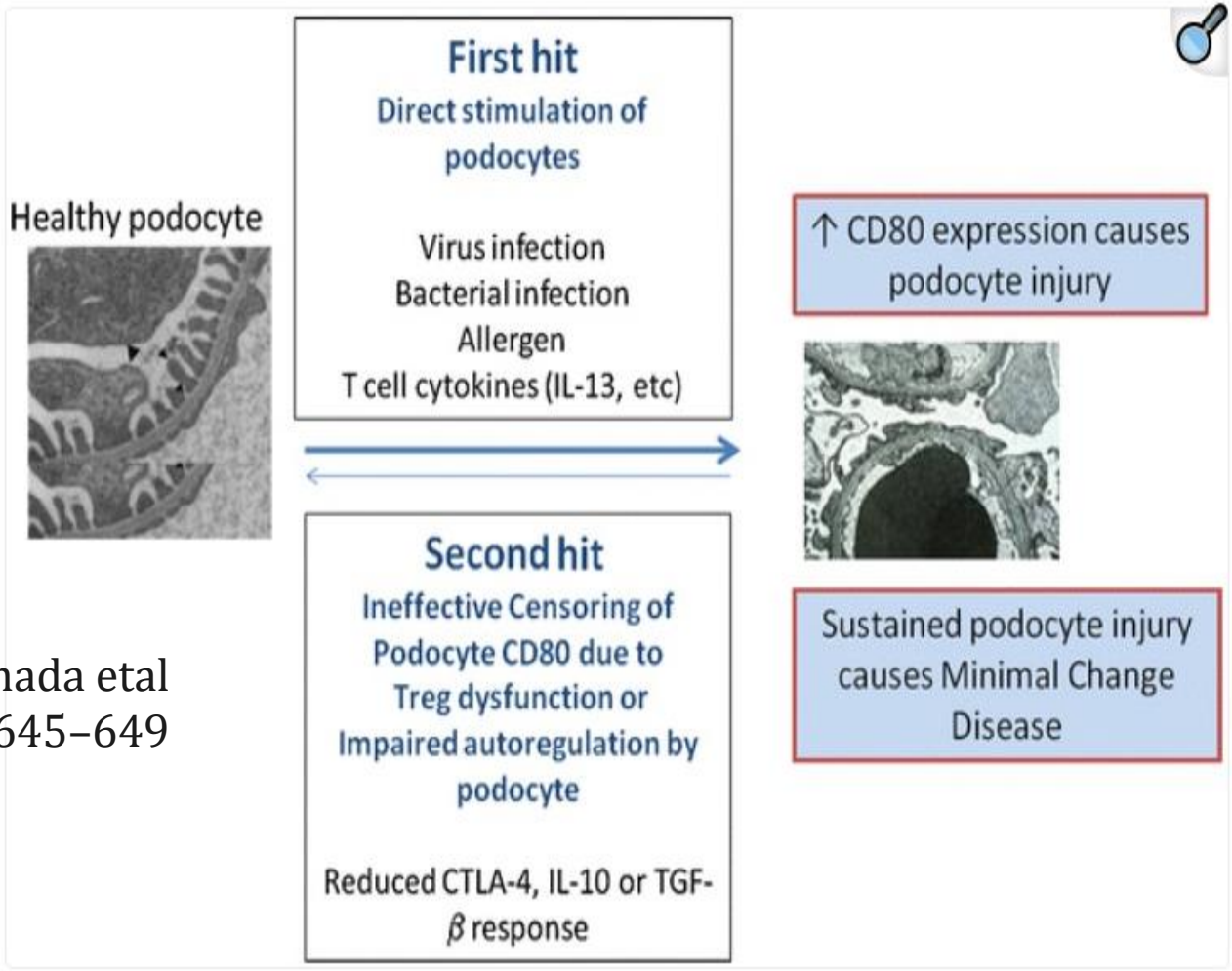
Normal

MCD

Van den Berg, Weening, Clinical Science (2004) **107, 125–136**


Idiopathic nephrotic syndrome (NS)
Steroid-sensitive NS
Steroid-resistant NS
Ciclo-sensibility
Recurrence after transplantation
T-cell disorder
Circulating permeability factor
Structural anomalies of the glomerular filtration barrier
- No recurrence after transplantation
- Possible development of antibodies leading to proteinuria?

two-hit" theory that included the induction of CD80 (or B7-1) and regulatory T-cell (Treg) dysfunction, with or without impaired autoregulatory function of the podocytes

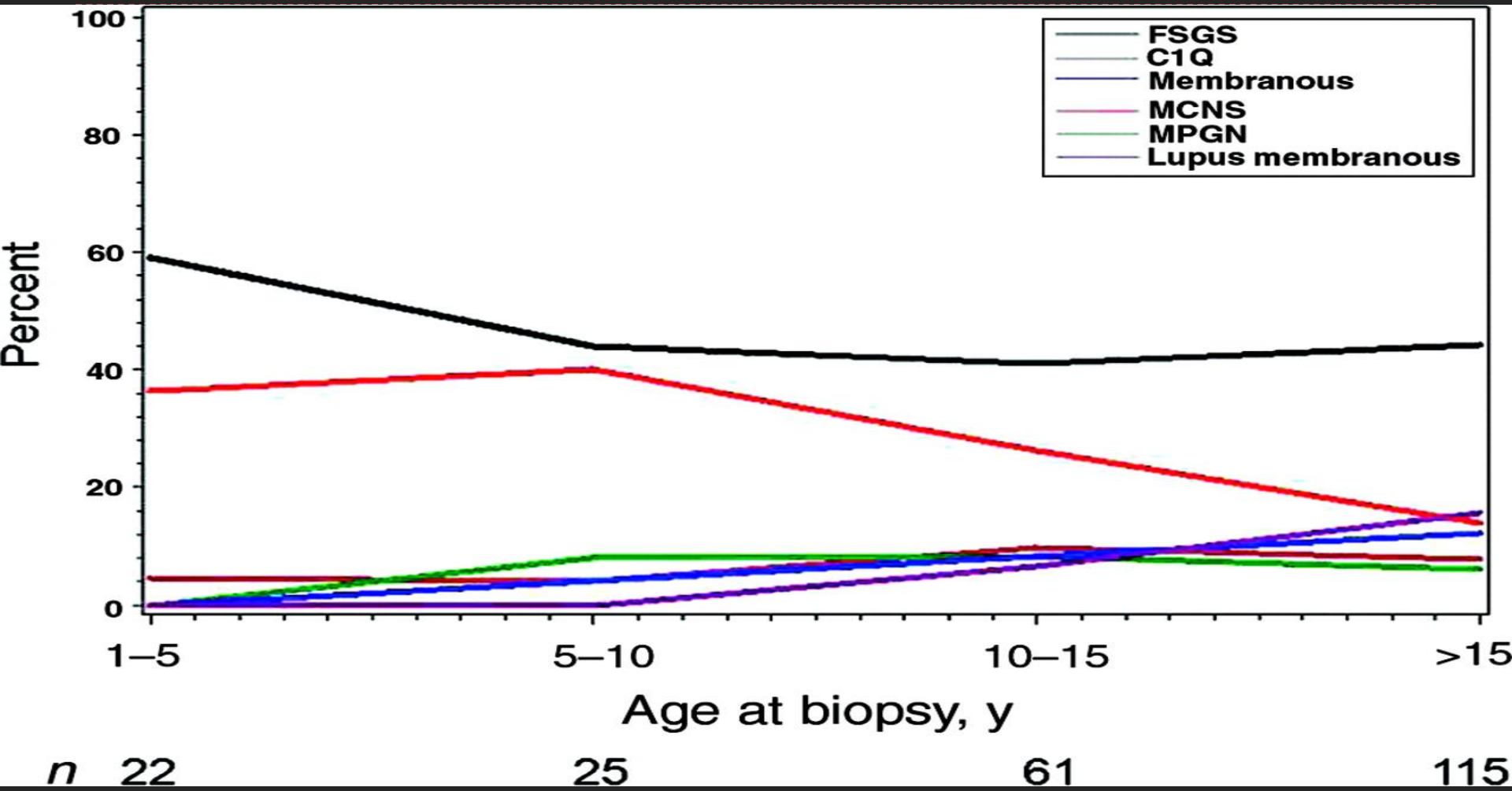


bhrol. Shimada etal
2011;26:645–649

Minimal Change Disease

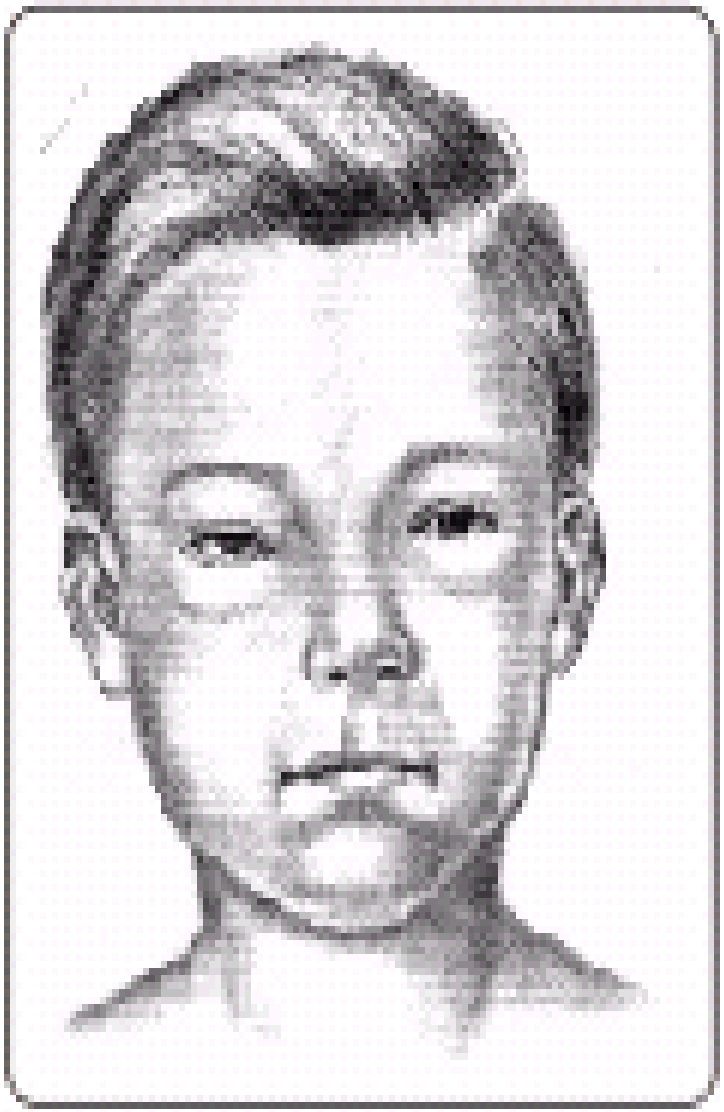
- 1-6 years of age (80% before 6yr of age)
- Absence of hypertension
- Absence of hematuria
- Normal complement levels
- Normal renal function

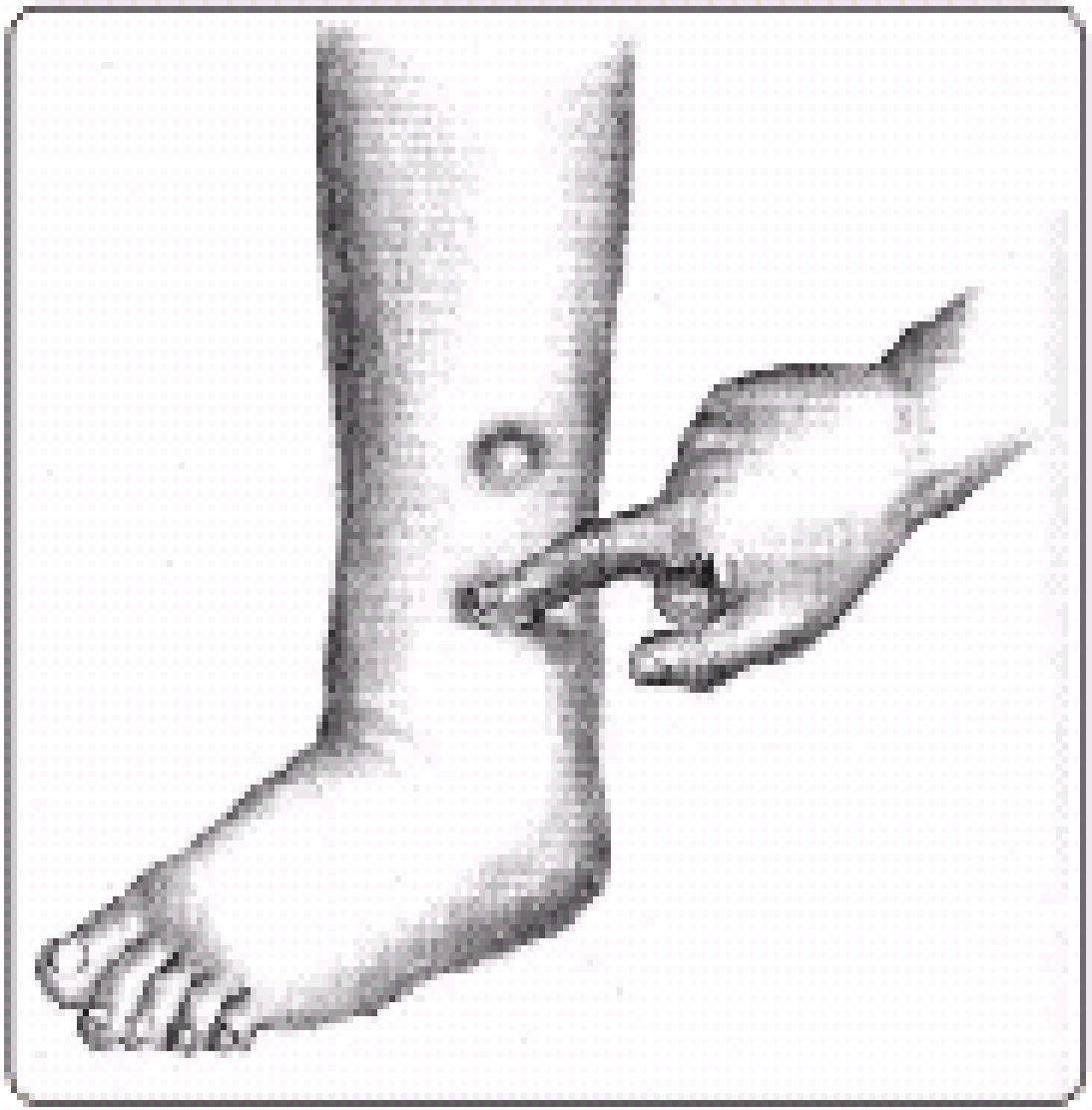
Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). n = number of patients.



Gipson D S et al. Pediatrics 2009;124:747-757

CLINICAL MANIFESTATIONS





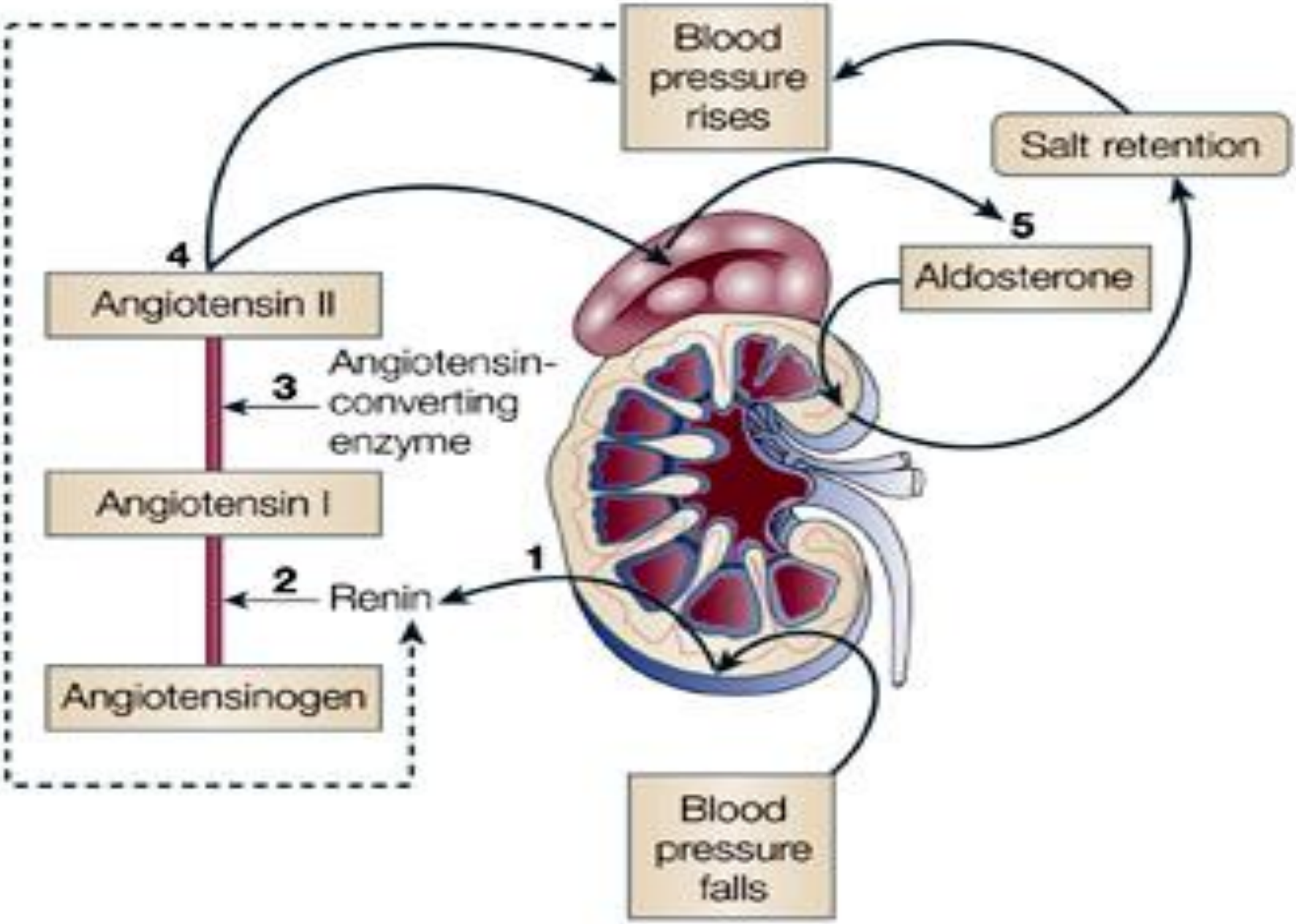
EDEMA

Mechanism of edema formation in nephrotic syndrome:

The underfill hypothesis

- high-grade proteinuria results in hypoalbuminemia, leading to a reduction in plasma oncotic pressure with consequent leakage of plasma water into the interstitium, generating edema. The resultant diminished intravascular volume which activates compensatory neurohormonal mechanisms such as the renin-angiotensin-aldosterone system (RAAS) and increased vasopressin with salt and water retention, thus exacerbating edema.

- Biomedicines 2024 Mar 3;12(3):569


Blood pressure rises
Salt retention
5
Aldosterone
4
Angiotensin II
3
Angiotensin-converting enzyme
Angiotensin I
1
2
Renin
Angiotensinogen
Blood pressure falls

Management

- Objectives :

Induce remission

Prevent relapses

Avoid side effects

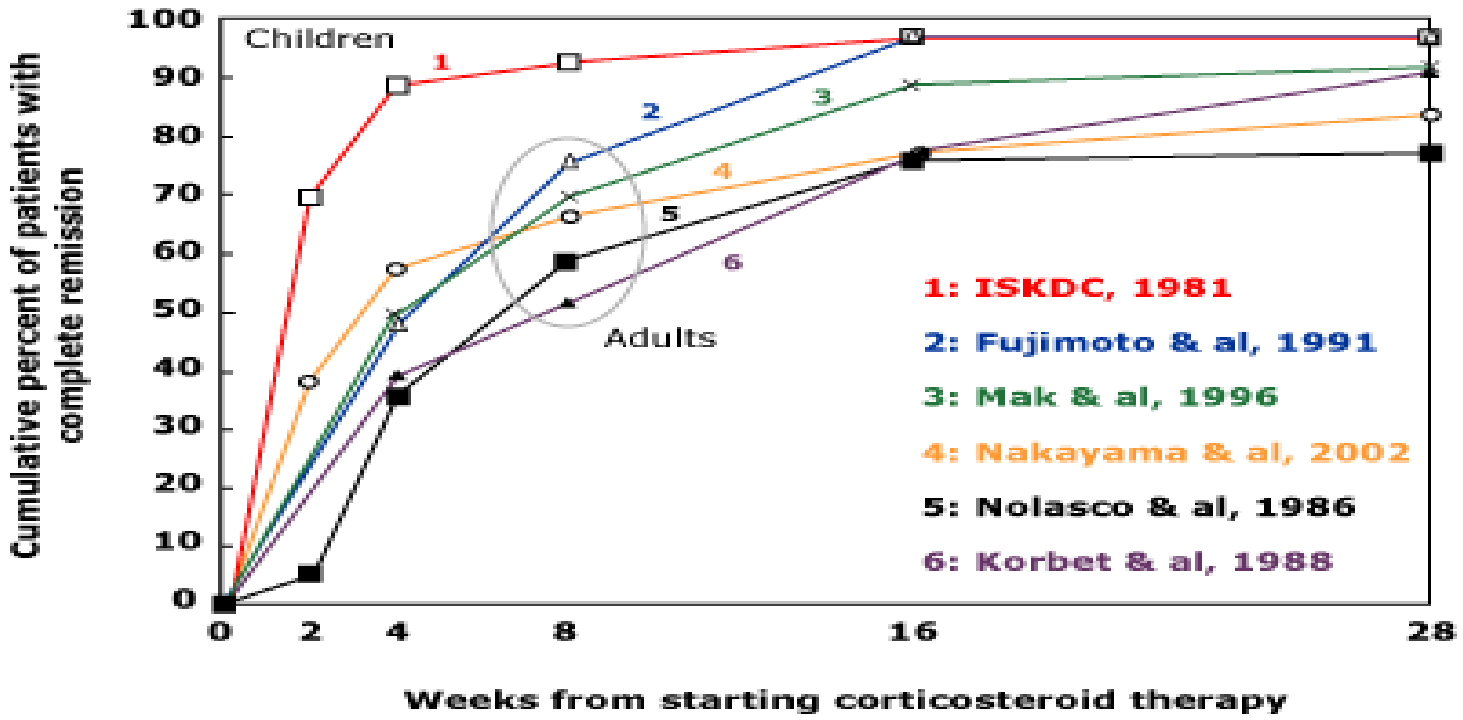
Initial Therapy vs Biopsy

- Older than 1 year and less than10 years of age .
- None of the following clinical findings are present: hypertension, gross hematuria, and a marked elevation in serum creatinine
- Normal complement levels

- High-dose steroid
  - 90% response in children
  - Recur 60% if steroid is stopped

50% relapse frequently or become steroid dependent .
50–70% of children being relapse-free at 5 years.
85% relapse free at 10 years.

Cumulative rate of remission in response to steroids in MCD



The rate of response of minimal change disease to corticosteroid therapy is lower in adults compared with children, and more prolonged therapy is required to achieve a remission.

Adapted with permission from: Nakayama, M, Katafuchi, R, Yanase, T, et al. Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. Am J Kidney Dis 2002; 39:503.

KDIGO guidelines 2021

Initial therapy

Recommendation 1

The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/ prednisolone 60 mg/m2 /d or 2 mg/kg/d (maximum 60 mg/d) for 4 weeks followed by alternate day prednisone/prednisolone, 40 mg/m2 , or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60 mg/m2 /d (maximum 60 mg/d) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m2 , or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks.glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) (1B).

Recommendation2:

For children with frequently relapsing and steroid-dependent nephrotic syndrome who are currently taking alternate-day glucocorticoids or are off glucocorticoids, we recommend that daily glucocorticoids 0.5 mg/kg/d be given during episodes of upper respiratory tract and other infections for 5–7 days

Practice Point:

1: The initial approach to relapse should include oral prednisone/prednisolone as a single daily dose of 60 mg/m2 /d or 2 mg/kg/d (maximum 60 mg/d) until the child remits completely for 3 days.

2: After achieving complete remission, reduce oral prednisone/prednisolone to 40 mg/m2 or 1.5 mg/kg (maximum 50 mg) on alternate days for 4 weeks.

3: For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses.(1C).

4.For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose alternate-day (optimally 0.5 mg/kg/d) can be prescribed to prevent relapse

Recommendation 3:

For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone (1B).

Practice Point 1:
Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs).
Coadministration of glucocorticoids is recommended for 2 weeks following initiation of glucocorticoid-sparing treatment.

Practice Point 2:
Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome

IPNA 2023

- We recommend the introduction of one of the following steroid-sparing agents (alphabetical order): calcineurin inhibitors (CNIs), cyclophosphamide (CYC), levamisole (LEV), and mycophenolate mofetil (MMF)/mycophenolic sodium (MPS) (grade A, strong recommendation)

IPNA

- When using CNIs, we recommend therapeutic drug monitoring to ensure optimal dosing (see below) (grade B, moderate recommendation).
- When using cyclosporin A (CsA), we recommend a starting dose of 3–5 mg/kg/day (maximum dose 250 mg) divided into 2 doses (every 12 h) to achieve trough blood levels of 60–100 ng/mL or 2 h post-dose levels of 300–550 ng/mL (grade B, moderate recommendation).
- When using tacrolimus (TAC), we recommend a starting dose of 0.1–0.2 mg/kg/day (maximum dose 10 mg) in 2 doses (every 12 h) to achieve trough blood levels of 3–7 ng/mL (grade C, moderate recommendation).

Primary immunosuppressive treatment of idiopathic NS IPNA

- We recommend administering oral PDN as a single morning dose for the treatment of the initial episode and subsequent relapses (grade B, moderate recommendation).
- We do not recommend a tapering schedule during alternate day dosing (grade A, strong recommendation).
- We suggest that PDN dose should be calculated by either weight or body surface area based on the estimated dry weight (grade B, weak recommendation).

Cyclophosphamide

Dose is 2-2.5 mg/kg/day for 12 weeks**.**

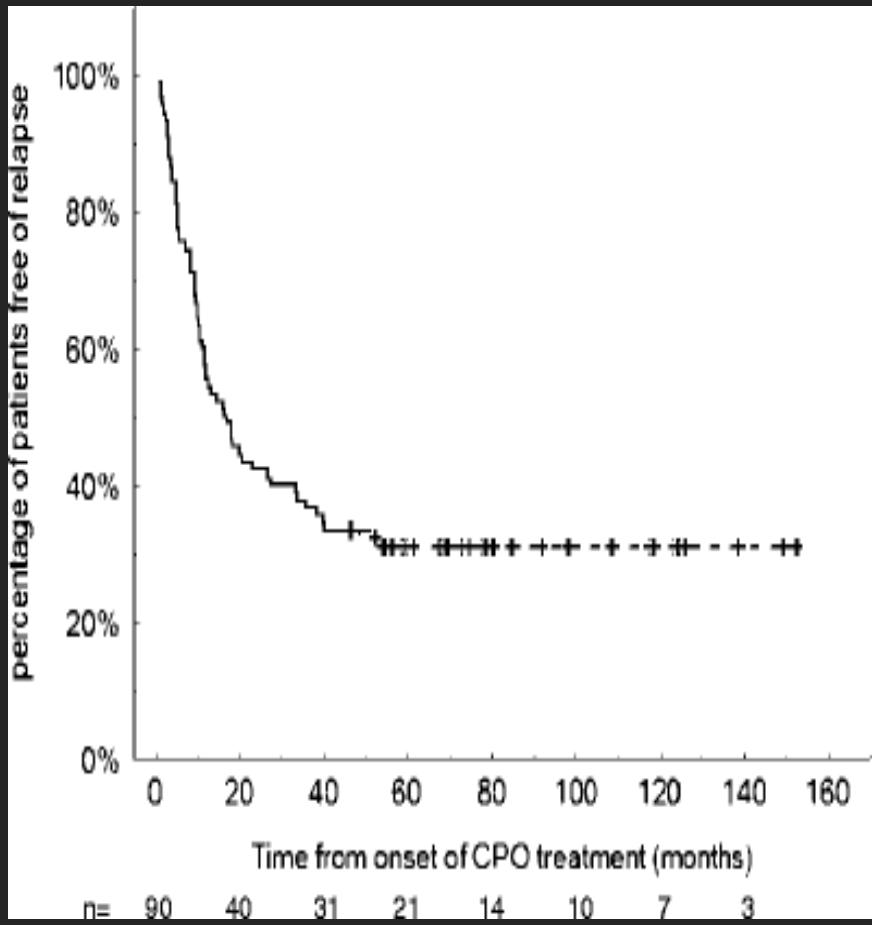
Prednisolone is co-administered at a dose of 1.5 mg/kg on alternate days for 4 weeks, followed by 1 mg/kg for the next 8 weeks.

Steroid therapy is tapered and stopped over the next 2-3 months.

Therapy with cyclophosphamide should be instituted preferably following remission of proteinuria.

Latta K, von Schnakenburg C, Ehrich JHH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol 2001; 16: 271-28

The percentage of patients in complete remission after CPO treatment was 57% (CI 47–68) at 1 year, 42% (CI 32–53) at 2 years, and 31% (CI 21–41) at 5 years. More than 80% of relapses occurred within 2 years of CPO initiation and no patients relapsed after 4.5 years in remission. Pediatric Neph.2011,Vol.20



Levamisole

Stimulate T-lymphocyte function, in NS was first described by Tanphaichitr et al. in an uncontrolled study.

in three trials levamisole significantly reduced the risk for relapse in comparison with prednisone alone.

The Cochrane Database…2001

- Trials showed that levamisole reduces the risk of a relapse during treatment (relative risk 0.60, 95% confidence interval 0.45–0.79). no conclusions can be drawn on the steroid-sparing effect, the long-term efficacy, and safety, as well as possible differences in efficacy in different subgroups of SSNS patients.

- JCJ. C. Davin M. P. Merkus
- Ped.Neph.2005, volume20,no 1,Pages 10-14

We recommend levamisole at a dose of 2–2.5 mg/kg given on alternate days (with maximum dose of 150 mg) after remission was achieved by PDN at recommended dose (grade B, moderate recommendation).

We recommend ANCA measurement at baseline, if available and every 6–12 months during therapy (grade X, moderate recommendation).

We recommend monitoring clinically for rash and measuring complete blood count and hepatic transaminases every 3–4 months (grade X, moderate recommendation)

IPNA 2023

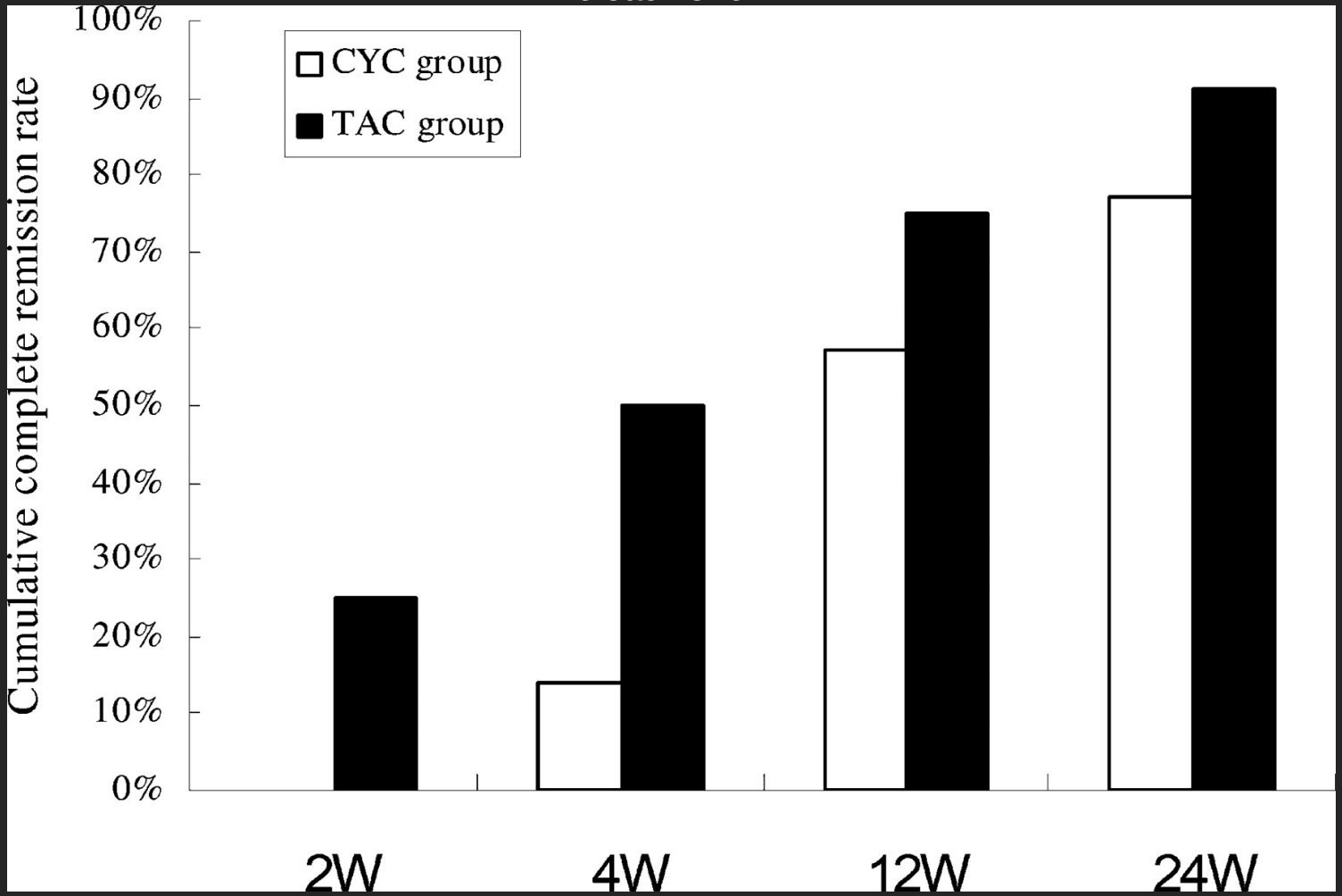
Tacrolimus

Tacrolimus is an alternative agent, administered at a dose of 0.1-0.2 mg/kg daily for 12-24 months. Side effects include hyperglycemia, diarrhea and rarely neurotoxicity (headache, seizures). The use of tacrolimus is preferred especially in adolescents, because of lack of cosmetic side effects. Blood levels of createnine and glucose should be estimated every 2-3 months.

Westhoff TH, Schmidt S, Zidek W, Beige J, van der Giet M. Tacrolimus in steroid-resistant and steroid-dependent nephrotic syndrome. Clin Nephrol 2006; 65: 393-400

- CsA or TAC was more effective than intravenous CPH (78% vs. 40%; risk ratio 1.98 [95% CI 1.25–3.13])
- TAC was more effective when compare with MMF in order to maintain remission (90% vs. 45%; risk ratio 2.01 [95% CI 1.32–3.07) . When CsAwas compared with placebo, no treatment, or MPDN, no differences were detected in the number of patients developing ESKD but event numbers were very small
- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome Pediatric Nephrology (2020) 35:1529–1561

Cumulative CR rates in patients receiving CYC or TAC. Although the rate of CR was not significantly different between the two groups at the end of 24 weeks therapy, the tendency of higher rate of CR was seen more often in the TAC group than CYC group before 4 weeks treatment.



Li X et al. Nephrol. Dial. Transplant. 2008;23:1919-1925

NDT Nephrology Dialysis Transplantation

MMF

Mycophenolate mofetil (MMF) inhibits T- and B-cell proliferation. mycophenolate mofetil (MMF) is effective in increasing the duration of remission in children with idiopathic NS

MMF

Long-term therapy with MMF results in significant steroid sparing and reduction in relapse rates in patients with SDNS. Therapy with MMF and tapering doses of prednisolone appears to be a promising intervention in children with SDNS

٢٠٠٣ .Am J Kidney Dis .Dec;42(6):1114-20

MMF versus CycA for remission maintenance in nephrotic syndrome

a multi-centre randomized controlled trial to compare the efficacy of mycophenolate mofetil (MMF) to that of cyclosporine A (CsA) in treating children with frequently relapsing nephrotic syndrome and biopsy-proven minimal change disease.

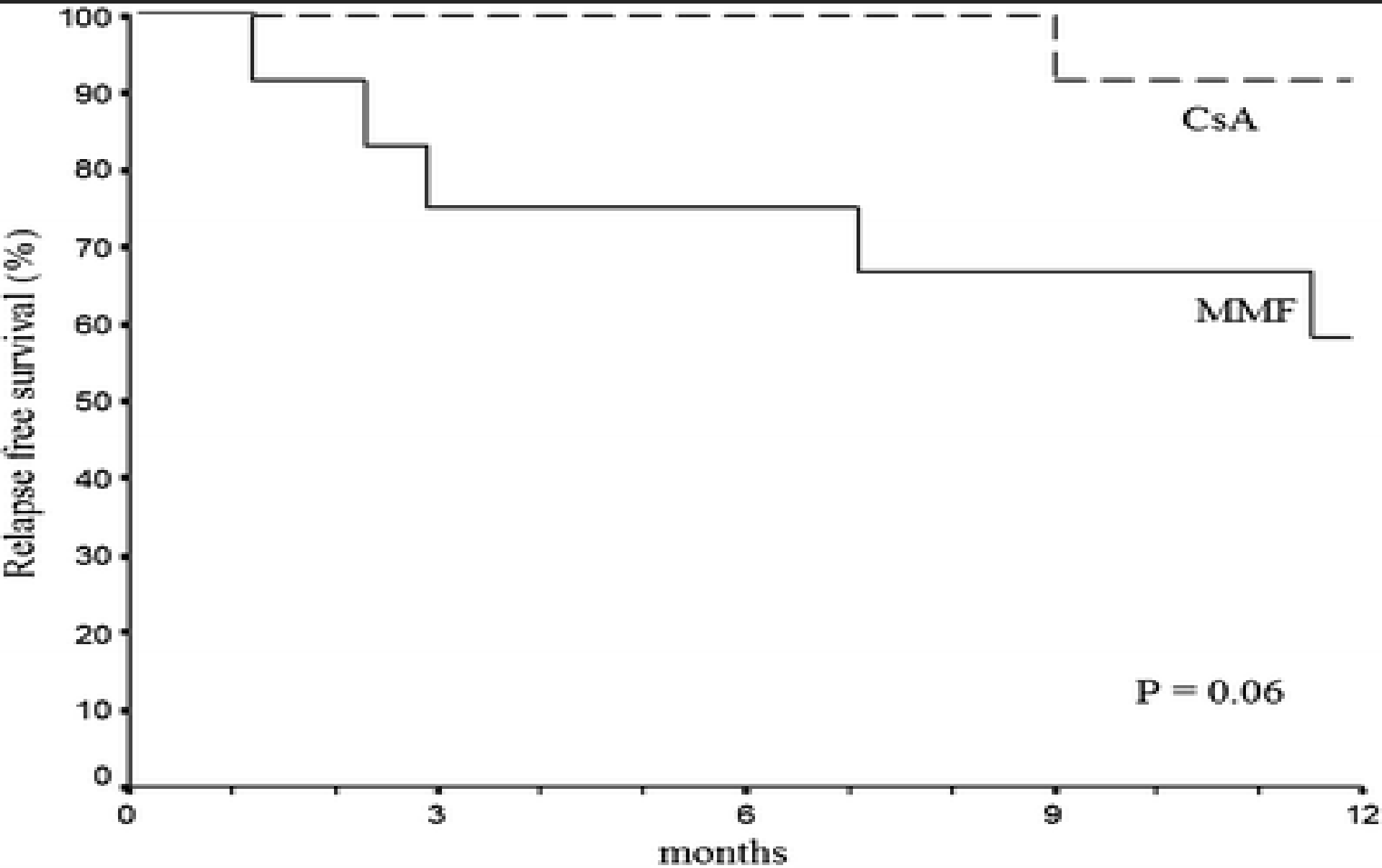
pediatric neph.,2008Volume23 ،Number11, Pages 2013-2020

Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome

- 12 CyC A group 5mg/kg for 12 months
- 12 MMF group 1200 mg/kg for 12 months
- . Relapse rate in the MMF group was 0.83/year compared to 0.08/year in the CsA group ($p = 0.08$).
- MMF has a favourable side effect profile compared to CsA; however, there is a tendency towards a higher relapse risk in patients treated with MMF.

Ped.Neph.2008, Volume 23, Number 11 Pages 2013-2020

- relapse rate in the MMF group (0.83/year±1.27 SD) the CsA group (0.08/year±0.29 SD),



Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. JAm Soc Nephrol. 2013 Oct;24

- a randomized, multicenter, open-label, crossover study comparing the efficacy and safety of a 1-year treatment with mycophenolate mofetil (MMF; target plasma mycophenolic acid trough level of 1.5-2.5 µg/ml) or CsA (target trough level of 80-100 ng/ml) in 60 pediatric patients with FR-SSNS

1Department of Pediatric Nephrology, Charité Universitätsmedizin Berlin CVK, Berlin, Germany

- More relapses per patient per year occurred with MMF than with CsA during the first year (P=0.03), but not during the second year (P=0.14). No relapses occurred in 85% of patients during CsA therapy and in 64% of patients during MMF therapy (P=0.06). However, the time without relapse was significantly longer with CsA than with MMF during the first year (P<0.05), but not during the second year (P=0.36). These results indicate that MMF is inferior to CsA in preventing relapses in pediatric patients with FR-SSNS, but may be a less nephrotoxic treatment option.

MMF is given at a dose of 800-1200 mg/m² along with tapering doses of prednisolone for 12-24 months The principal side effects include gastro-intestinal discomfort, diarrhea and leukopenia. Leukocyte counts should be monitored every 1-2 months; treatment is withheld if count falls below 4000/mm3.

Afzal K,etal. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. Pediatr Nephrol 2007; 22: 2059- 2065

Nephrotic Syndrome and Rituximab Facts and Perspectives

Pediatr Nephrol (2009) 24:1433–1438

Can induce remission in NS
Effective as sparing treatment
When effective no CD20=no relapse
No CD20 threshold for predicting relapse

Correct dosage……?
Long term therapeutic strategy……?

Vincent Guigonis, Pediatr Nephrol (2008) 23:1269–1279

Mechanisms of action

- Immune –mediated (B cell-dependent) mechanisms leading to disappearance of B-cells from peripheral circulation:
  - Apoptosis – programmed cell death (PCD)
  - Antibody-dependent cytotoxicity (ADCC)
    - Cells bearing Fcγ receptors (NK, macrophages, monocytes)
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cellular phagocytosis (ADCP)
  - Other (lysosome-dependent non-apoptotic cell death, adaptive cell immunity – activated T cells and dendritic cells)

- Non-immune (B cell-independent) mechanisms:
  - The RTX/OFA bind sphingomyelin phosphodiesterase acid-like 3b protein (SMPDL-3b) and acid sphingomyelinase (ASM) on the surface of podocytes

Ravani Et al, Clin J Am Soc Nephrol 2016; 11: 710-720

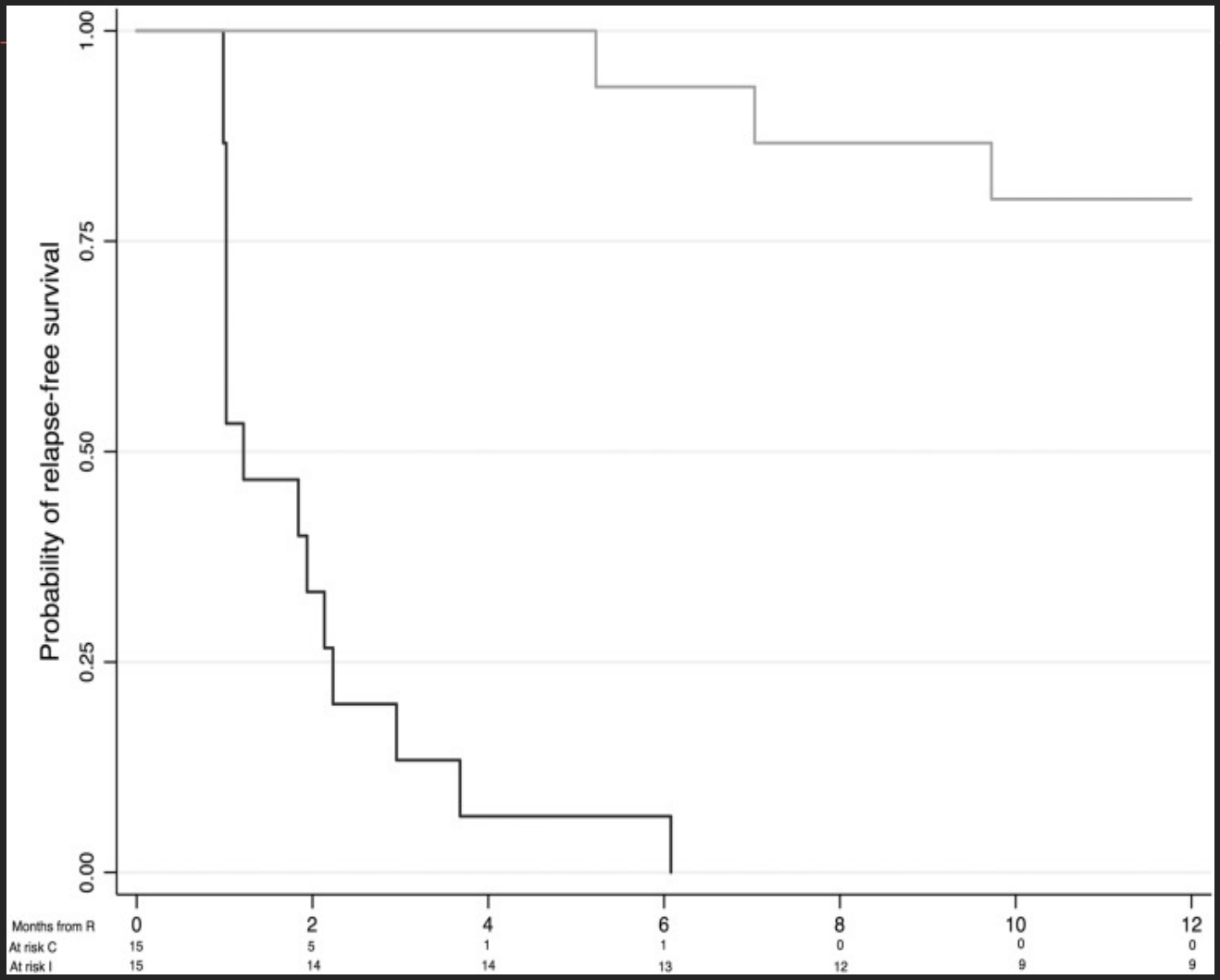
Therapeutic indications and rationale

- Target populations:
  - Steroid-dependent NS
  - Frequently relapsing NS
  - Steroid/treatment resistant NS

- Therapeutic goals:
  - Minimize steroid toxicity and morbidity
  - Minimize calcineurin inhibitor toxicity
  - Induce long-lasting remission
  - Induce remission in treatment-resistant patients

an open-label, randomized controlled trial at four sites in Italy tested whether rituximab is non inferior to steroids in maintaining remission in juvenile SDNS. enrolled children age 1-16 years who had developed SDNS in the previous 6-12 months and were maintained in remission with high prednisone doses . participants were assigned randomely to continue prednisone alone for 1 month (control) or to add a single intravenous infusion of rituximab (375 mg/m. Prednisone was tapered in both groups All but one child in the control group relapsed within 6 months; median time to relapse in the rituximab group was 18 months (95% confidence interval, 9 to 32 months).

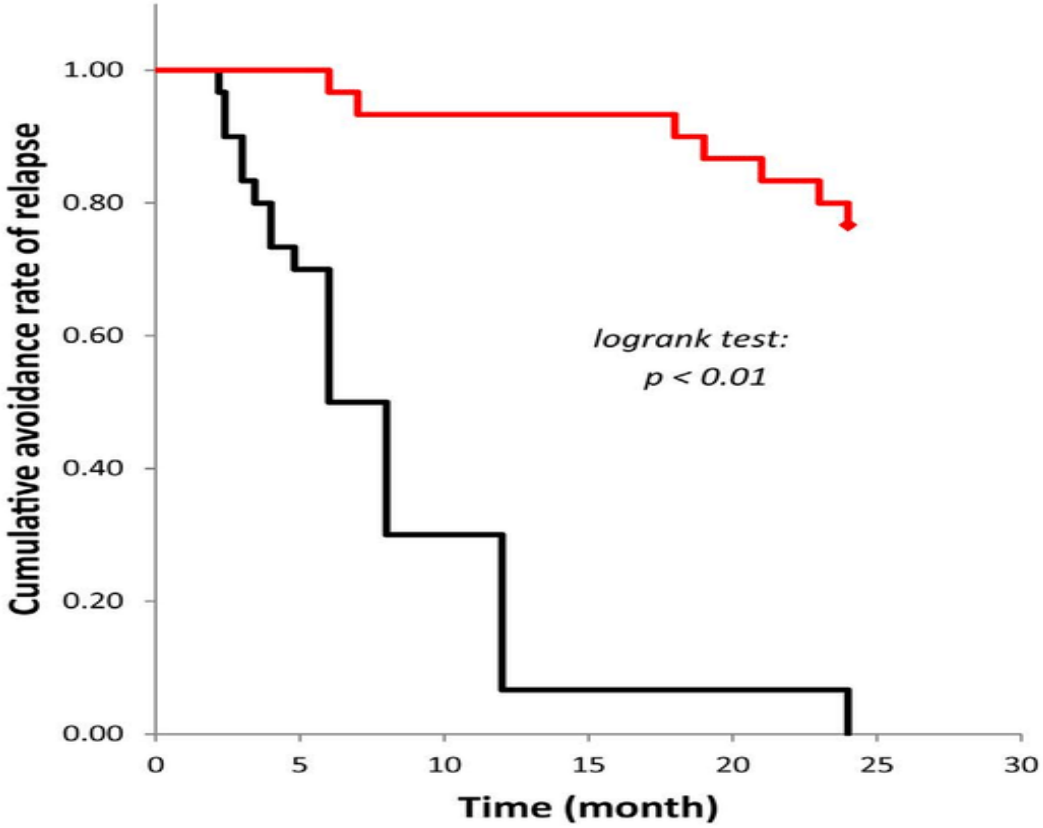
Rituximab in Children with Steroid-Dependent Nephrotic Syndrome: A Multicenter, Open-Label, Noninferiority, Randomized Controlled Trial

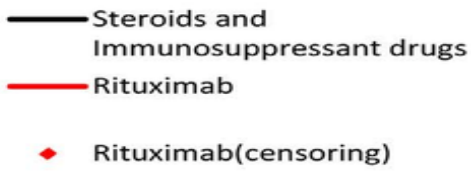


One-year relapse-free survival by treatment group in the prednisone (control; dark gray) and rituximab (intervention; light gray) groups. The risk of relapse was reduced by 98% in children treated with rituximab J Am Soc Nephrol 2015

Rituximab therapy - SDNS

(a)



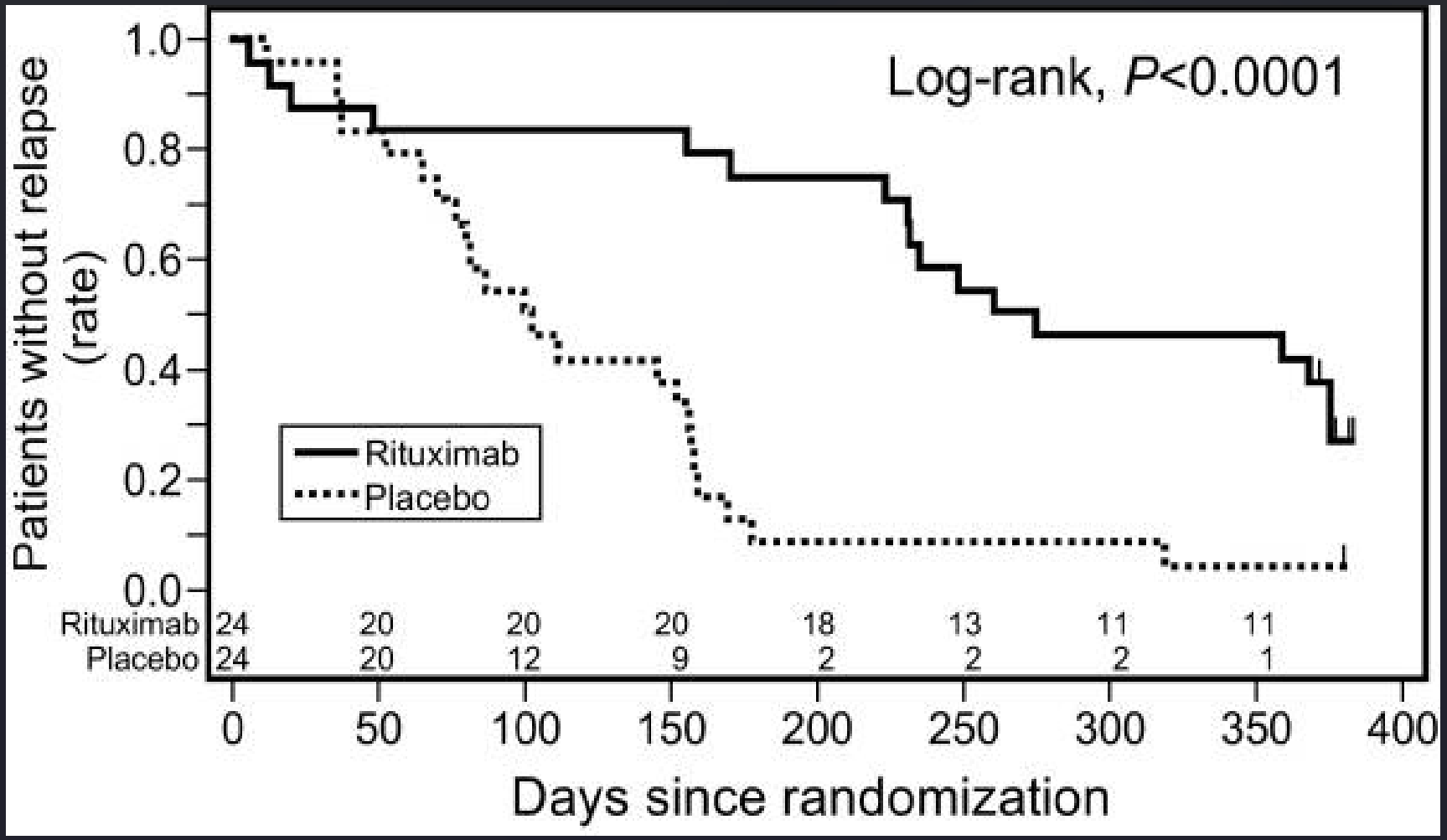


(b)

Follow up months	0	5	10	15	20	25
- Steroids and Immunosuppressant drugs (n)	30	21	9	2	2	0
- Rituximab (n)	30	30	28	28	27	24

Kim et al, Kidney Res Clin Pract 2017; 36(3): 257-263

Steroid-sensitive nephrotic syndrome relaps free survival probability



Iijima et al, Pediatr Nephrol 2018; 33: 1449-1455

Side effects

Rituximab is associated with several serious adverse events, including fatal hepatitis induced by rituximab reactivation of hepatitis B virus and progressive multifocal Leukoencephalopathy , fulminant myocarditis , pneumocystis pneumonia, immunemediated ulcerative colitis and agranulocytosis.

Rituximab IPNA 2023

We recommend using RTX as a steroid-sparing agent in children with FRNS or SDNS who are not controlled on therapy after a course of treatment with at least one other steroid-sparing agent at adequate dose, especially in case of non-adherence (grade B, moderate recommendation). This is especially preferable, both in terms of safety and of effectiveness, above the age of 7–9 years (grade C, weak recommendation)

What are the treatment recommendations for children with steroid resistant NS

Indications for genetic testing and renal biopsy

- We recommend, if available, that genetic testing be performed in all children diagnosed with primary SRNS
- We suggest giving priority to genetic testing in familia cases (family history of proteinuria/hematuria or CKD of unknown origin), cases with extra-renal features, and those undergoing preparation for renal transplantation
- We recommend a kidney biopsy in all children diagnosed with SRNS, except in known infection or malignancyassociated secondary disease or potentially in patients with familial and/or syndromic cases or genetic causes ofSRNS
- We do not recommend performing genetic testing in patients

with initial steroid sensitivity who subsequently develop steroid resistance later in their disease course .

- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome Pediatric Nephrology (2020) 35:1529–1561

First-line immunosuppressive treatment in children with SRNS *IPNA guideline*

- We recommend that CNI (cyclosporine or tacrolimus) should be the first-line immunosuppressive therapy inchildren with SRNS and started once the diagnosis is
- We suggest tapering PDN treatment once diagnosis of SRNS is established and discontinuing PDN therapy after 6 months .
- We recommend withholding or delaying CNI treatment in patients with an eGFR < 30 ml/min/1.73 m2, AKI, and/oruncontrolled hypertension .
- We recommend withholding CNI and stopping PDN treatment in patients with evidence for a monogenic form of SRNS .
- When CNIs are not available or unaffordable, we suggestusing cyclophosphamide (CPH) intravenous or po with or without high-dose steroids .

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome Pediatric Nephrology (2020) 35:1529–1561

Alkylating agents

- When compared with PDN/placebo, CPH showed no difference in the outcome of complete remission (risk ratio 1.06 95% CI 0.61–1.87) [60, 61]. Overall, 36% children on CPH compared with 35% on PDN achieved complete remission

- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome Pediatric Nephrology (2020) 35:1529–1561

- Patients with SRNS who fail to achieve at least partial

remission with CNIs We suggest administering two rituximab infusions at a dose of 375 mg/m2 per infusion in order to reduce the CD19 cell count below 5 per microliter or 1% (usually 1–2 infusions within 2 weeks)

- IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome Pediatric Nephrology
- (2020) 35:1529–1561

Rituximab in SRNS

Rapid remission of steroid and mycophenolate mofetil (MMF)-resistant Minimal Change Nephrotic Syndrome after Rituximab therapy.

(few reports)

Nephrol Dial Transplant. 2008 Jan;23(1):377-80. Epub 2007 Nov 2

- Observational studies showed complete remissions in ~ 30% of patients treated with rituximab as a rescue therapy for multidrug-resistant SRNS

Calcium, magnesium, and vitamin D supplementations

Administering oral calcium if hypocalcemia exists based on ionized and/or albumin-corrected calcium levels (grade C, weak recommendation).

Supplementing with cholecalciferol or ergocalciferol if 25-OH-vitamin D levels are low (< 30 ng/mL) (grade C, moderate recommendation).

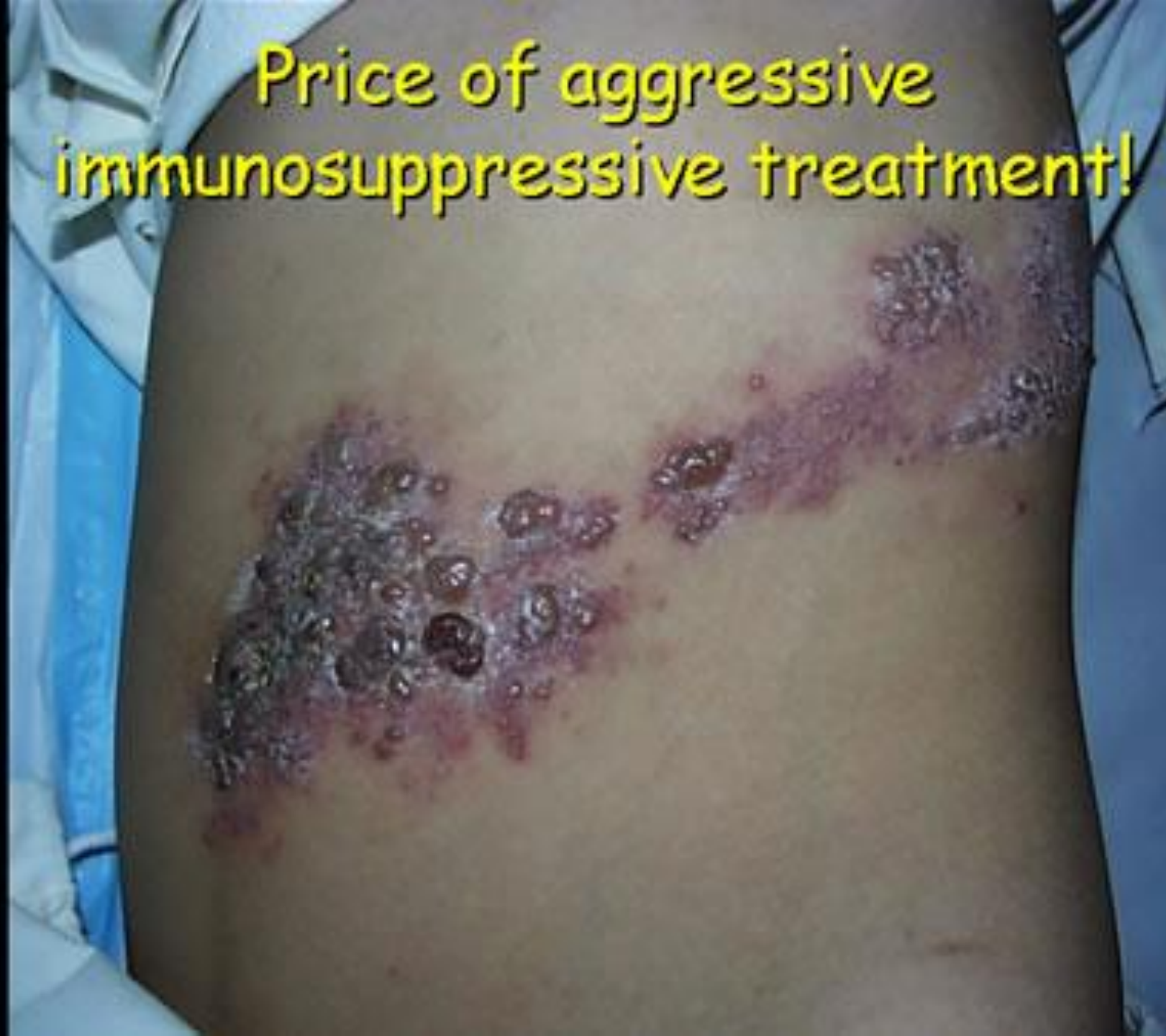
Administering oral magnesium in case of symptomatic hypomagnesemia (grade D, weak recommendation).

IPNA Guidelines 2020

SUMMARY AND RECOMMENDATIONS

- In children with nephrotic syndrome (NS) who have a high probability of having MCD empiric therapy with oral prednisone is recommended thus avoiding renal biopsy.
- Children with steroid-responsive NS, who are frequent relapsers and/or are steroid dependent, , steroid sparing agents are recommended.

- Ten percent of children will fail to respond to steroid therapy. are at increased risk for developing end-stage renal disease.
- Mutations of the NPHS2 gene and WT1 gene account for 20 percent of cases of steroid-resistant NS . immunosuppressive therapy is not recommended.


Price of aggressive
immunosuppressive treatment!

NOCTURNAL ENURESIS

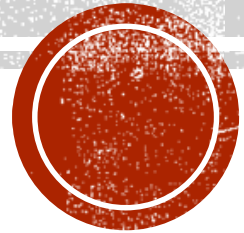
IPNA
International Pediatric Nephrology Association

FIRST IPNA TEACHING COURSE , JORDAN 5/12/5024

NOCTURNAL ENURESIS

- Terminology
- Epidemiology and natural history
- Pathogenesis
- Causes
- Evaluation
- Management

TERMINOLOGY



TERMINOLOGY

- Refers to discrete episodes of urinary incontinence during sleep in children ≥5 years of age.

- Enuresis is divided into monosymptomatic and non-monosymptomatic forms, although the pathogenesis and evaluation of the two forms overlap.

- Monosymptomatic nocturnal enuresis usually is divided into primary and secondary forms.

- Non-monosymptomatic enuresis is defined as enuresis in children with other lower urinary tract symptoms.

MONOSYMPTOMATIC NOCTURNAL ENURESIS

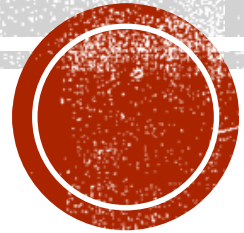
- Primary : in which the child has never achieved a satisfactory nighttime dyness , accounts for about 80% of the cases

- Secondary :in which the child develops enuresis after at least six months of nighttime dryness .

NON-MONOSYMPTOMATIC ENURESIS

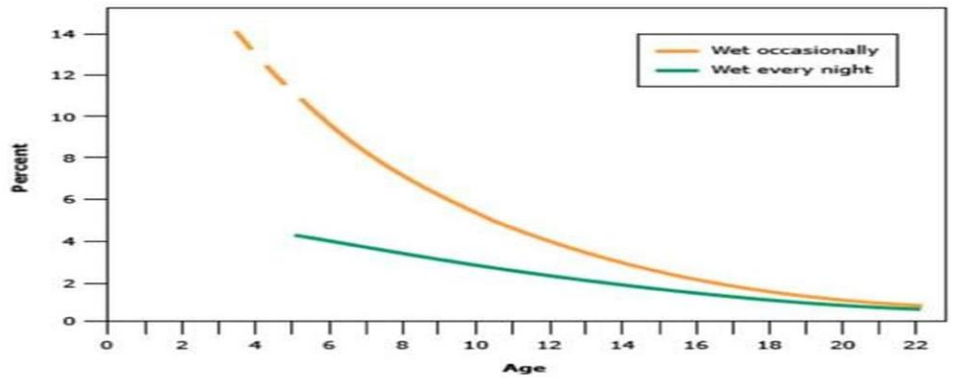
- Consistently increased or decreased frequency of voiding
- Urgency
- Hesitancy
- Daytime incontinence
- Straining
- Weak stream
- Intermittancy
- Holding maneuvers
- Genital or urinary tact pain

EPIDMIOLGY



EPIDEMIOLOGY

Epidemiology and prognosis of monosymptomatic enuresis



Reproduced with permission from: Nevéus T, Eggert P, Evans J, et al. Evaluation and treatment of monosymptomatic enuresis - a standardisation document from the International Children's Continence Society (ICCS). Copyright © 2009 ICCS.

Graphic 58087 Version 3.0

- Monosymptomatic nocturnal enuresis is common in children. The prevalence varies according to age
  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

- Monosymptomatic nocturnal enuresis is twice as common among male compared with female individuals. It resolves spontaneously at a rate of approximately 15 percent per year

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

PATHOGENESIS

PATHOGENESIS

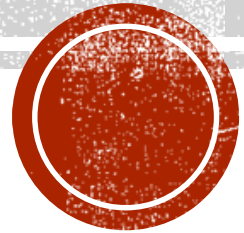
- Maturational delay - In almost all cases, monosymptomatic nocturnal enuresis resolves spontaneously .
- Genetic factors: There is a genetic tendency toward nocturnal enuresis. The concordance among monozygotic twins is almost twice that among dizygotic twins (68 versus 36 percent.When one parent has a history of prolonged nighttime wetting, approximately 50 percent of the offspring are affected; when both parents have a history, approximately 75percent of offspring are affected.

- Nocturnal polyuria and Antidiuretic horomone : Increased nighttime urine output appears to play an important role in nocturnal enuresis.

- Small bladdar capacity :At birth, bladder volume is approximately 60 mL (2 ounces); bladder volume increases with age at a relatively steady rate of approximately 30 mL (1ounce) per year until 10 years of age, Children with NE have been noted to have smaller bladdar capacity .

- Detrusor overactivity:They may have a defect in the circadian rhythm of detrusor inhibtion and pelvic floor activity .

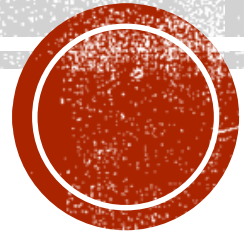
PATHOLOGICAL CAUSES OF NE



CAUSES

- Bladder dysfunction (usually associated with daytime symptoms)
- Urinary tract infection
- Chronic kidney disease associated with poor growth or weight loss, hypertension, abnormal urinalysis.
- Posterior urethral valves (associated with incomplete bladder emptying).
- Obstructive sleep apnea .
- Fecal incontinence and constipation
- Sickle cell disease (may be associated with positive family history, abnormal urinalysis decreased specific gravity, hematuria, proteinuria])
- Seizures (associated with paroxysmal,stereotyped behaviors)
- Diabetes mellitus (associated with polyuria,polydipsia, weight loss, and glucosuria)
- Arginine vasopressin disorders, previous called diabetes insipidus
- Spinal dysraphism (may be associated with abnormal overlying skin)
- Pinworms (associated with perianal excoriation)

EVALUATION



EVALUATION /HISTORY

- Daytime wetting or lower urinary tract symptoms including urgency,holding maneuvers, interrupted micturition,weak stream, and straining. Urologic and neurologic disorders are more common among children with daytime symptoms.

- Whether the child ever had a prolonged period of dryness (ie, six months).

- Frequency and trend of nocturnal enuresis (eg,number of wet nights per week or month, number of episodes per night, time of episodes).

- Fluid intake diary. Consuming the majority of fluids during the late afternoon and evening may be associated with nocturnal polyuria

- Stooling history and history of soiling

- Medical history eg, review of systems for symptoms of sleep apnea, diabetes, sickle cell disease, urinary tract infection [UTI], gait or neurologic abnormalities).

- Family history of nocturnal enuresis.

- Social history (particularly important in secondary enuresis).

- Assessment of how the problem has affected the child and the family

Important aspects of the history for a child with enuresis

Historical feature	Possible significance
Daytime symptoms	Dysfunctional voiding
Lower urinary tract symptoms (voiding ≥8 or ≤3 times per day, hesitancy, straining, weak stream, intermittent stream, incomplete emptying, postmicturition dribble, genital or lower urinary tract pain)	Dysfunctional voiding or anatomic abnormality (eg, posterior urethral valves)
Prolonged period of dryness (>6 months)	Secondary enuresis more often associated with psychologic comorbidities
Frequency of episodes	Nightly enuresis is associated with persistence
Change in frequency of episodes over time	The natural history is of spontaneous resolution
Approximate volume of enuretic void	Estimate of bladder capacity
Fluid intake diary	May suggest etiology of nocturnal polyuria (increased afternoon/evening fluid intake; diabetes mellitus; diabetes insipidus; psychogenic polydipsia)
Stooling history	Constipation may contribute to decreased bladder capacity
Review of systems	May identify previously undiagnosed medical condition that contributes to enuresis
- Snoring	- Obstructive sleep apnea
- Weight loss, fatigue	- Diabetes, kidney disease
- Gait abnormalities	- Spinal dysraphism
- Staring spells	- Seizure disorder
- Perianal itching, vulvovaginitis	- Pinworms
- Excessive thirst, nighttime drinking	- Diabetes, kidney disease, psychogenic polydipsia
Family history of enuresis	Genetic factors may be contributing

Voiding and fluid intake diary

Name: _____ Date of birth: _____

Date: _____

Voiding diary

Time	Urine volume (mL)	Straining/ interrupted stream	Wetting: Damp/wet?	Urge	Comments/observations

Fluid intake diary

Time	Fluid intake (mL)

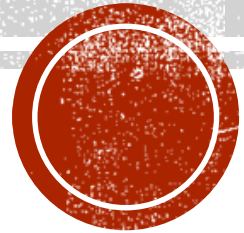
Instructions to caregivers or primary care provider on completing the voiding/drinking diary:

1. Fill out this chart on a day without school or kindergarten (weekend or holiday). This should start on one morning and continue through to the next morning. If possible, fill out the diary two days in a row, as this is even more reliable.
2. Talk to the child beforehand. They should tell you when they want to go to the toilet and should empty the urine into a measuring cup. Please measure the amount of urine and record it with the time of day. You do not have to collect the urine but can

EVALUATION /PHYSICAL EXAMINATION

- The physical examination of the child with primary monosymptomatic nocturnal enuresis usually is normal.
- Poor growth and/or hypertension may indicate renal disease.
- Tonsillar hypertrophy or "adenoid facies may indicate obstructive sleep apnea.
- Detection of wetness in the undergarments is a sign of daytime incontinence.
- Palpation of stool in the abdomen suggests constipation
- Detection of incomplete bladder emptying by percussion and/or palpation or observation of voiding that demonstrates slow urinary stream.
- Perineal excoriation or vulvovaginitis may indicate pinworm infection.
- Abnormalities of the lumbosacral spine may indicate occult spinal cord abnormalities .

MANAGMENT



MANAGEMENT/ BEHAVIORAL AND MOTIVATIONAL COUNSELING

- In primary monosymptomatic enuresis, the mainstay of management is education, and reassurance that no treatment is necessary.
- Void first thing in the morning and immediately before bed. ·
- Frequent voiding (aim for every 2 to 3 h, or 5 to 7 times/ day).
- Wearing a vibrating watch or timer may help decrease daytime LUTS ·
- Optimal posture for girls is to sit upright in the middle of the toilet with feet touching the ground or on a footstool .
- Fluid intake · Drink liquids in the mornings and afternoons, and drink less after dinner. Some studies recommend 80% of total daily fluid intake before 4:00 pm. ·
- Avoid caffeinated drinks .
- Address constipation. Active dietary management, including medication and nutritionist referral, may be needed, with one soft bowel movement per day being the goal.

MANAGEMENT/ ACTIVE THERAPIES/ALARM THERAPY

- Children and families with persistent distress despite education and reassurance, shared decision-making with patients and families should inform the use of active therapies.
- Alarms are used since the 1930s, the enuresis alarm wakes a sleeping child with a moisture sensor at the initial stage of voiding.
- Alarm studies have demonstrated varying success rates (success being defined as 14 consecutive dry nights), typically with an initial response of 60% to 80%, although up to one-half of children may relapse when alarm use is discontinued
- Nightly enuresis is more resistant to alarm therapy, while infrequent enuresis (less than once per week) does not allow sufficient opportunity for appropriate training. At least two episodes per week should be baseline for alarm use to be effective.

MANAGEMENT/ ACTIVE THERAPIES/DESMOPRESSIN

- Desmopressin is a synthetic vasopressin analog that has been used for enuresis since the 1970s.
- Desmopressin works by decreasing both urine volume and intravesical pressure at night.
- Desmopressin is effective for treating enuresis with a range of underlying mechanisms and may be especially useful for nocturnal polyuria with normal (rather than low) daytime bladder capacity (based on history, voiding diary use, and urine measurement).
- Daily use results in a full response in 30% of children, with another 40% experiencing a partial response . The relapse rate when medication is discontinued is up to 70%
- The usual melt dose is 120 mcg administered 30 to 60 min before sleep. The anti-enuretic effect has been observed soon after medication initiation but, if dryness is not achieved, the dose can be doubled to 240 mcg. The maximum dose for desmopressin is 360 mcg.
- Guidelines for continuous use of desmopressin suggest treatment for 3 months at a time, then reassessment with a medication break to determine resolution of enuresis symptoms.

RECOMMENDATIONS FOR CLINICIANS

- Education and reassurance are the mainstays of management for monosymptomatic or ‘simple’ enuresis (MSE).
- Conduct a history and physical exam to determine that enuresis is the correct diagnosis, to distinguish monosymptomatic from non-monosymptomatic enuresis, and to rule out common comorbidities, especially constipation, developmental and psychiatric conditions, and upper airway obstruction.
- lower urinary tract symptoms (LUTS) may not be evident unless clinicians specifically ask about them. When LUTS are present, they should be addressed first or concurrently with treatment for enuresis. Referral to urology is appropriate when symptoms are severe, numerous, or atypical.
- Work with patients and families to determine whether treatment is necessary or desired. Consider the impact of enuresis on the child’s self-esteem, and family factors such as motivation, support, and available resources.
- Patients experiencing distress related to their enuresis may respond well to active treatment, such as an enuresis alarm and/or the intermittent use of desmopressin.


THANK YOU

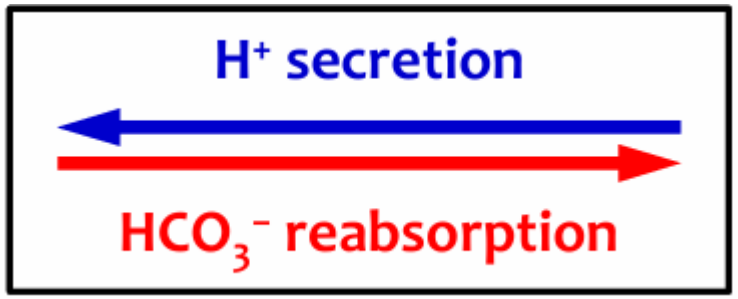
Renal tubular acidosis
the first IPNA teaching day withcollaborationn with the Hashemite university Jordan
5/12/2024

Renal tubular acidosis

DR REEM HANI AL-HADIDI
COSULTANT PEDIATRIC NEPHROLOGY
HUH-MOH
2024

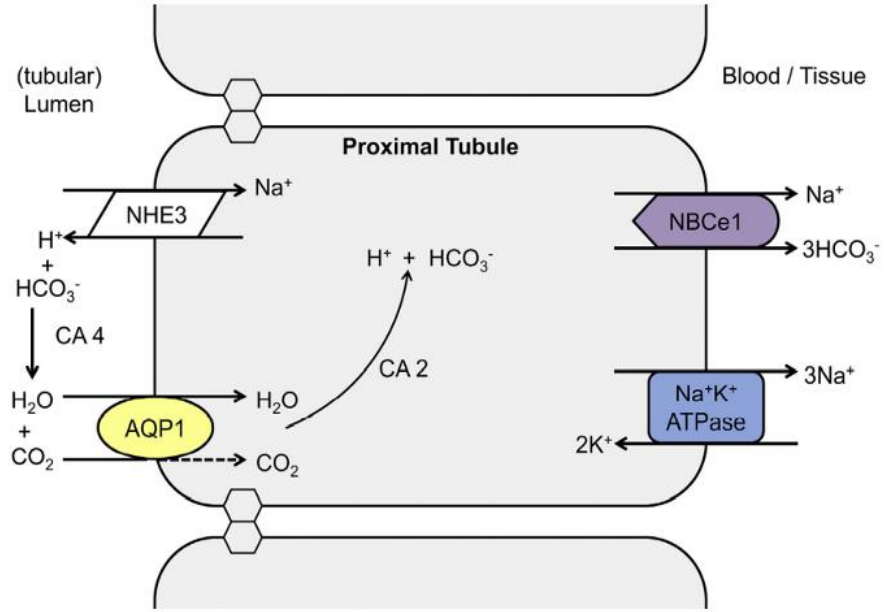
The renal acid load depends on the diet

- Animal proteins (rich in sulfur-containing amino acids) generate acids
- Most fruit and vegetables contain organic acids that are metabolized to bicarbonate
- A typical western diet generate a net renal acid load of =50 mmol
- The acid load is eliminated by the kidney through:

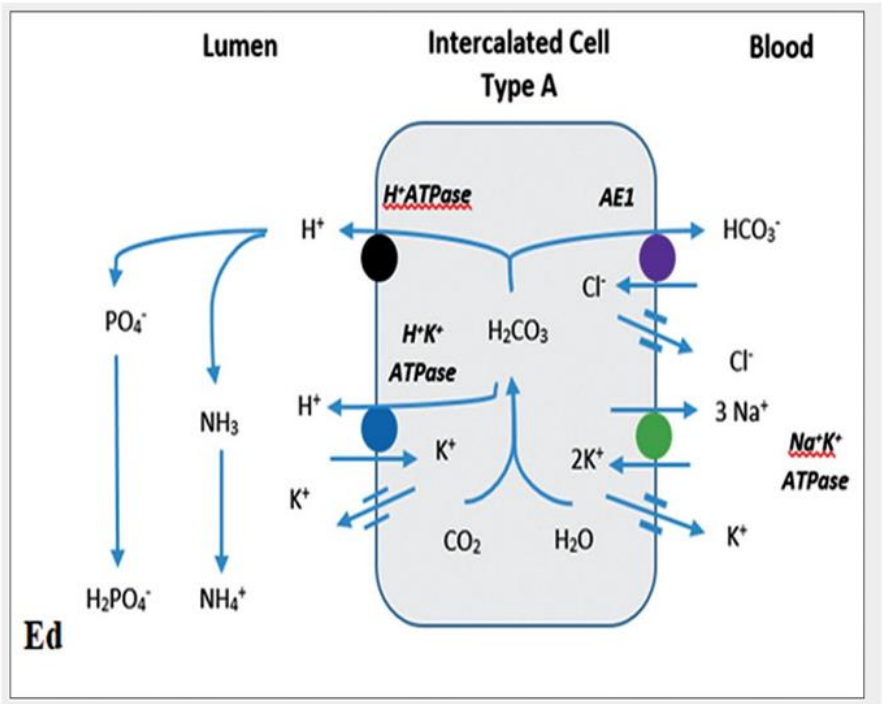


Acid Base Homeostasis

Bicarbonate absorption in proximal tubule



Distal urinary Acidification



Classification of renal tubular acidosis (RTA)

- type 1 RTA
  - inability of the distal convoluted tubule and the collecting tubule to maximally increase the urinary secretion of H+ in the presence of metabolic acidosis
- type 2 RTA
  - impaired HCO_3^- reabsorption in the proximal tubule
- type 3 RTA
  - mixed form of type 1 and type 2 RTA
- type 4 RTA
  - defective production of ammonium (NH_4^+) due to hyperkalemia resulting from either aldosterone deficiency or aldosterone resistance

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

Consequences of chronic metabolic acidosis

- Failure-to-thrive
- Fatigue
- Muscle weakness
- Protons replace calcium ions in bones and can cause:
  - rickets
  - hypercalciuria/nephrocalcinosis

Clinical features of RTA

- Failure to thrive, short stature
- Refractory rickets
- Hypokalemic symptoms (paralysis, paralytic ileus, neck flop, U waves on ECG)
- Polyuria/polydipsia/salt craving
- Ocular problems (e.g cataract)
- Global Developmental delay (Lowe syndrome, Galactosemia)
- Cholestasis in some cases of Proximal RTA
- Family history of rickets/hypokalemic symptoms (often in a consanguineous marriage)
- Hepatosplenomegaly in some causes of Proximal RTA
- Photophobia in cystinosis
- Nephrocalcinosis on ultrasonogram

Step-wise approach to RTA

- Step 1: Determine plasma anion gap= Na - (Cl + HCO3)
- Step 2: Estimate urine anion gap= (Na + K) – Cl
- Step 3: Determine Urine pH (pH meter)
- Renal ultrasonogram
- Genetic studies

Anion gap (AG)

$$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-) \text{ (n.v. 8-16)}$$

NB: the anion gap decreases if:

hypoalbuminaemia (□ 3 mEq per gr of albumin)-)

↑↑↑other cations, e.g. hypercalcemia, lithium intoxication, high Ig (cationic)

Anion gap (AG)

High AG acidosis

= acid gain

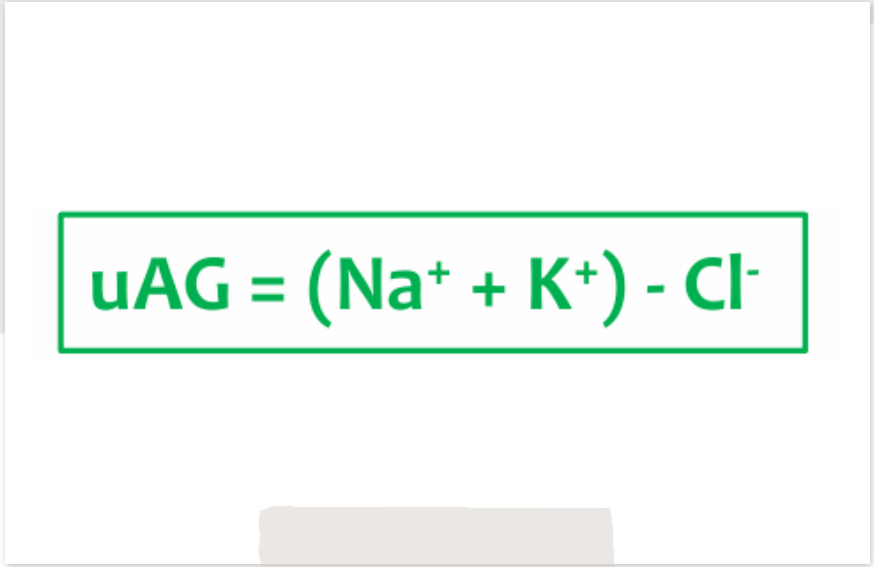
- Ketoacidosis
- Alcoholic (-hydroxybutyrate)
- Starvation
- Lactic acidosis
- Organic aciduria
- Uremia
- Toxins
- Intoxications: ethylene glycol, propylene glycol, methanol, paraldehyde, iron

Normal AG acidosis

=bicarbonate losses

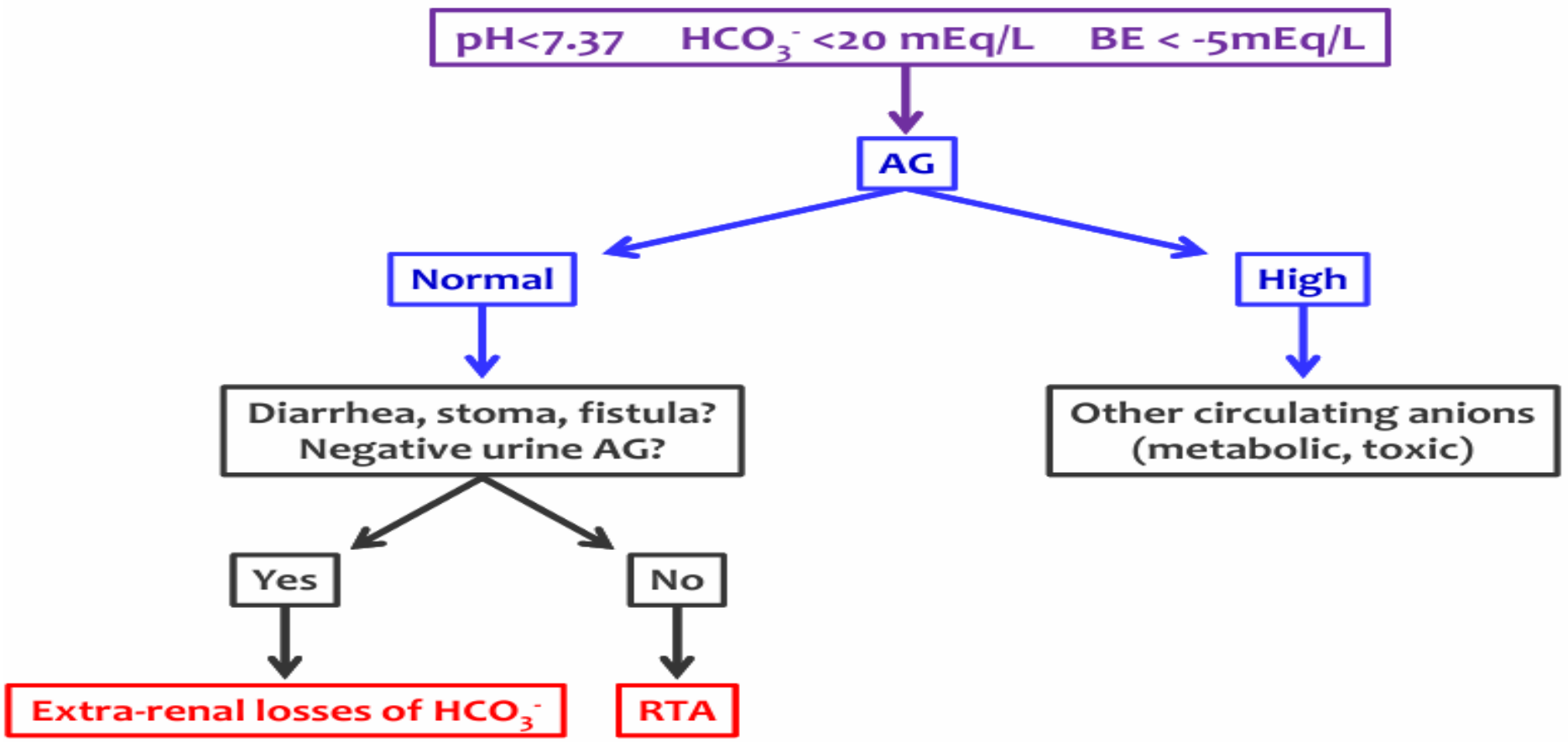
- Gastrointestinal losses of HCO3
- _Renal tubular acidosis
- Acetazolamide, (inhibitors of CA)
- Miscellaneous NH4+Cl ingestion Sulfur ingestion

Urinary anion gap (uAG)

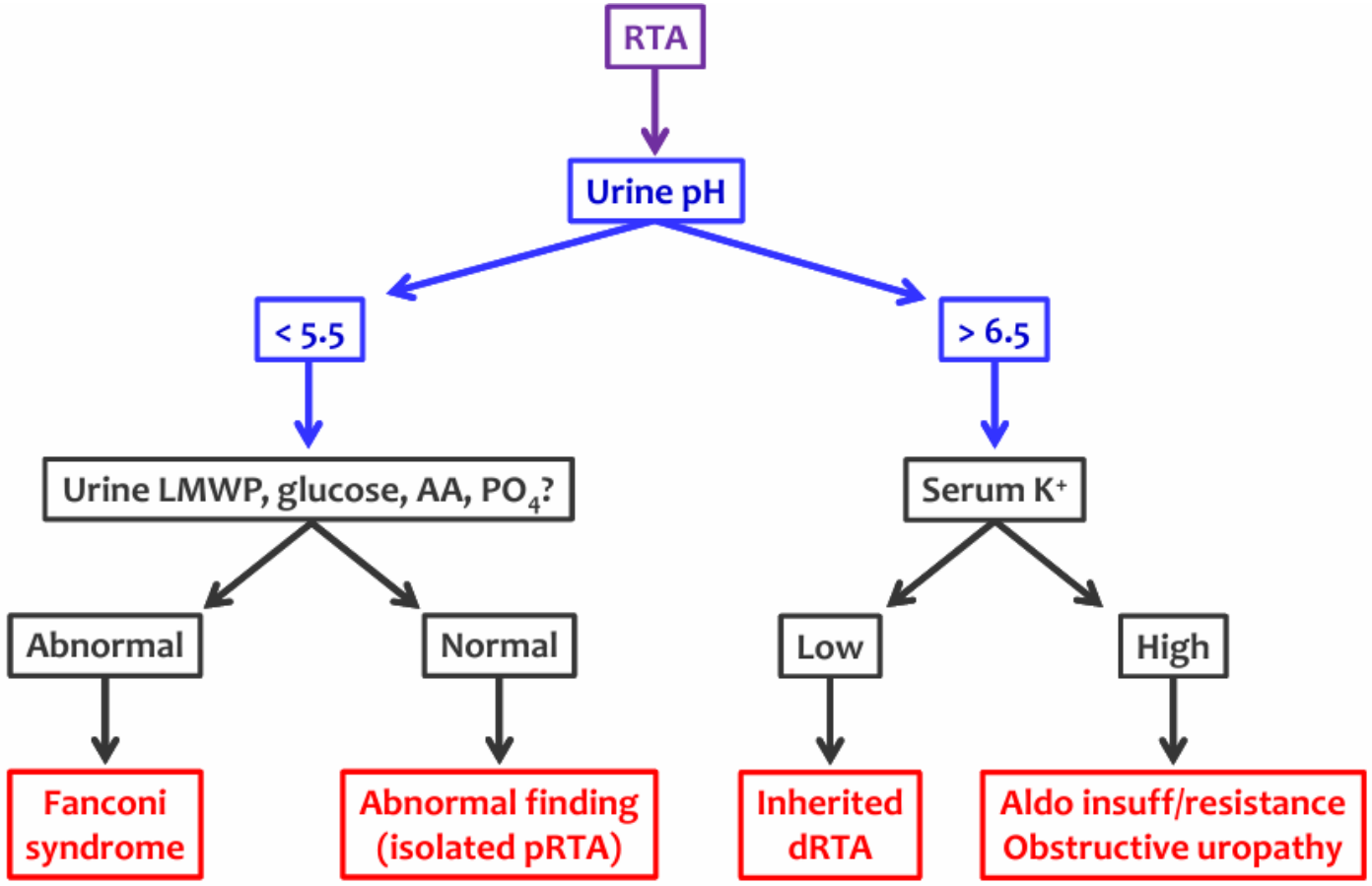


- Index of urinary NH4+ excretion (usually not measured because it is cumbersome)
- A positive uAG suggests low urinary NH4+ - renal tubular acidosis
- A negative uAG suggests high urinary NH4+ - extra-renal HCO3-losses (diarrhea…)
- NB: does not work well in neonates and young infants

Simplified diagnostic approach in patients with acidosis



Simplified diagnostic approach in patients with RTA



Distal renal tubular acidosis: type 1 dRTA

Dysfunction of the intercallated cells that fail to produce acid urine

Clinical diagnosis

pH urine > 5.5 when arterial pH < 7.34

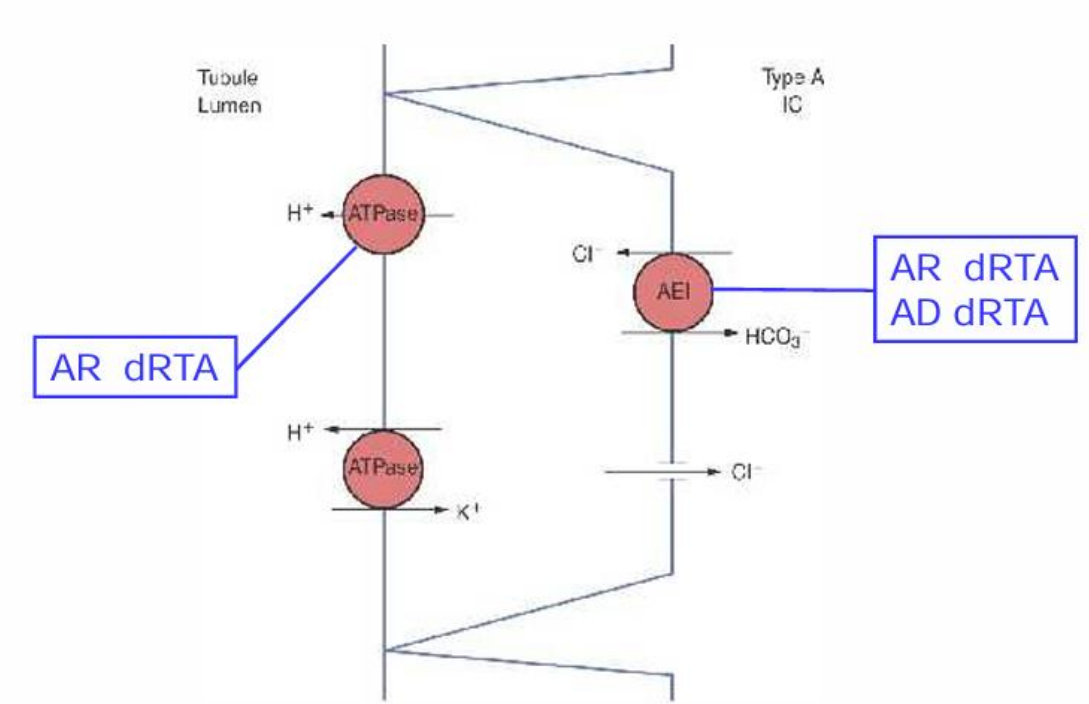
normal AG

normal GFR

- **Other features: hypokalemia nephrocalcinosis, nephrolithiasis metabolic bone disease**

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 in older children leading to mineralocorticoid resistant



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: type 2 pRTA

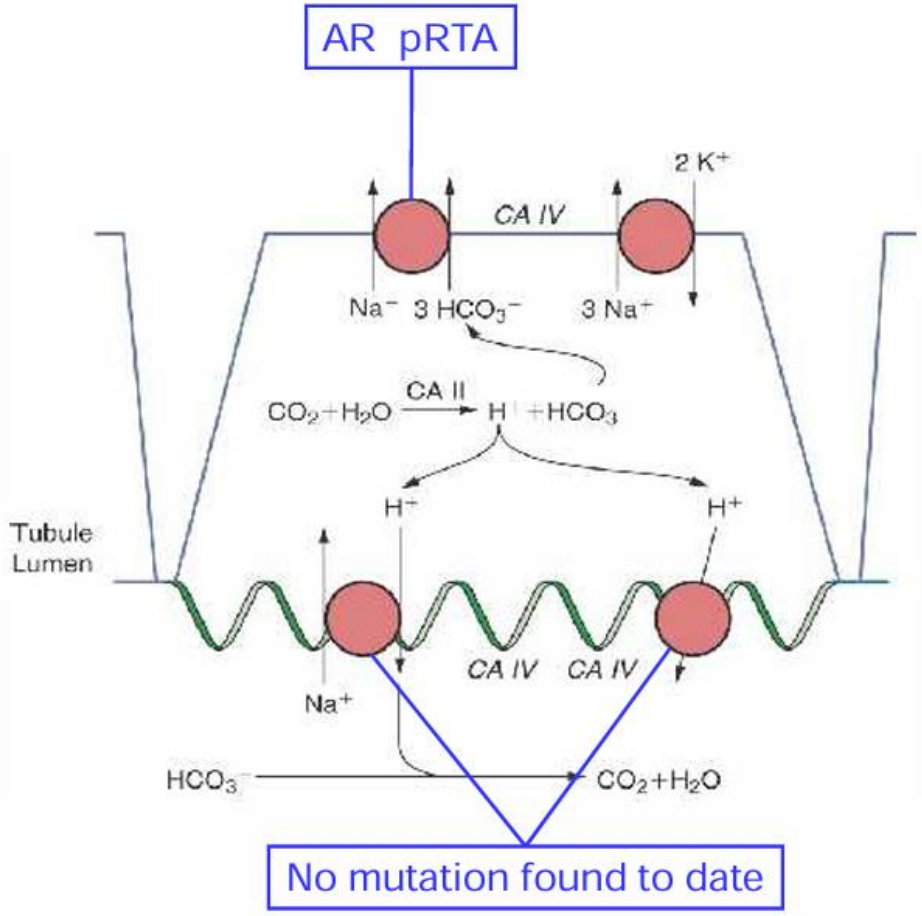
- Defect in PT capacity to reabsorb HCO3
  - Hypokalemia is not always present
  - Hypercalciuria/nephrocalcinosis are absent or less severe compared to dRTA

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

Pediatr Clin N Am 66 (2019) 135-157

Proximal renal tubular acidosis: type 2 pRTA



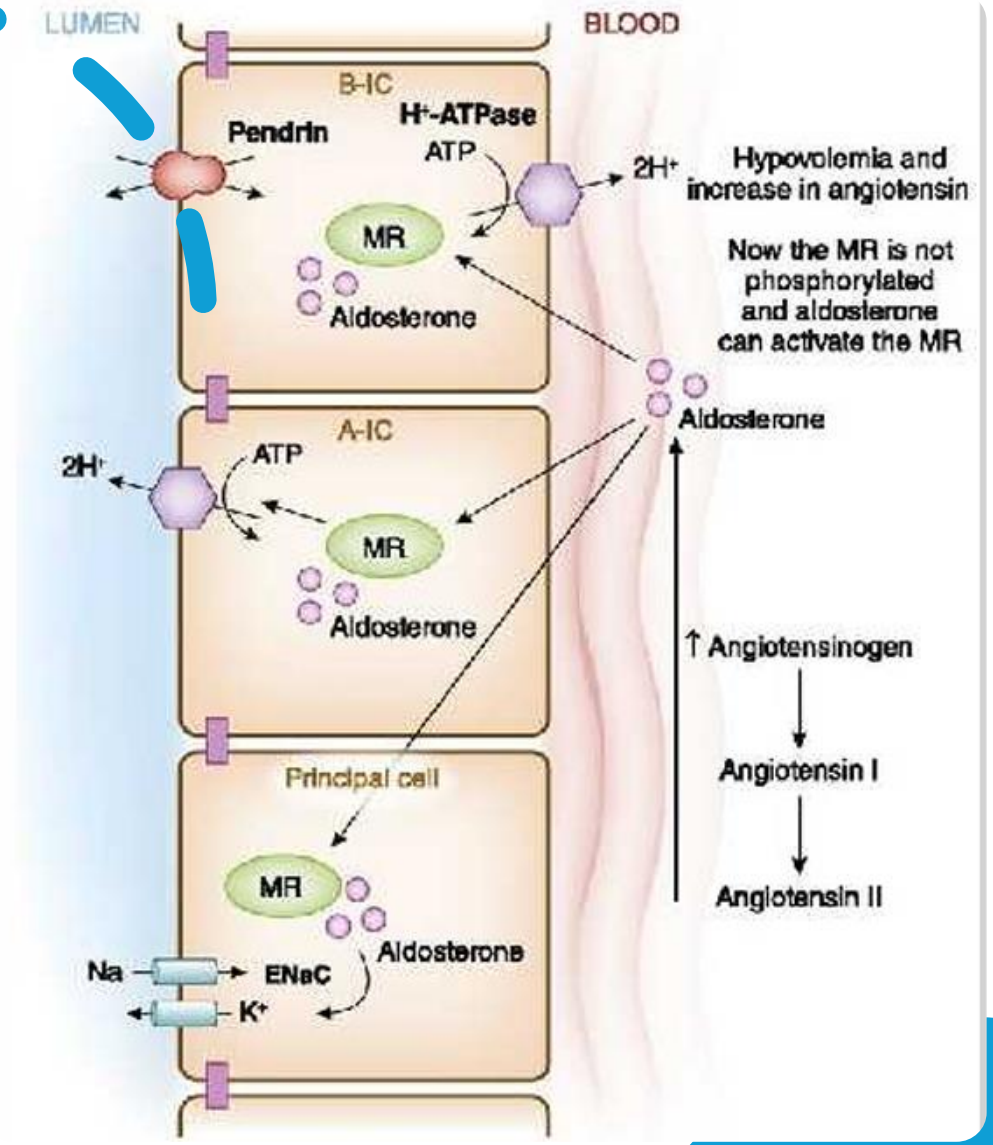
Combined RTA /Type 3

- 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

Obstructive uropathies can cause aldosterone resistance



Pseudohypoaldosteronism type 1 and 2 (PHA 1, PHA 2)

- Pseudohypoaldosteronism type 1 (PHA 1)
  - Renal Na+ waisting
  - Hyperkalemia
  - Hyponatremia(hypotension)
  - Metabolic acidosis
  - High renin and aldosterone levels
  -

  Pseudohypoaldosteronism type 2 (PHA 2) (Gordon syndrome)
  - Hyperkalemic hypertension, low level of renin
  - (mild)acidosis
    - Impaired removal of distal NaCl cotransporter in DCT
    - Increased expression of ENaC
    - Decreased expression of ROMK in CD

Differentiating between types of RTA

	Type 1 RTA	Type 2 RTA	Type 3 RTA	Type 4 RTA
Urine pH	>5.5	<5.5	>5.5	<5.5
U-B pCO_2	<20	>20	<20	>20
Urine NH_4^+	Low	Normal	Low	Low
Plasma K^+	Low/high	Low/normal	Low/normal	High
FE HCO_3^-	<5%	>10-15%	>5%	>5-10%
Aminoaciduria	No	Yes	No/yes	No
Hypercalciuria	Yes/normal	Usually no	Yes	No/high

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 reabsorption is 88-95%.

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

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

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

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)

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)*

Treatment

- Correction of acidosis:
  - Na bicarbonate
  - Kcitrate citrate-

    pRTA10-15 meq/kg/day

    dRTA2-4meq/kg/day in 4 doses)

- Further treatment depending on the cause

- 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.

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

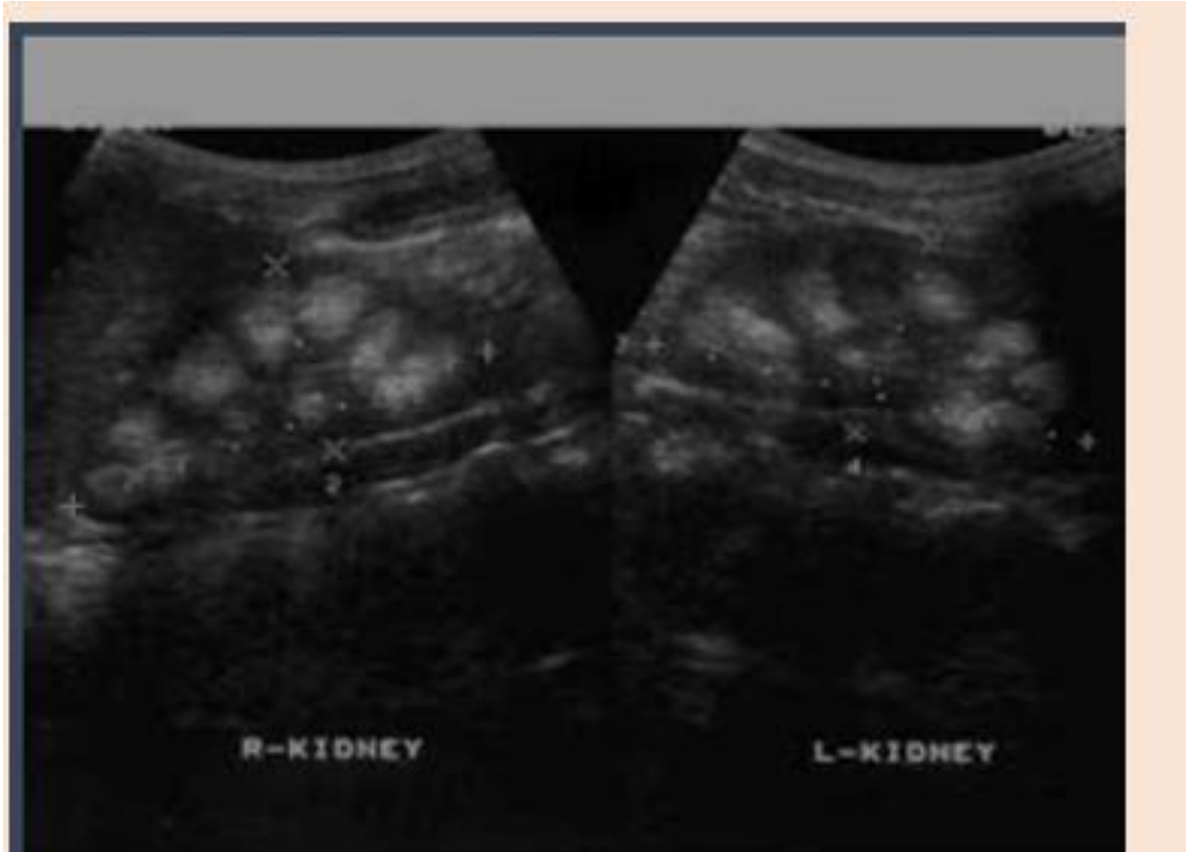
UAG=10

- 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

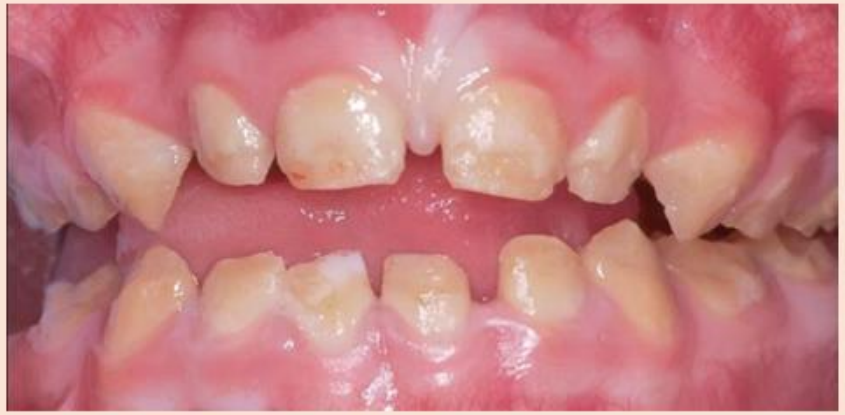
- Eye evaluation

- 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
- Urinary anion gap may help to differentiate type of RTA
- • Molecular genetics
  - To establish diagnosis or for picking up the co-morbid conditions (reverse phenotyping)
  - Genetic counselling

Thank You

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THE 1ST IPNA TEACHING COURSE IN PEDIATRIC NEPHROLOGY

(KNOWLEDGE FOR SAFE PRACTICE)

Hypertension in Children: Case-Based Discussion

Ibrahim F. Shatat, MD, MSCR, FAAP

Pediatric Nephrology and Hypertension

سدرة للطب
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I do not have any relevant financial relationship with commercial interest to disclose

Objective

Case-based discussion focused on identification and management of children with hypertension

Prevalence & Relevance

- 3.5% of children have HTN; another 10-11% have elevated BP, and the prevalence is much higher in obese children (up to 25%).
  - High BP in childhood increases the risk for adult HTN and cardiovascular disease –Tracking.
  - Even youth with HTN have evidence of accelerated vascular aging, TOD, cognitive impairment and school performance.

In the ER

10-year-old boy, previously healthy, presented to the emergency room with signs and symptoms of otitis media. His father is hypertensive on medications.

The child is crying from ear pain. His vital signs are HR 110 BPM, BP 139/85

On physical exam: right ear tympanic membrane is erythematous and bulging. You prescribe pain killer and antibiotics. Repeat BP is 130/80.

You plan to discharge the patient home when the child's father asks you: do I need to worry about his BP? Does my child have hypertension?

Your next step in management?

A. Start antihypertensive medication

B. Refer to specialist

C. Repeat blood pressure measurement at later occasion in a different setting

D. Order workup (CBC, kidney US, ECHO, kidney function test and urinalysis)

E. Reassure parents that no further action is needed

Definition and Methodology

Hypertension—average SBP and/or DBP that is greater than or equal to the 95th percentile for sex, age, and height on 3 or more occasions.

- Adolescents ≥13 y/o with BP ≥130/80 are considered to be hypertensive

Elevated BP —average SBP or DBP levels that are greater than or equal to the 90th percentile, but less than the 95th percentile.

- Adolescents ≥13 y/o with BP levels greater than or equal to **120/80** mmHg should be considered to have elevated BP

What to Do about the Child with an Elevated BP?

- Repeat Elevated BP's
- Blood pressure in childhood is quite **labile** and can **fluctuate** widely, e
- T lings, o TN c
- E **auscultation**
- Use online calculators or cell phone apps to help you classify BP

Definition of HTN (1-18y)

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

Flynn et al, Pediatrics 2017; 140:e20171904

Use the Correct Sized Cuff

- Proper cuff size is crucial to accurate BP measurement
- Manufacturer's recommendations on cuffs may not be accurate due to obesity-associated increased arm circumference
- Ideally arm circumference should be measured and the proper size cuff chosen
- A variety of cuff sizes must be kept on hand in the office

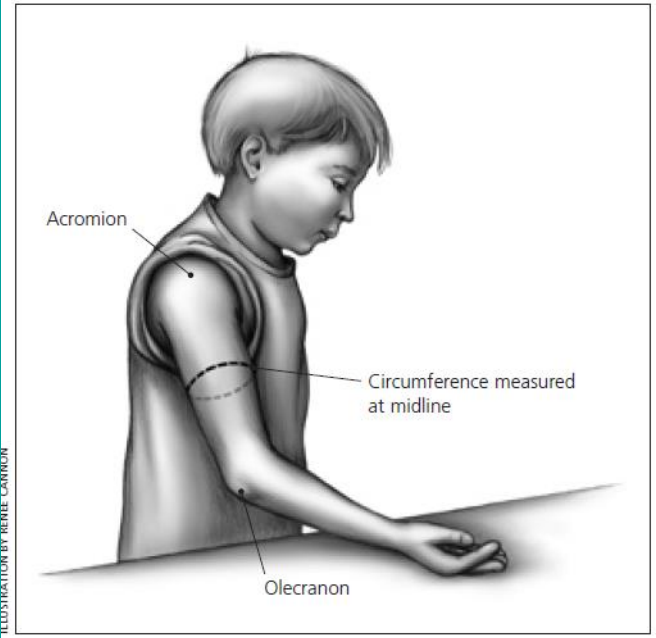


Figure 1. Arm circu[illegible]hould be measured midway between the olecra[illegible]acromial process.

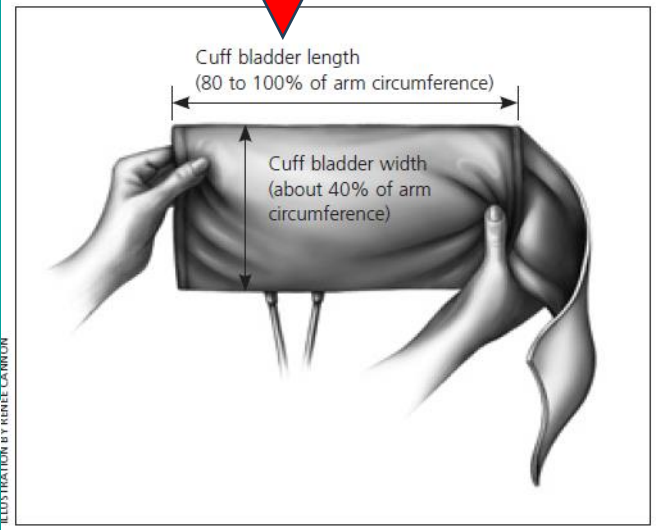
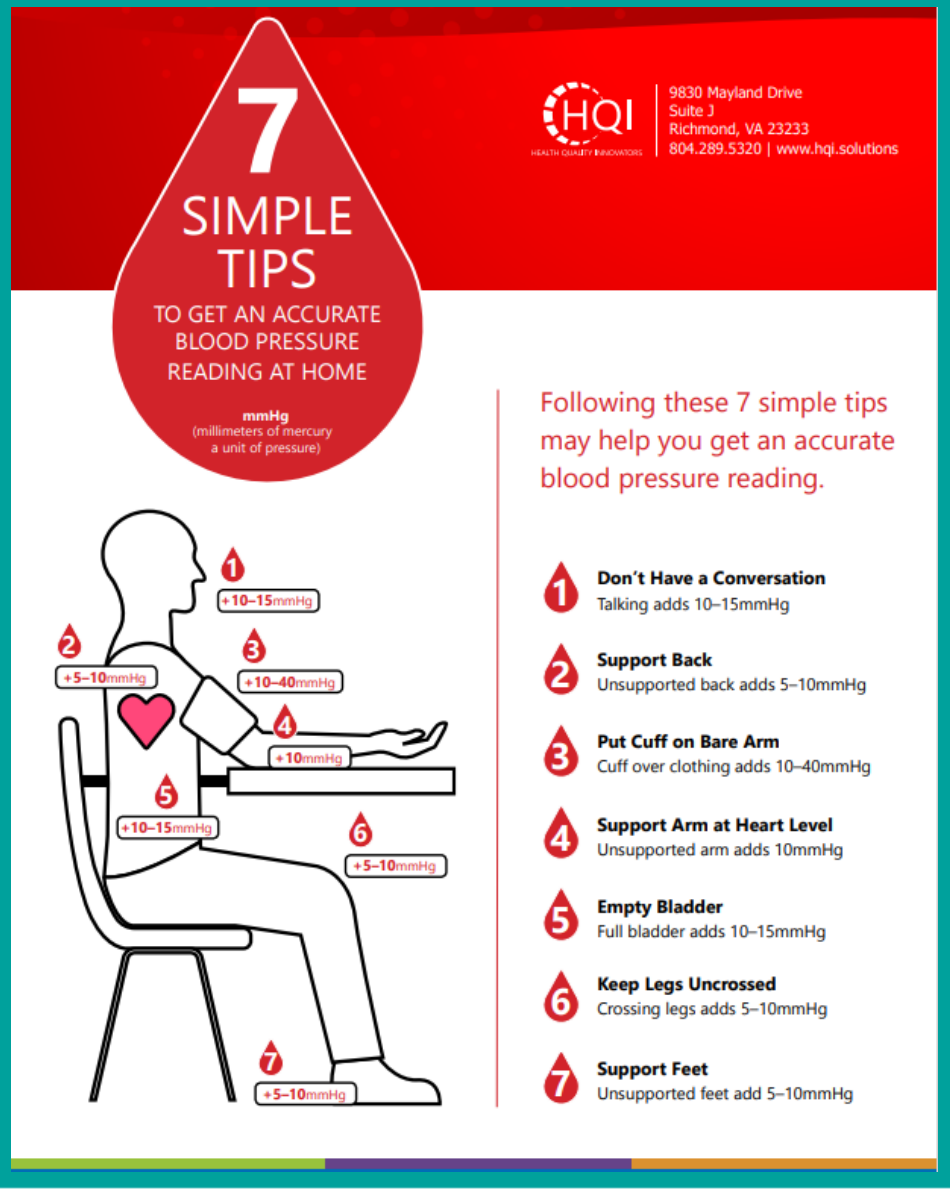


Figure 2. Blood pressure cuff showing size estimation based on arm circumference.

Technique

- Rest for 5 minutes
- Use correct sized cuff
- Repeat at 1-min intervals



In the ICU

You get a call from the PICU staff to evaluate the BP of a 10-year-old girl, previously normotensive, known to have CP & seizure disorder admitted with status epilepticus.

During her hospitalization, she was intubated and sedated. Yesterday, the ICU team managed to extubate her and currently she is on CPAP due to respiratory distress.

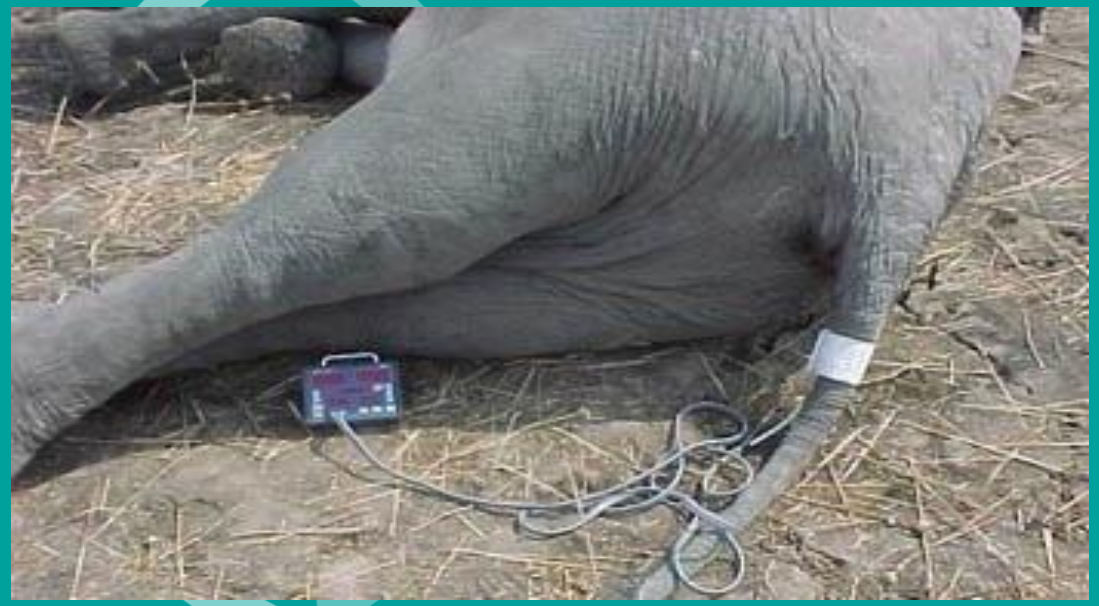
On exam: you noticed the blood pressure cuff to be on her right leg. BP 140/90, HR 80, RR 20. Her neuro exam shows her to have increased muscle tone.

Her current medications include anti-epileptics, clonidine weaning dose, stress dose steroids.

What are the possible contributing factors to the elevated BP in this child?

A. Wrong placement of the BP cuff
B. Respiratory distress
C. Rebound hypertension
D. Stress-dose steroids
E. Increased muscle tone
F. All the above

Take home massages



- Technique is important
- BP in children is labile
- Frequently the child with elevated BP does not require a workup or medications

The obese child

- Age: 12 years, Male
- During routine checkup: Fatigue, snoring at night.
- Family History: Hypertension, type 2 diabetes
- No significant medical history, not on any meds.
- Enjoys playing video games and ordering food from fast-food chains.

- BP Readings on multiple occasions averaged: 140/90 mmHg (stage2 HTN range)
- Weight: BMI > 99th percentile, + acanthosis nigricans.

What is the most appropriate approach for this boy?

A. Have the boy return for a repeat blood pressure measurement in 6 months.

B. Provide lifestyle counseling to increase physical activity and lower dietary salt and repeat blood pressure measurement in 6 months.

C. Begin diagnostic evaluation for stage 2 hypertension.

D. Admit to the hospital for immediate blood pressure reduction.

Patient Evaluation & Management by BP Level

BP Category (see Table 3)	BP Screening Schedule	Lifestyle Counseling (Weight, Nutrition)	Check Upper and Lower Extremity BP	ABPM	Diagnostic Evaluation	Initiate Treatment	Consider Sub-specialty Referral
Normal	Annual	X					
Elevated BP	Initial measurement	X					
	Second measurement: Repeat in 6 months	X	X				
	Third measurement: Repeat in 6 months	X		X	X		X
Stage 1 HTN	Initial measurement	X					
	Second measurement: Repeat in 1-2 weeks	X	X				
	Third measurement: Repeat in 3 months	X		X	X	X	X
Stage 2 HTN	Initial measurement	X	X				
	Second measurement: Repeat/refer to specialty care within 1 week	X		X	X	X	X

Flynn et al, Pediatrics 2017; 140:e20171904

Relevant Guidance from the 2017 AAP CPG

Children and adolescents ≥6 y of age do **not** require an extensive evaluation for secondary causes of HTN **if** they have a positive family history of HTN, are overweight or obese, and/or do not have history or physical examination findings suggestive of a secondary cause of HTN.

TABLE 10 Screening Tests and Relevant Populations

Patient Population	Screening Tests
All patients	Urinalysis
	Chemistry panel, including electrolytes, blood urea nitrogen, and creatinine
	Lipid profile (fasting or nonfasting to include high-density lipoproteina and total cholesterol)
	Renal ultrasonography in those <6 y of age or those with abnormal urinalysis or renal function
In the obese (BMI >95th percentile) child or adolescent, in addition to the above	Hemoglobin A1c (accepted screen for diabetes)
	Aspartate transaminase and alanine transaminase (screen for fatty liver)
	Fasting lipid panel (screen for dyslipidemia)
Optional tests to be obtained on the basis of history, physical examination, and initial studies	Fasting serum glucose for those at high risk for diabetes mellitus
	Thyroid-stimulating hormone
	Drug screen
	Sleep study (if loud snoring, daytime sleepiness, or reported history of apnea)
	Complete blood count, especially in those with growth delay or abnormal renal function

Initial Diagnostic Evaluation

ABPM is done, demonstrating sustained hypertension while awake and asleep, with only 7% SBP dipping.

Urinalysis is normal. Creatinine is 0.7 mg/dL (62 µmol/L)

Random glucose elevated. Triglycerides and LDL cholesterol elevated. HDL cholesterol low

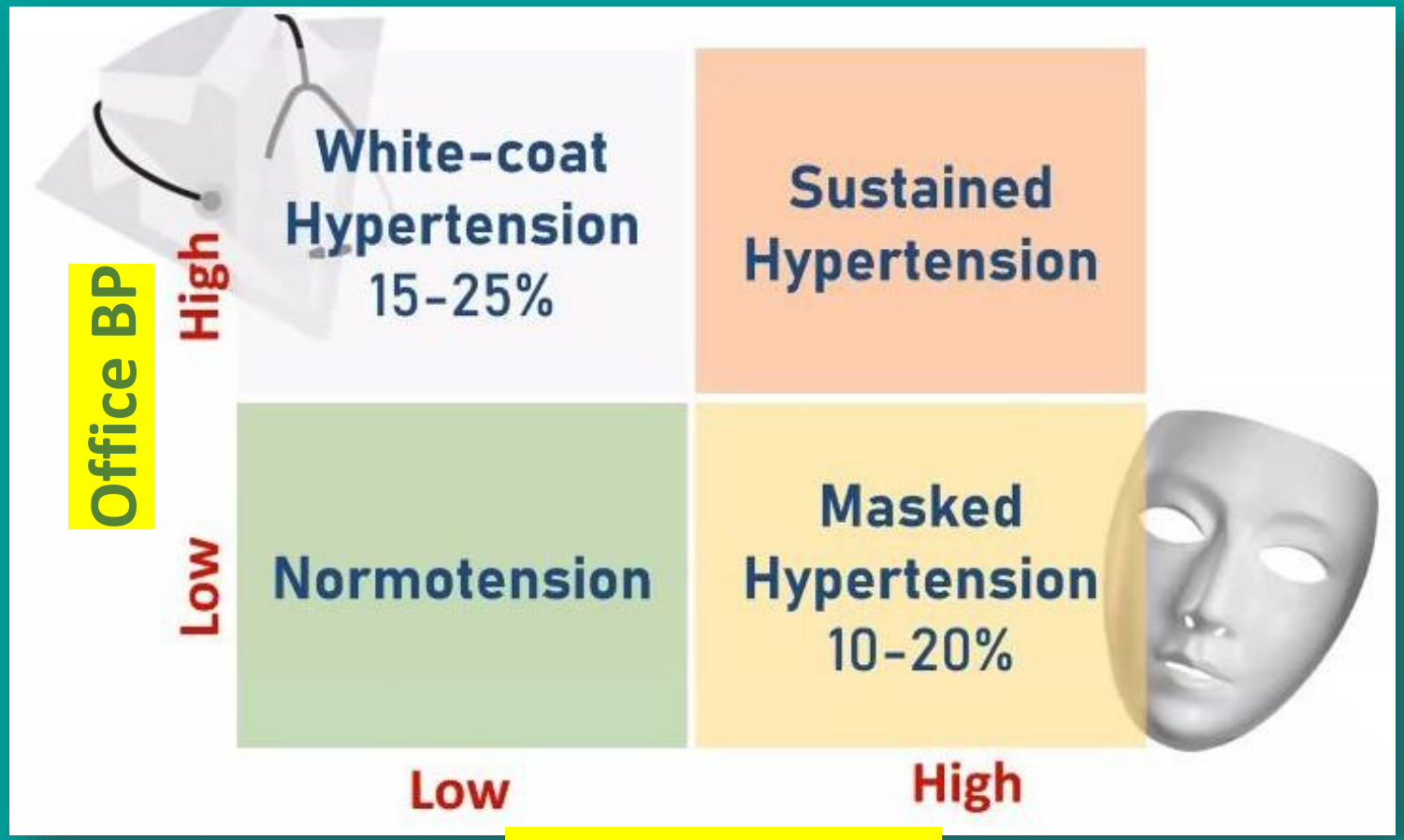
Uses of ABPM – 2017 AAP CPG

- Confirm diagnosis of HTN after 3 high office BP readings
  - White coat vs. sustained ambulatory HTN
- Assess adequacy of BP treatment
  - CKD: 24-hr MAP <50th percentile
  - Repeat ABPM in all treated patients

TABLE 12 High-Risk Conditions for Which ABPM May Be Useful

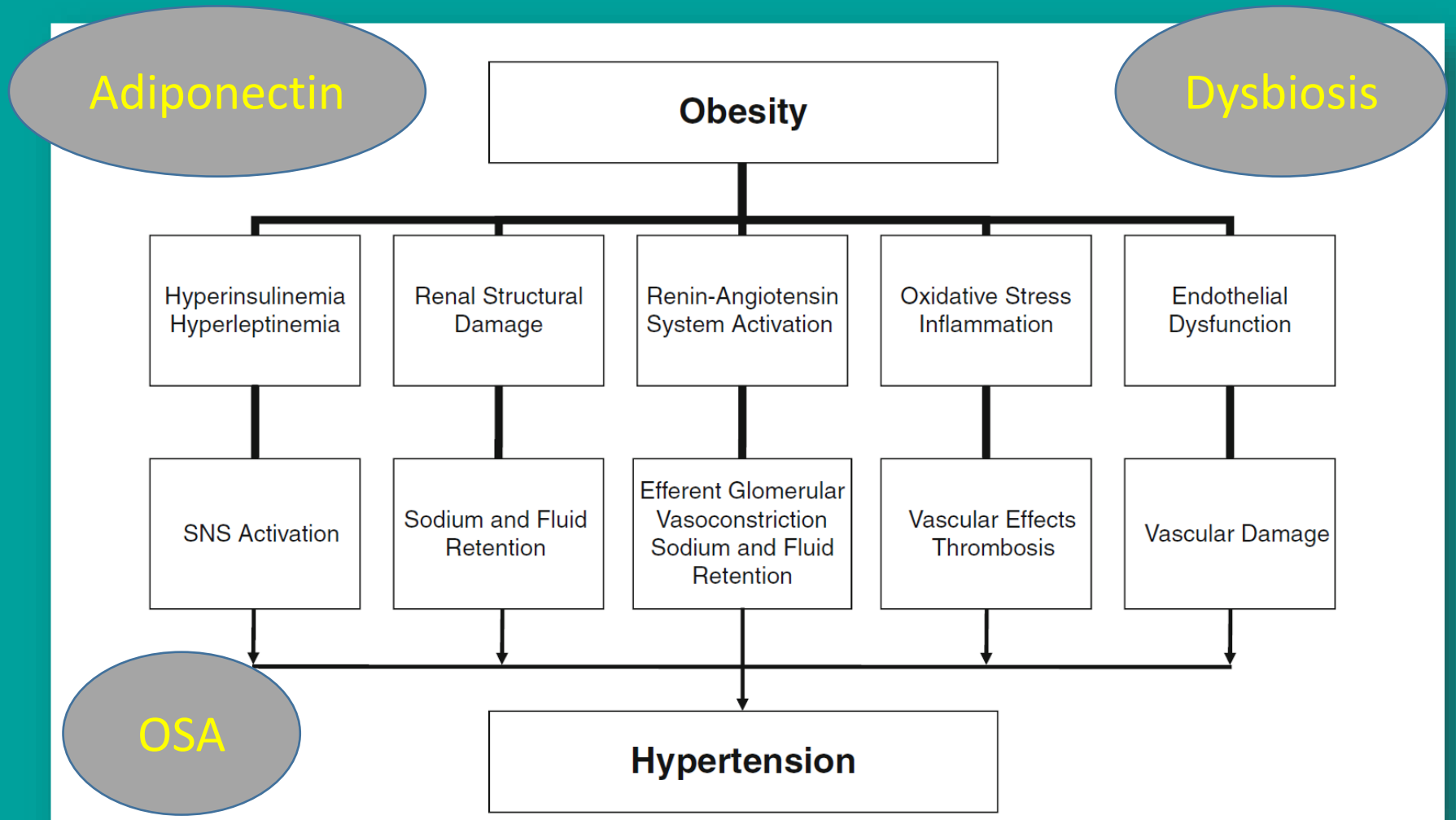
Condition	Rationale
Secondary HTN	Severe ambulatory HTN or nocturnal HTN indicates higher likelihood of secondary HTN[161,167]
CKD or structural renal abnormalities	Evaluate for MH or nocturnal HTN,[168–172] better control delays progression of renal disease[173]
T1DM and T2DM	Evaluate for abnormal ABPM patterns,[174,175] better BP control delays the development of MA[176–178]
Solid-organ transplant	Evaluate for MH or nocturnal HTN, better control BP[179–188]
Obesity	Evaluate for WCH and MH[23,189–192]
OSAS	Evaluate for nondipping and accentuated morning BP surge[43,46,193,194]
Aortic coarctation (repaired)	Evaluate for sustained HTN and MH[58,112,113]
Genetic syndromes associated with HTN (neurofibromatosis, Turner syndrome, Williams syndrome, coarctation of the aorta)	HTN associated with increased arterial stiffness may only be manifest with activity during ABPM[58,195]
Treated hypertensive patients	Confirm 24-h BP control[155]
Patient born prematurely	Evaluate for nondipping[196]
Research, clinical trials	To reduce sample size[197]

BP Patterns by Office & Ambulatory BP



Which of the following is likely true about this child's BP?

A. Component of the metabolic syndrome (secondary to obesity)
B. Wrong technique of BP measurement (cuff size)
C. Possibly related to obstructive sleep apnea
D. Likely related to his life-style
E. All the above


Adiponectin
Obesity
Dysbiosis
Hyperinsulinemia
Hyperleptinemia
Renal Structural
Damage
Renin-Angiotensin
System Activation
Oxidative Stress
Inflammation
Endothelial
Dysfunction
SNS Activation
Sodium and Fluid
Retention
Efferent Glomerular
Vasoconstriction
Sodium and Fluid
Retention
Vascular Effects
Thrombosis
Vascular Damage
OSA
Hypertension

Management of HTN in Children & Adolescents

Treatment includes 3 components:

- Non-pharmacologic measures
- Antihypertensive medications
- Ongoing monitoring

Therapy: Initial Approach

Weight loss is primary therapy but difficult to achieve

Increased Physical Activity

- 2017 AAP CPG: “Vigorous” physical activity 3-5 d/wk, 30-60 min/session
- Aerobic exercise or combination of aerobic exercise plus resistance training
- Try to find an activity child is already participating in and intensify it

Nutritional Counseling

- 2017 AAP CPG: Provide advice on the DASH diet
- DASH eating plan: increased fruits and vegetables, low-fat dairy products ± sodium restriction (www.dashdiet.org)
- AHA: Reduce sodium intake to 1500-2300 mg/day

Outcome

He met with a nutritionist who taught him about healthy eating

- Reduced sodium intake
- Cut down on snacks and portion sizes at meals

His father started taking him to the gym 4 days per week

- He used the treadmill and did weight training

Over a 2-year period he lost 9 Kg, and his BMI dropped to the 93rd percentile

His blood pressure fell to the elevated BP range – 120's/70s

Who Needs Pharmacologic Treatment?

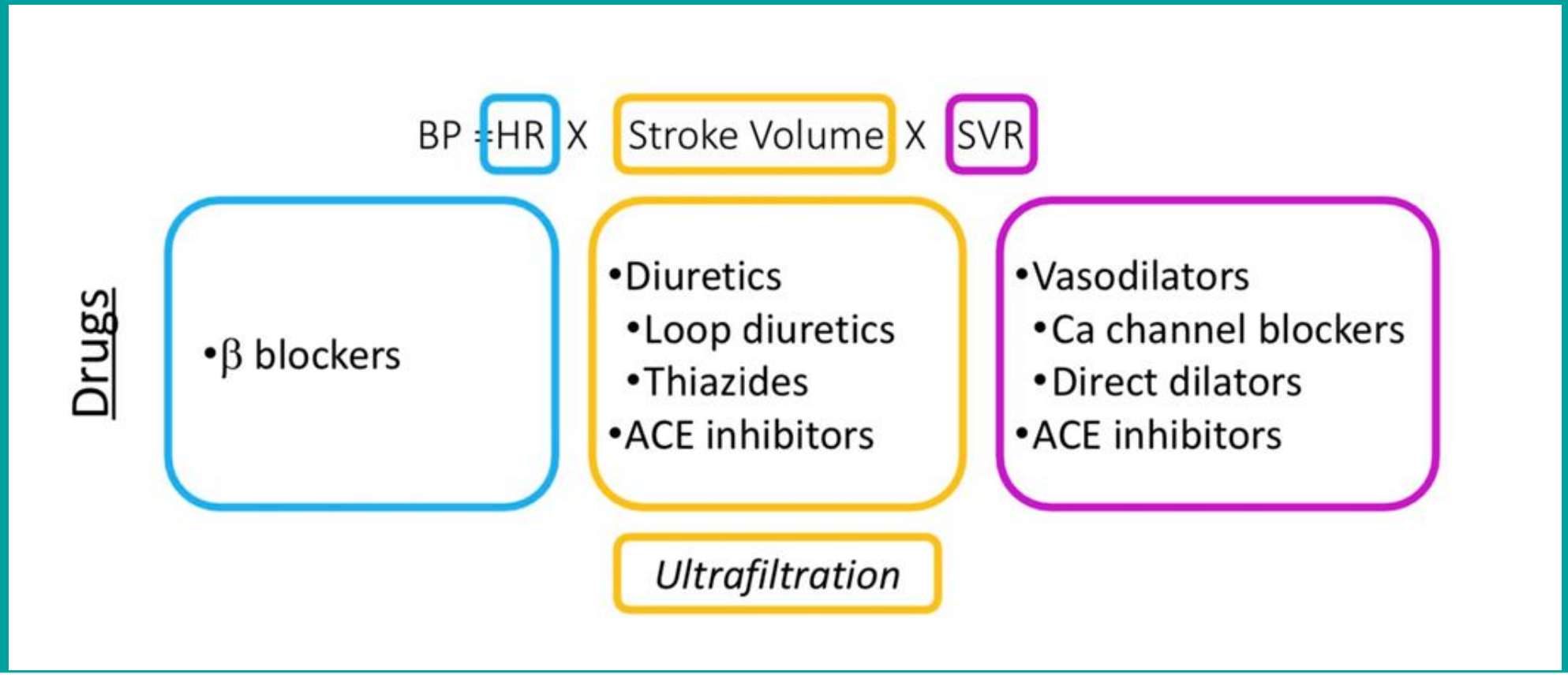
In hypertensive children and adolescents who:

-Symptomatic hypertension
-Secondary hypertension
-Hypertensive target-organ damage
-Diabetes (Types 1 and 2)
-Persistent hypertension despite non-pharmacologic measures
-Stage 2 hypertension

Clinicians should initiate pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic.

Flynn et al, Pediatrics 2017; 140:e20171904

Using Physiology to Treat Hypertension



Goal for Antihypertensive Treatment in Children

In children and adolescents diagnosed with HTN, the treatment goal with non-pharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to <90th percentile and <130/80 mm Hg in adolescents ≥ 13 years old.

- C, moderate

Children or adolescents with both CKD and HTN should be treated to lower 24-hr MAP <50th percentile by ABPM

- B, strong

Flynn et al, Pediatrics 2017; 140:e20171904

Approach to Prescribing Anti-hypertensives

Pediatricians should only prescribe drugs that have published pediatric efficacy & safety data
Follow "stepped care" approach

- Begin with starting dose of a single drug
- Increase dose until goal BP or maximum dose reached, or adverse effects occur
- Add another drug from a different class, etc.

Multiple-drug regimens usually needed to reach goal BP, even in primary HTN

Pediatric Nephrology (2020) 35:2049–2065
https://doi.org/10.1007/s00467-019-04314-7

REVIEW

Antihypertensive agents: a long way to safe drug prescribing in children

Nida Siddiqi [1] · Ibrahim F. Shatat [2,3,4]

Received: 31 May 2019 / Revised: 12 July 2019 / Accepted: 23 July 2019 / Published online: 1 November 2019

The young child

8-year-old boy, known to have ADHD, otherwise previously healthy was found to have a BP of 160/100 during his developmental pediatrics clinic visit. BP was repeated multiple times and confirmed manually with almost the same range.

Upon further detailed history, the family reported that the child occasionally complains of headaches, fatigue, and episodes of dizziness.

Physical Exam Findings:

- A**bdominal Exam:** No palpable masses, + abdominal bruit, + multiple hyperpigmented lesions on the trunk and back.
- **Heart Exam:** Normal S1, S2; no murmurs, strong pulses X4.

  Lower limb BP 170/110

- No history prematurity, past trauma, surgery, or medication intake.

Labs, imaging studies ordered

Started on amlodipine which resulted in BP reduction to the 140's/90's range.

Normal urinalysis, normal creatinine, normal electrolytes, elevated renin and aldosterone

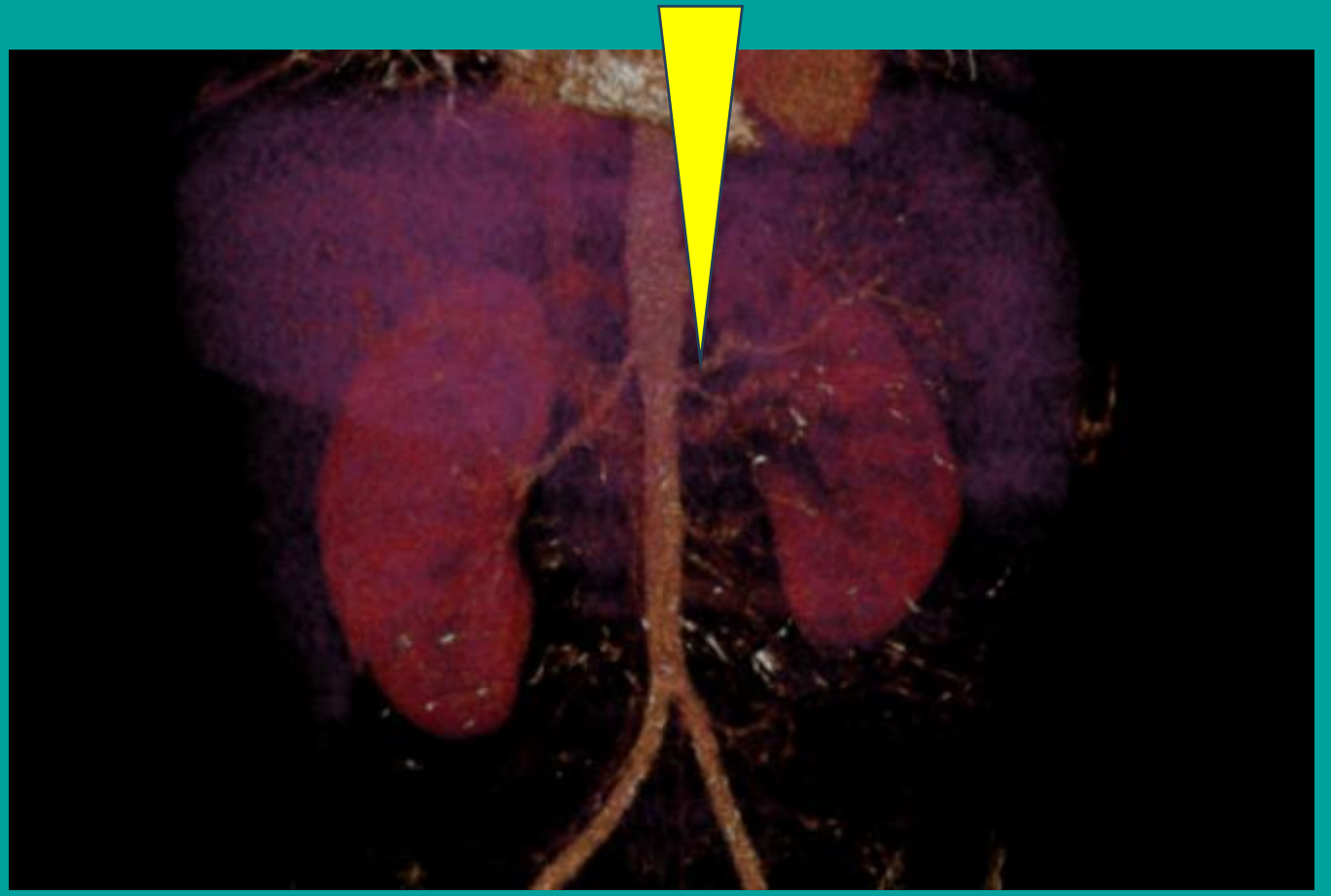
Echocardiogram: structurally normal heart with LVH

Complete kidney US: kidneys of normal appearance and size bilaterally

Renal doppler: 2 LF renal arteries, 1 RT renal artery. Patent. Inconclusive.

CT- angiogram performed: Both renal arteries are patent, but there is minimal irregularity of the caliber of the left renal artery as it branches off from the abdominal aorta, of uncertain clinical significance.

Genetic testing ordered & confirmed diagnosis as NF1



Follow up

BP was better controlled with addition of a B-Blocker: 130's/90's

Child developed a TIA, underwent a whole-body MRI/MRA which confirmed vascular lesion in the brain consistent with moyamoya disease

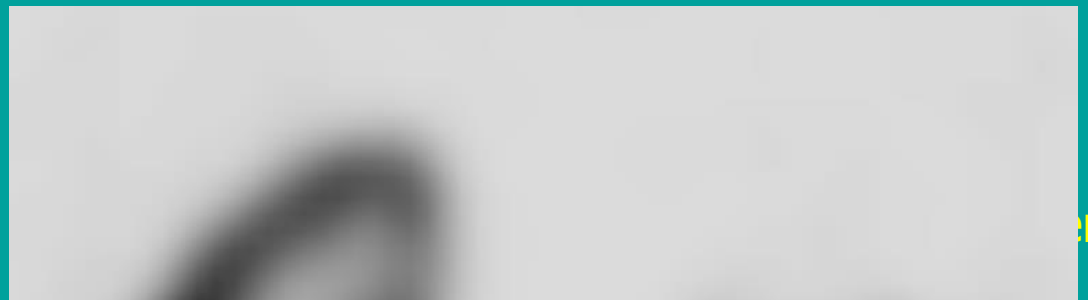
He underwent a bypass surgery to help improve brain circulation.

On the MRI/MRA: Interim reduction in left renal bipolar length (Left Kidney: 7.9 cm, previously 9.0 cm) with reduced left renal upper-mid polar parenchymal thickness/bulk suggesting ongoing vascular insult.

Control BP & maintain brain perfusion .. A small dose of ACEi was added and resulted in BP 120's/70-80

Repeat echo 6 mo later – improved LVH

ntion.



IMPRESSION:

1. Markedly decreased left renal function (18%) with severe photopenia of the left upper pole and relatively preserved lower pole uptake. The pattern correlates with known duplicated left renal arteries and attenuated upper pole arterial supply seen on recent MRA.
2. Findings are consistent with segmental renal ischemia affecting the left upper pole, likely chronic given the degree of functional impairment.
3. Right kidney demonstrates compensatory increased function (81% split function) without focal abnormalities.

Recommend interventional radiology versus surgical consultation.

Take home massages

Always check for upper and lower extremity BP

Feel for femoral pulses

Auscultate for abdominal bruits

In children with renovascular disease genetic testing (yield up to 19-40%).

The younger the child, the higher the BP, the more sustained the BP => the more likely it is secondary

NF vascular lesions are dynamic and may affect multiple organs, look for other organ involvement, CoArc and don't forget Pheos.

Based on the local expertise, the lesions and the kidney function: a wide range of interventions can be performed (balloon, reconstruction, reimplantation, avoid stents in growing children) and have a vascular surgeon on standby.

Relevant Guidance from the 2017 AAP CPG

Doppler renal ultrasonography may be used as a noninvasive screening study for the evaluation of possible RAS in normal wt children and adolescents ≥8 y of age who are suspected of having renovascular HTN and who will cooperate with the procedure.

- C, moderate

In children and adolescents suspected of having RAS, either CTA or MRA may be performed as noninvasive imaging studies.

- D, weak

Causes of Childhood HTN

	Infants	School-age	Teens
Primary	1%	15-30%	85-95%
Secondary	99%	70-85%	5-15%
Renal Parenchymal Disease	20%	60-70%	
Renovascular	25%	5-10%	
Endocrine	1%	3-5%	
Coarctation	35%	10-20%	
Reflux Nephropathy	0%	5-10%	
Neoplastic	4%	1-5%	
Miscellaneous	20%	1-5%	

The baby

13 mon boy, ex 32 weeker found to be hypertensive during a scheduled MRI brain which was being completed due to multiple cafe au lait spots
blood pressure was 185/95 mmHg

Child met the criteria for NF1, and later the diagnosis was genetically confirmed.

Initial management to reduce the BP to a safe range.

Now BP controlled on 3 medications: Amlodipine, Atenolol and Enalapril

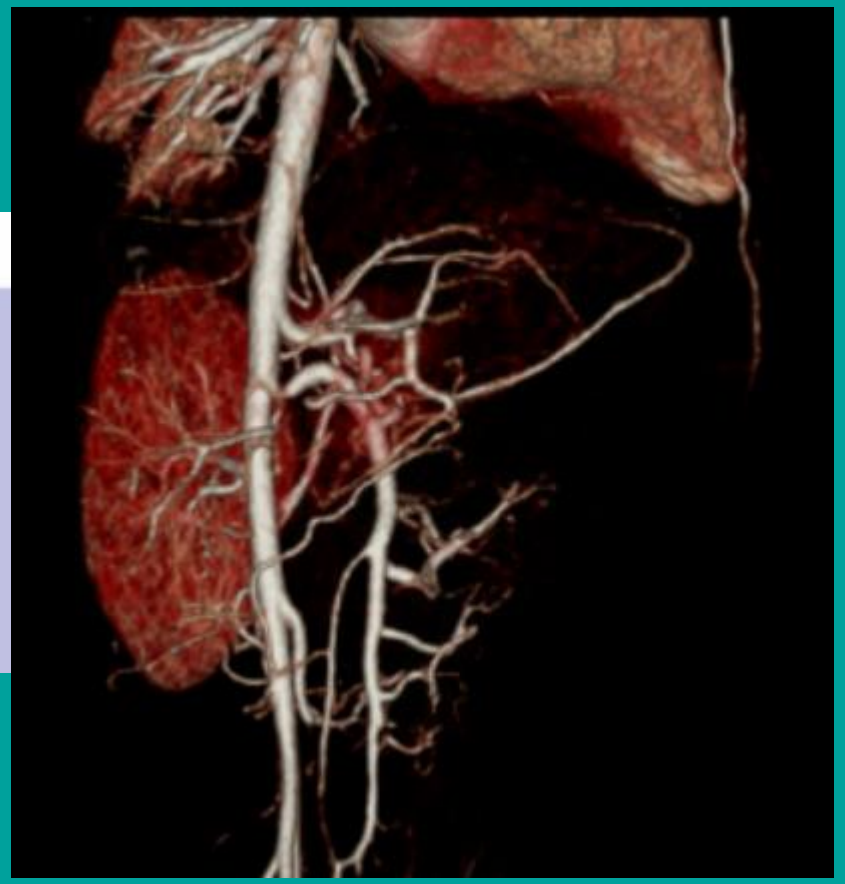
Last BP was 105/60

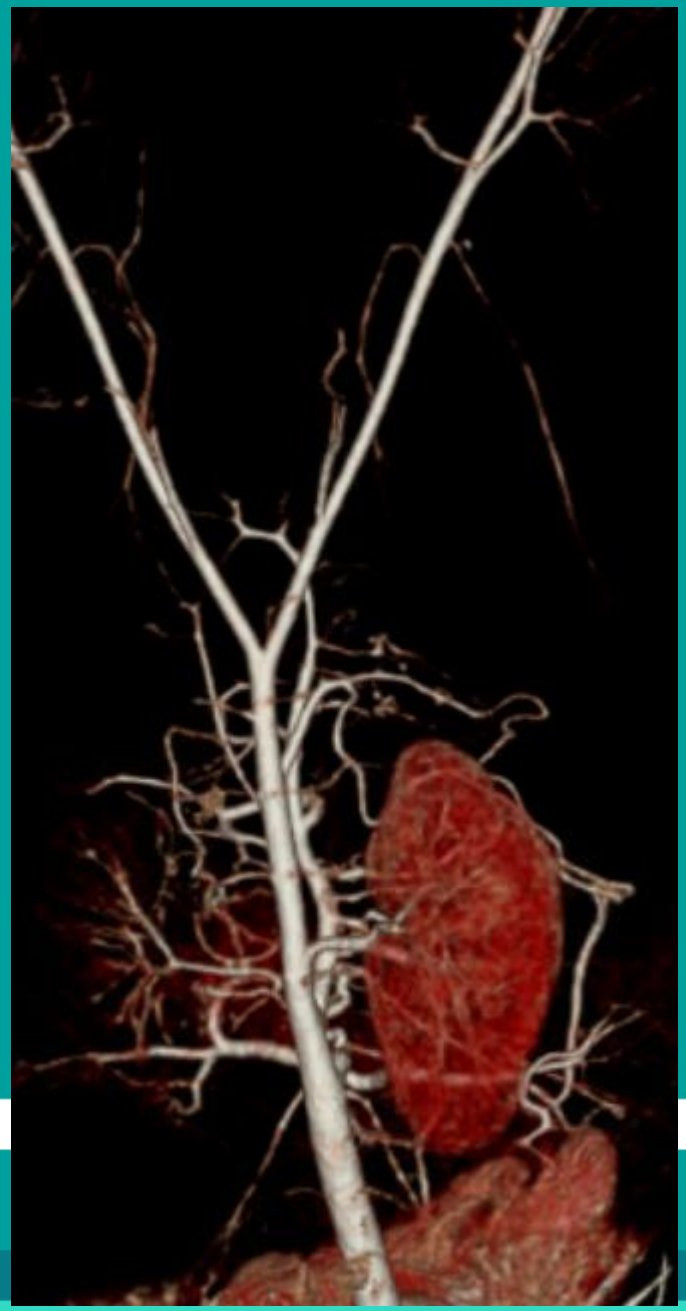
DMSA

Posterior

(Counts)	Left	Right
	341K	006K
Total	341K	006K

(% Ratios)	Left	Right
	98.30	1.70
Total	98.30	1.70





BP controlled on 3 medications. Split function 2%/98%

What resources are available for you at your institution?

Will you keep the child on 3 medications or consider nephrectomy?

Will the child come off antihypertensive medications after nephrectomy?

Can the disease affect the other kidney?

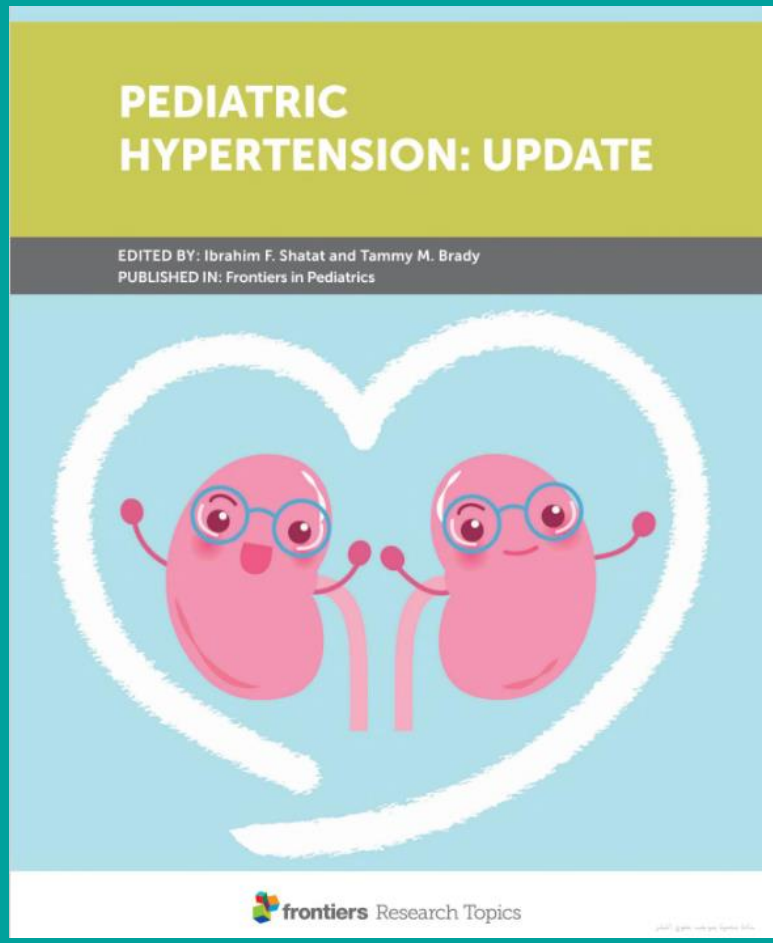


Table of Contents

FREE TO DOWNLOAD AT :
www.frontiersin.org/research-topics/5269/pediatric-hypertension-update#overview
2017 AAP CPG: https://pediatrics.aappublications.org/content/140/3/e20171904.long

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