



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Pediatric Nephrology and CKD Through the Lifespan

Alexis C Gomez, MD

Attending, Division of Nephrology

Boston Children's Hospital

Mass General Brigham

Instructor of Pediatrics

Harvard Medical School



AC Gomez, MD



Perelman School of Medicine at the University of Pennsylvania

Internal Medicine and Pediatrics Residency: Baylor College of Medicine

Nephrology Fellowship: MGB

Pediatric Nephrology Fellowship: Boston Children's Hospital

Transplant Nephrology Fellowship: Massachusetts General Hospital

Clinical Focus

- Transitions of care in CKD and Transplant



DISCLOSURES

I have no relevant financial relationships with ineligible companies.



OBJECTIVES

- Understand the approach to common pediatric nephrology problems encountered by adult nephrologists
- Distinguish pediatric and adult definitions of and approaches to nephrotic syndrome and hypertension
- Recognize childhood kidney conditions that present a risk of CKD in young adults
- Understand core elements of transitions from pediatric to adult kidney care



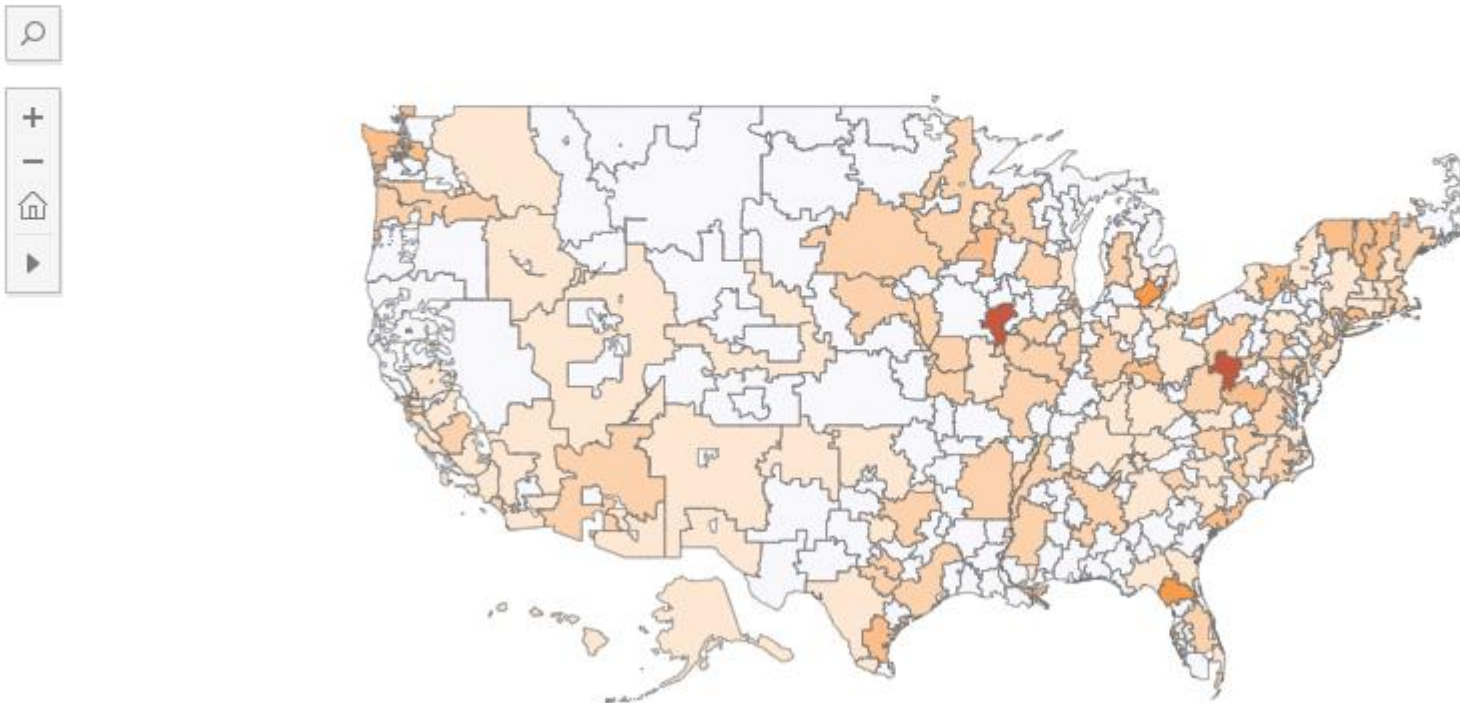
Why is pediatric nephrology important?

US-Based Pediatricians Currently Certified in
Pediatric Nephrology
651

Average # per HRR
2.121

Average # per 100,000 Children by HRR
0.60

Those Certified in Pediatric Nephrology by Hospital Referral Region, per 100,000 children



Pediatric Nephrotic Syndrome



Case One

- Previously healthy 4-year-old presents in spring with rhinorrhea and eye swelling
- Initially referred to allergy and immunology for management of seasonal allergies
- At that visit noted to have 3 kg weight gain from recent well child check
- As such referred to nephrology clinic for evaluation
- BP normal, Cr 0.3 mg/dL
- Albumin 1.2 g/dL
- UA 3+ protein, spot UPCR 3 mg/mg



Next Best Step?

- A) Kidney biopsy to help identify cause of nephrotic syndrome
- B) Genetic testing to identify cause of possible podocytopathy
- C) Initiation of empiric glucocorticoid therapy
- D) Initiate loop diuretics for edema and 3kg weight gain



Next Best Step?

- A) Kidney biopsy to help identify cause of nephrotic syndrome
- B) Genetic testing to identify cause of possible podocytopathy
- C) Initiation of empiric glucocorticoid therapy
- D) Initiate loop diuretics for edema and 3kg weight gain



Pediatric Nephrotic Syndrome Definition

- Proteinuria
 - Spot UPCR $> 2\text{g/g}$
 - $> 1000\text{ mg/m}^2/\text{day}$
- Hypoalbuminemia
 - Serum albumin $\leq 2.5\text{ g/dl}$
- Hyperlipidemia
- Edema

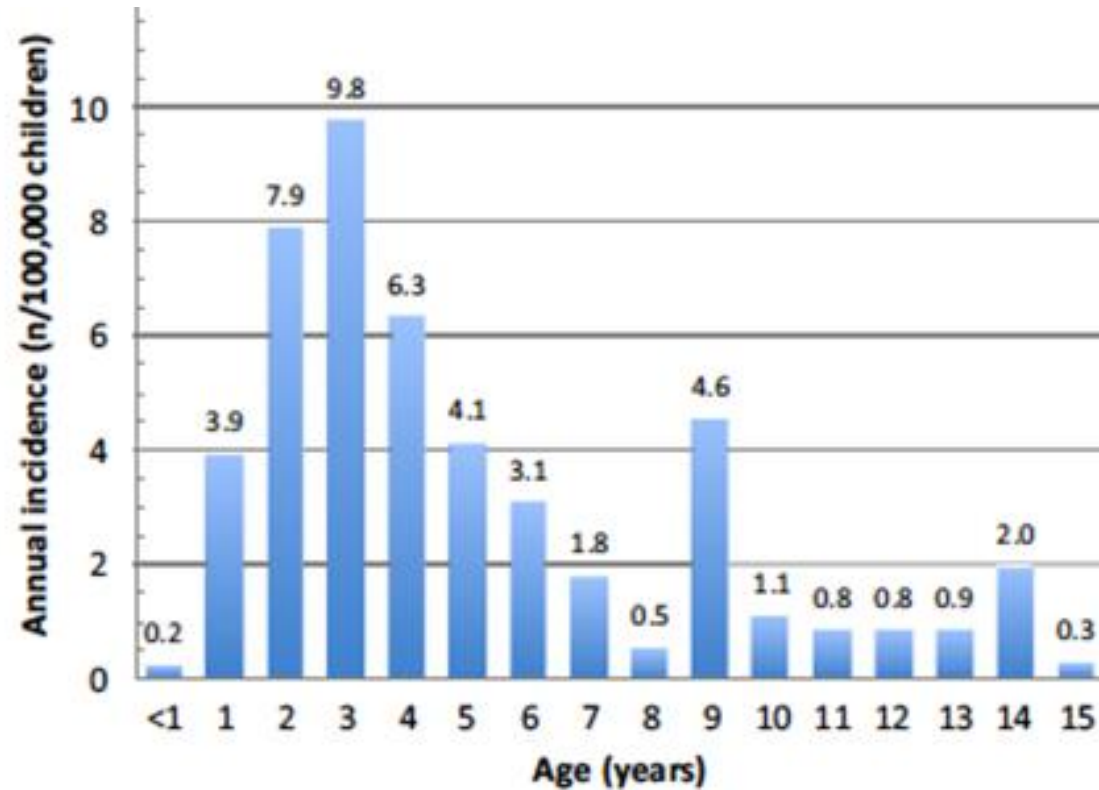


Practical Tips

- Spot urine protein/creatinine ratio is used in children given difficulty of 24 hour collections
- Always ensure it is a first morning urine dipstick (in non toilet trained children can put cotton balls in diaper overnight)
- Trace/microscopic hematuria can be seen in minimal change disease



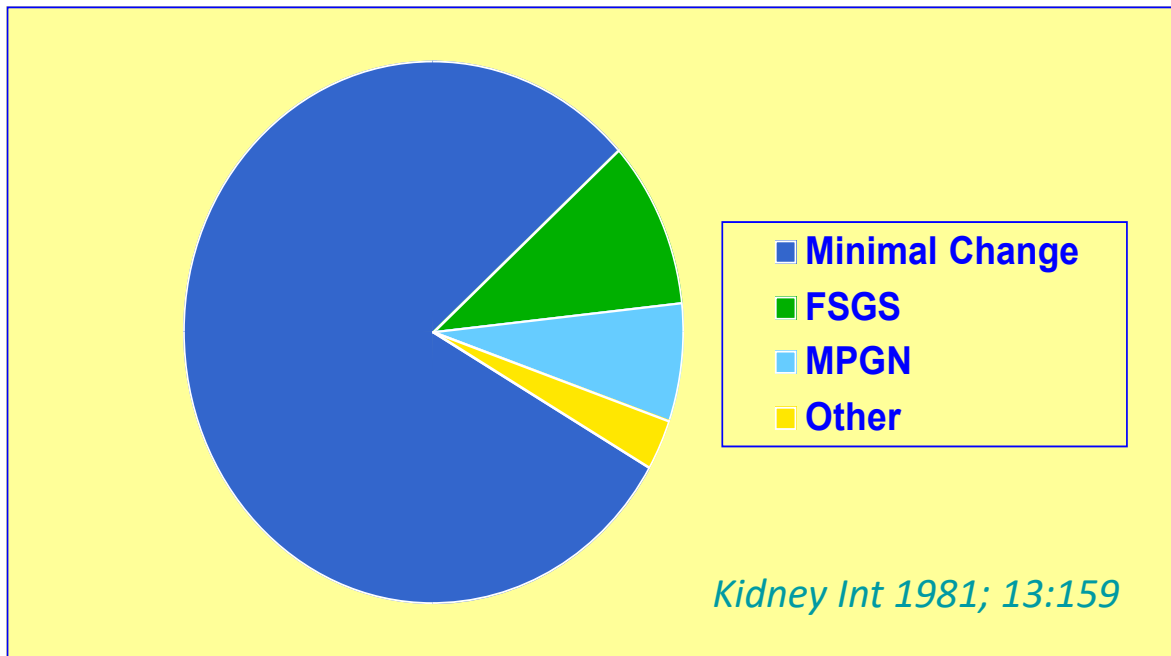
Pediatric Nephrotic Syndrome: Incidence by Age



- Childhood nephrotic syndrome is rare at any age
- However incidence is highest in pre-school age children
- Pre-adolescence incidence in boys:girls 2:1, post puberty incidence is similar

Dossier C et al, Pediatr Nephrol 2019; 34: 671-678

Histology of Pediatric Nephrotic Syndrome



- 1981 study where all children were biopsied at presentation
- Found 80% had MCD, 10% with FSGS

Presentation of Pediatric Nephrotic Syndrome

MCD vs FSGS

CHARACTERISTIC	MINIMAL CHANGE	FOCAL SCLEROSIS
Age $\leq$ 6 years old	80%	50%
Boys	60%	70%
Hypertension	20%	50%
Microhematuria	25%	50%
Elevated creatinine	30%	40%



When and Why of Empiric Steroids?

When to treat empirically?

- Preschool or young school age child
- Normal blood pressure
- Normal kidney function
- Non nephritic urine sediment on exam

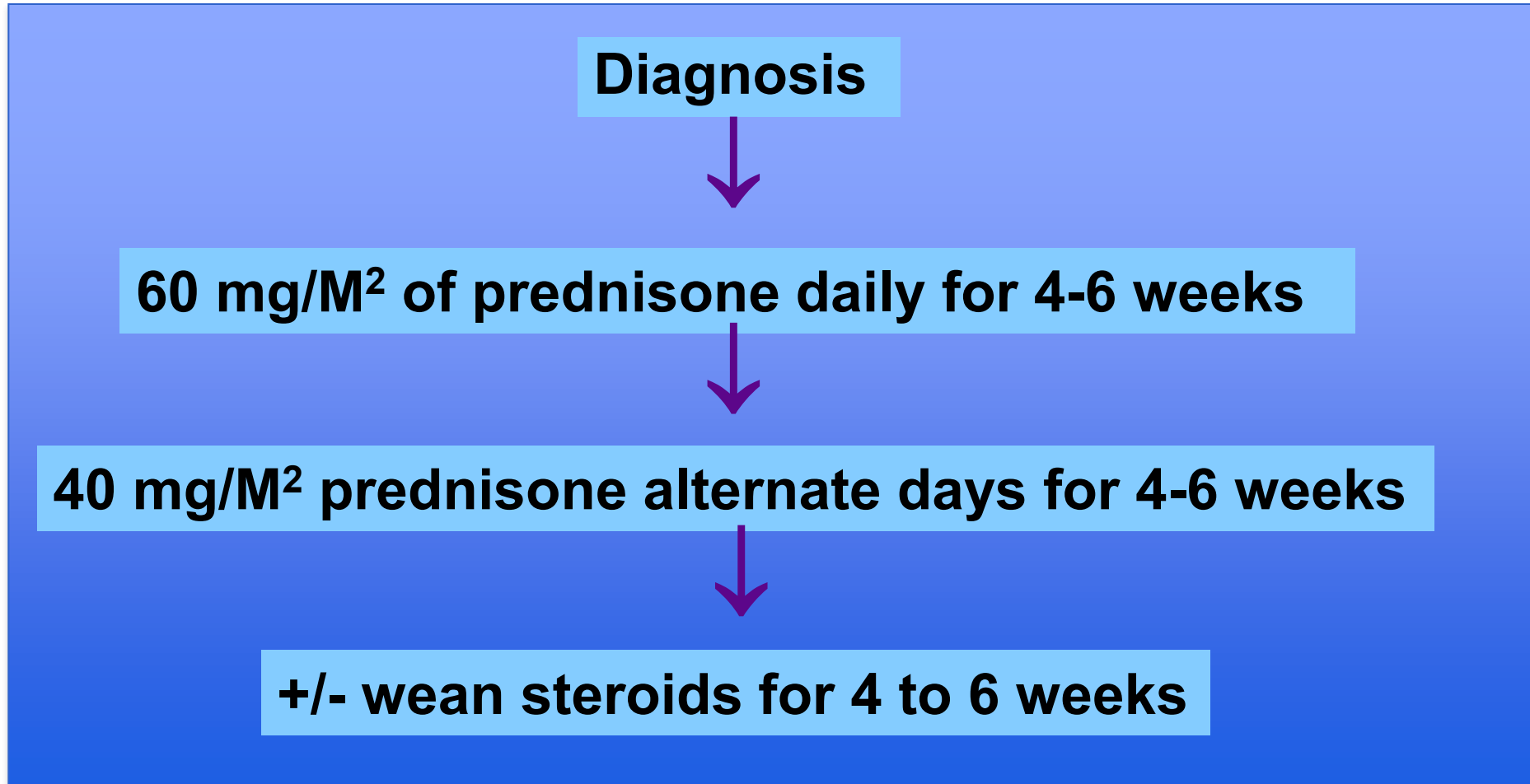
When to consider biopsy or genetic testing?

- Infantile or congenital nephrotic syndrome (children < 1 year of age)
- Sustained hypertension
- Kidney dysfunction
- Gross hematuria or RBC casts on urine sediment
- Low complement, other systemic features

Board Pearl: In childhood nephrotic syndrome in the absence of atypical features, the best “test” for etiology is response to steroids

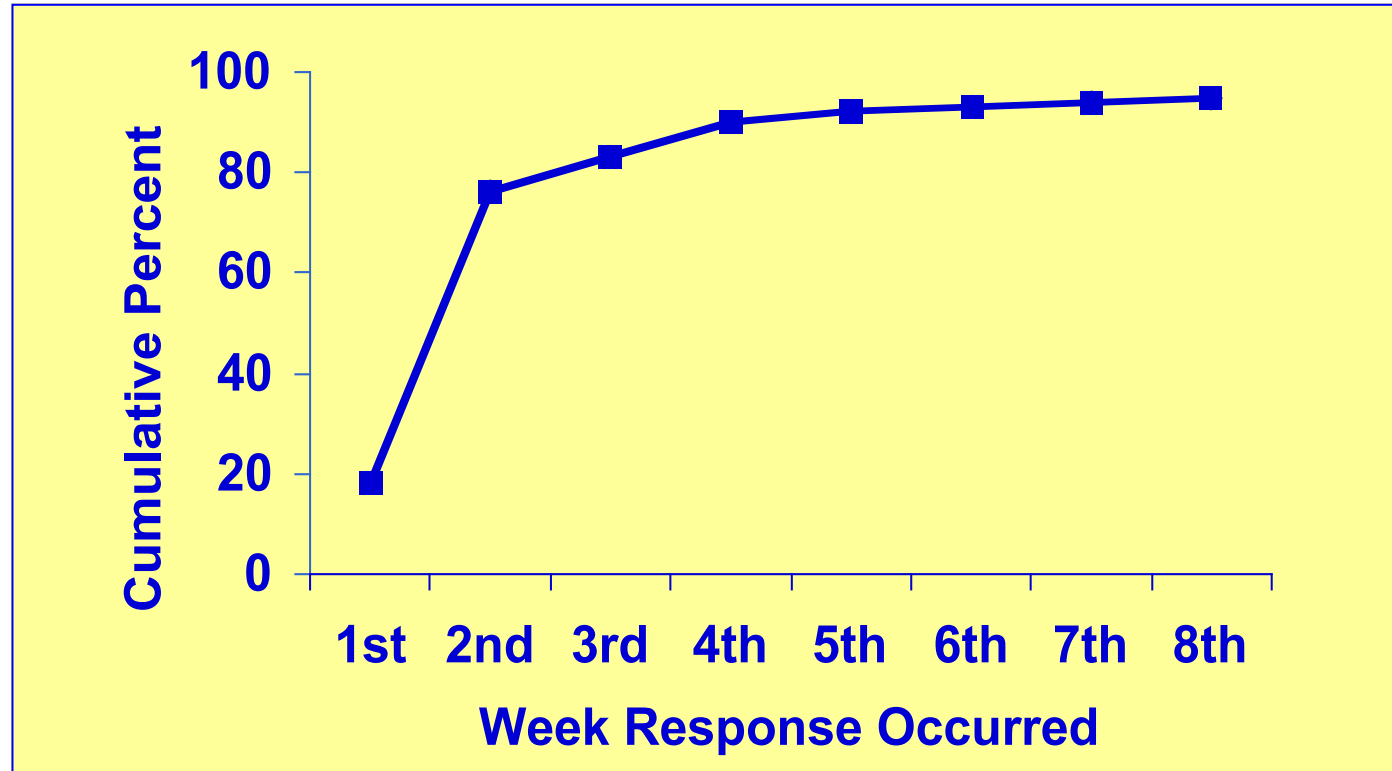


Steroid Therapy in Children



Steroid Therapy – Time to Response

ISKDC *Kidney Int* 1981; 13:159



- Average time to response = 10 days
- >90% of responders respond by 4 weeks



Nephrotic Syndrome Relapses

	Pediatrics
Steroid Responsive	Complete remission within 4-8 weeks
Steroid Dependent	Response to therapy with a relapse during steroid course or within two weeks of stopping
Steroid Resistant	Failure to achieve complete remission within 4-8 weeks
Frequently Relapsing	Two or more relapses within the first six months or 4 or more relapses in any 12 month period



Steroid Sparing Therapies

- MMF
 - Pros: not nephrotoxic, typically no drug level monitoring needed
 - Cons: increased risks of skin cancer, data showed better outcomes if dosed by AUC rather than BSA but this is much more difficult to do
- Rituximab
 - Pros: infusion, children less likely to revert back to frequently relapsing or steroid dependent after rituximab
 - Cons: infusion, variable duration of benefit
- CNI
 - Pros: stabilization of podocyte cytoskeleton, more standard drug monitoring than MMF
 - Cons: nephrotoxic, need for frequent drug monitoring

Ultimately, preferences vary center to center and patient to patient



Pediatric Nephrotic Syndrome – Important Adult Considerations

- Need to know original presentation and biopsy status
- Steroid sensitivity and relapse pattern (this can change over time)
- Prior MMF, CNI, rituximab or other immunosuppressive agent exposure (timing, duration)
- Steroid toxicity (need monitoring of growth, bone health, eye health, metabolic complications)
- Vaccination and infection history
- Reproductive counseling needs



Pediatric Hypertension



Case 2

- 10 year old boy presents for a routine well child check
- Former 28 week old male initially required ventilatory support in the NICU
- Periodic febrile illnesses in the first few years of life
- Height 25th percentile, weight 40th percentile
- BP at well child check 130s-140s/80s on oscillometric blood pressure machine
- Cr 0.6mg/dL, BMP within normal limits
- Urinalysis unremarkable



Next Best Step?

- A) Kidney ultrasound with doppler
- B) Plasma renin and aldosterone
- C) Initiate amlodipine at 0.1mg/kg BID
- D) Confirm cuff size and measure manual blood pressure
- E) Diet and exercise counseling with recheck in 3-6 months



Next Best Step?

- A) Kidney ultrasound with doppler
- B) Plasma renin and aldosterone
- C) Initiate amlodipine at 0.1mg/kg BID
- D) Confirm cuff size and measure manual blood pressure**
- E) Diet and exercise counseling with recheck in 3-6 months



Pediatric BP measurement

- Width > 40% of mid-arm circumference
- Bladder length > 80% of arm circumference
- If you don't want to remember these rules, you can measure arm circumference and manual BP cuffs will have the range they fit written on them
- Always confirm oscillometric readings with manual ones
 - 2001 Tampa school-based screening of 7,000 children age 5-17 years found oscillometric readings higher by 10mm Hg systolic and 5 mm Hg diastolic
- Always use upper extremity BP



Park et al. Arch Pediatr Adolesc Med 2001; 155:50-53.



Hypertension Definitions

Age < 13

- Normal: BP < 90th percentile
- Elevated Blood Pressure: BP $\geq$ 90th percentile but < 95th percentile
- Stage I Hypertension: $\geq$ 95th to 95th percentile + 12 mmHg
- Stage II Hypertension: BP $\geq$ 95th percentile + 12 mmHg

Age $\geq$ 13

- Normal: < 120/<80
- Elevated Blood Pressure: BP 120/<80 to 129/<80
- Stage I Hypertension: BP 130/80 to 139/89
- Stage II Hypertension: BP > 140/90

Percentiles are based upon sex, age, and height

If any of the percentile cutoffs for age < 13 exceed the age >13 BP cutoffs, use whichever is lower



Case 2 Additional Evaluation

- Kidney ultrasound revealed normal left kidney, right kidney with 2cm focal upper pole scarring
- Subsequent VCUG with grade 3 right sided reflux



Evaluation of Pediatric Hypertension

- Repeat manual BP
- Ensure correct cuff size
- Consider ABPM (should be done for all children in whom it is developmentally appropriate)
- Urinalysis, BMP, and metabolic screening
- Renal ultrasound if indicated
- Sleep evaluation if indicated (particularly if ABPM reveals nocturnal hypertension)
- Obtain echocardiogram if considering pharmacologic treatment or assessing suspected target end-organ effects



Treatment of Pediatric Hypertension

- Choice of agent should be based on underlying pathophysiology
 - ACEi/ARB if proteinuria
 - Thiazides for volume mediated hypertension
 - CCB often best tolerated
- Check pediatric dosing (mg/kg dosing and frequency)
- Titrate up to max dose as needed
- Target BP < 90% or < 130/80, whichever is lower



Pediatric CKD and Relevance to Adult CKD Management



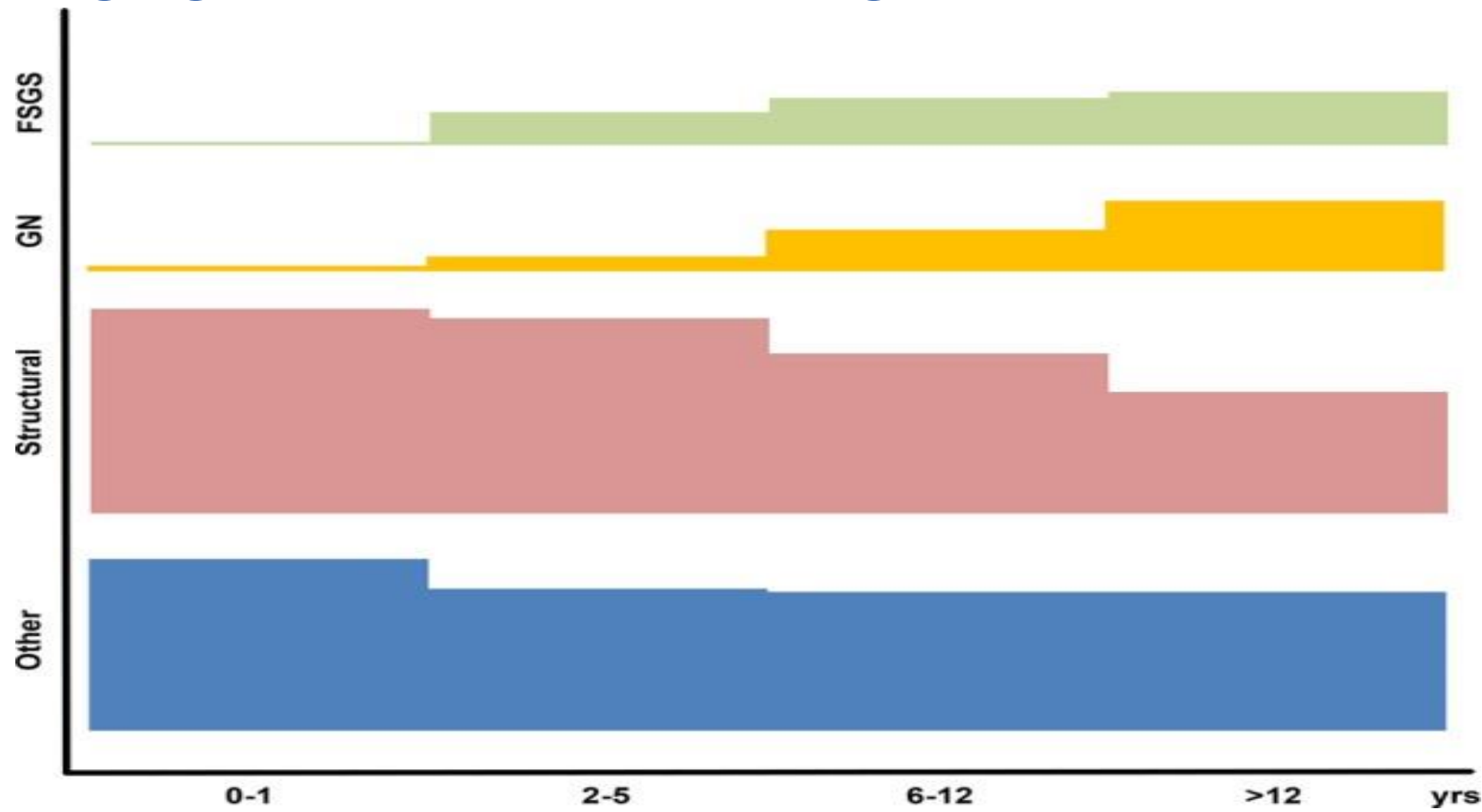
Causes of Pediatric CKD

CKD		ESRD	
Etiology	Percentage (Range)	Etiology	Percentage (Range)
CAKUT	48-59%	CAKUT	34-43%
GN	5-14%	GN	15-29%
HN	10-19%	HN	12-22%
HUS	2-6%	HUS	2-6%
Cystic	5-9%	Cystic	6-12%
Ischemic	2-4%	Ischemic	2%

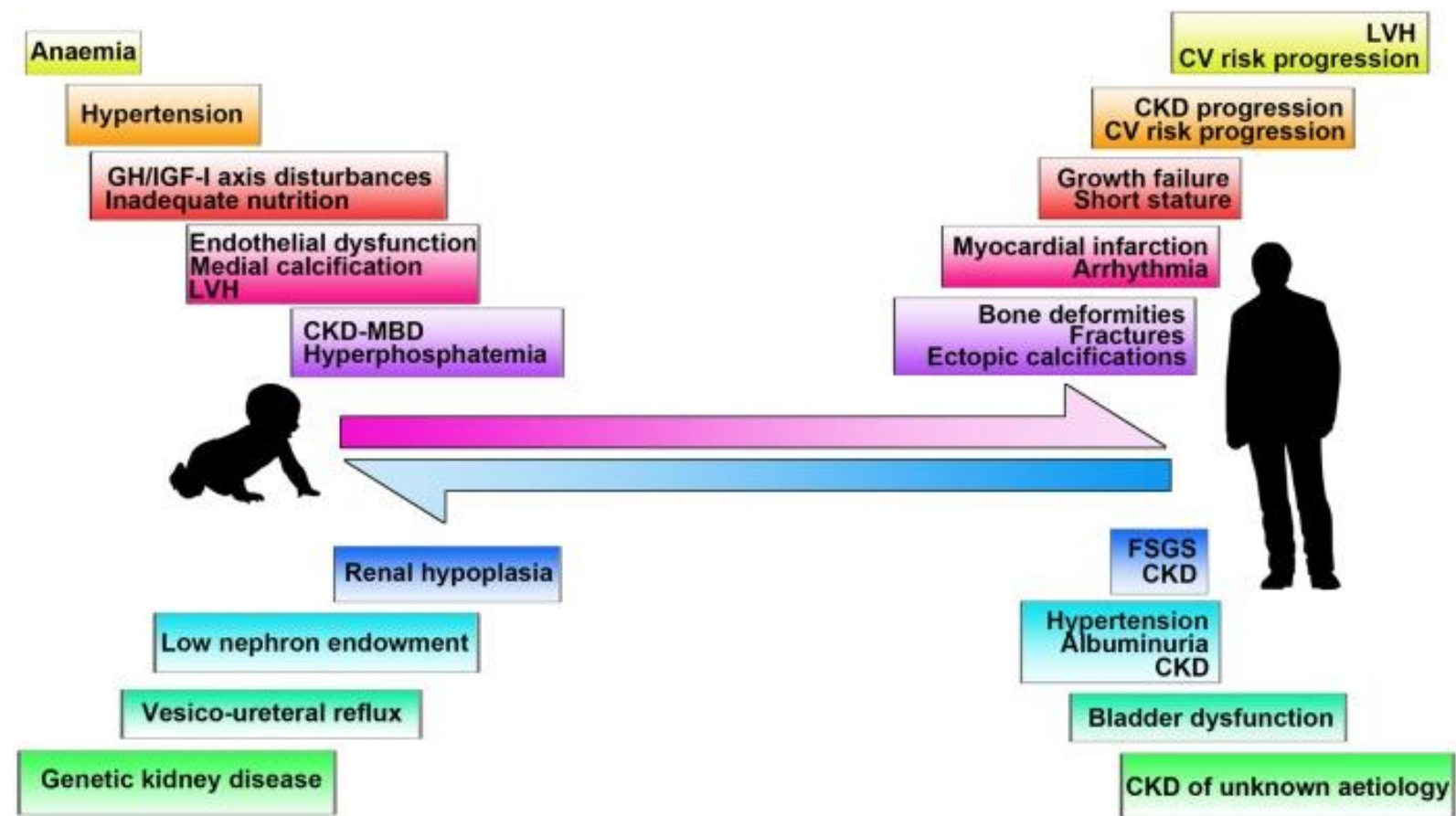
Source: Ingelfinger et al. World Kidney Day 2016: Averting the legacy of kidney disease. Focus on childhood.



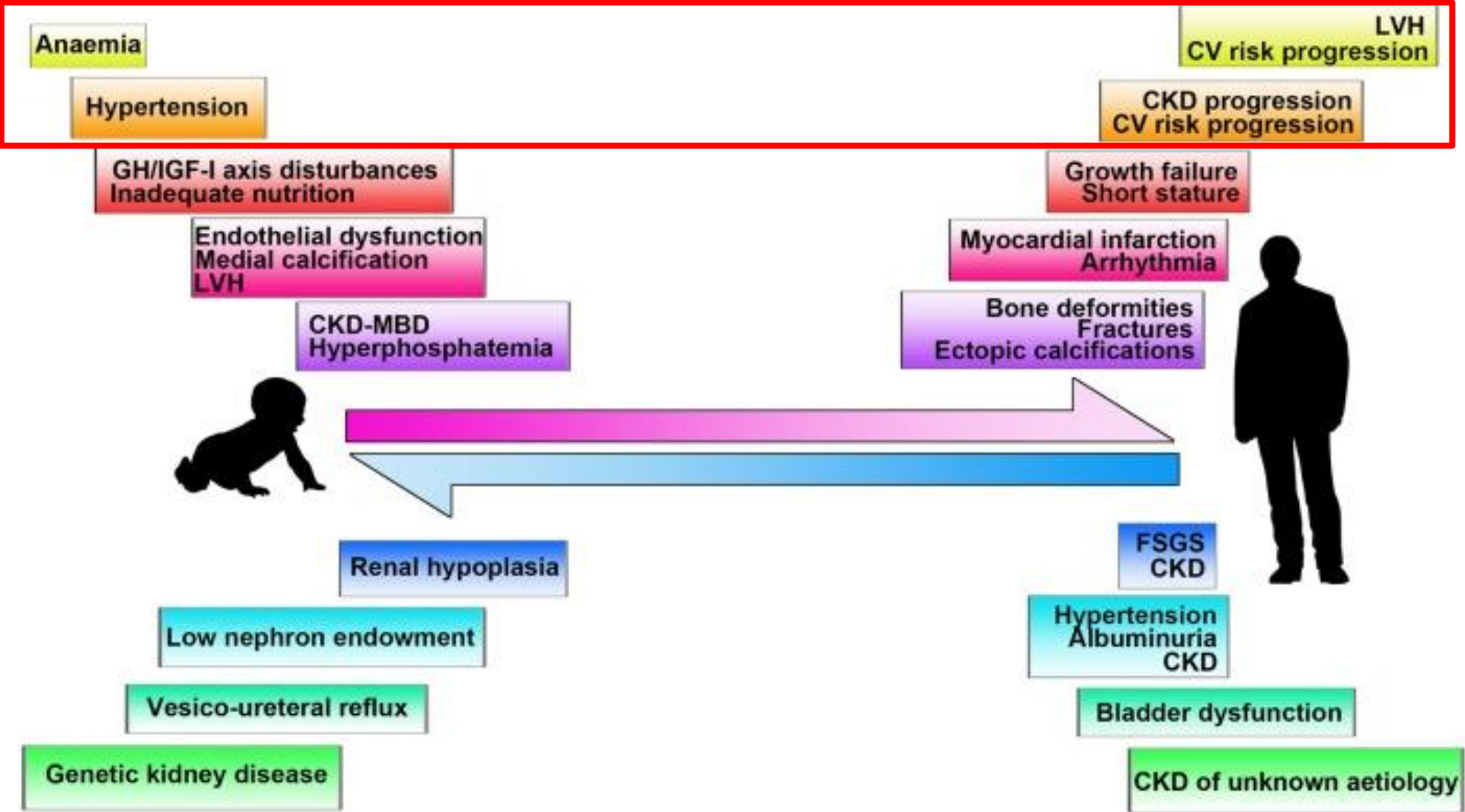
Changing Causes of CKD with Age



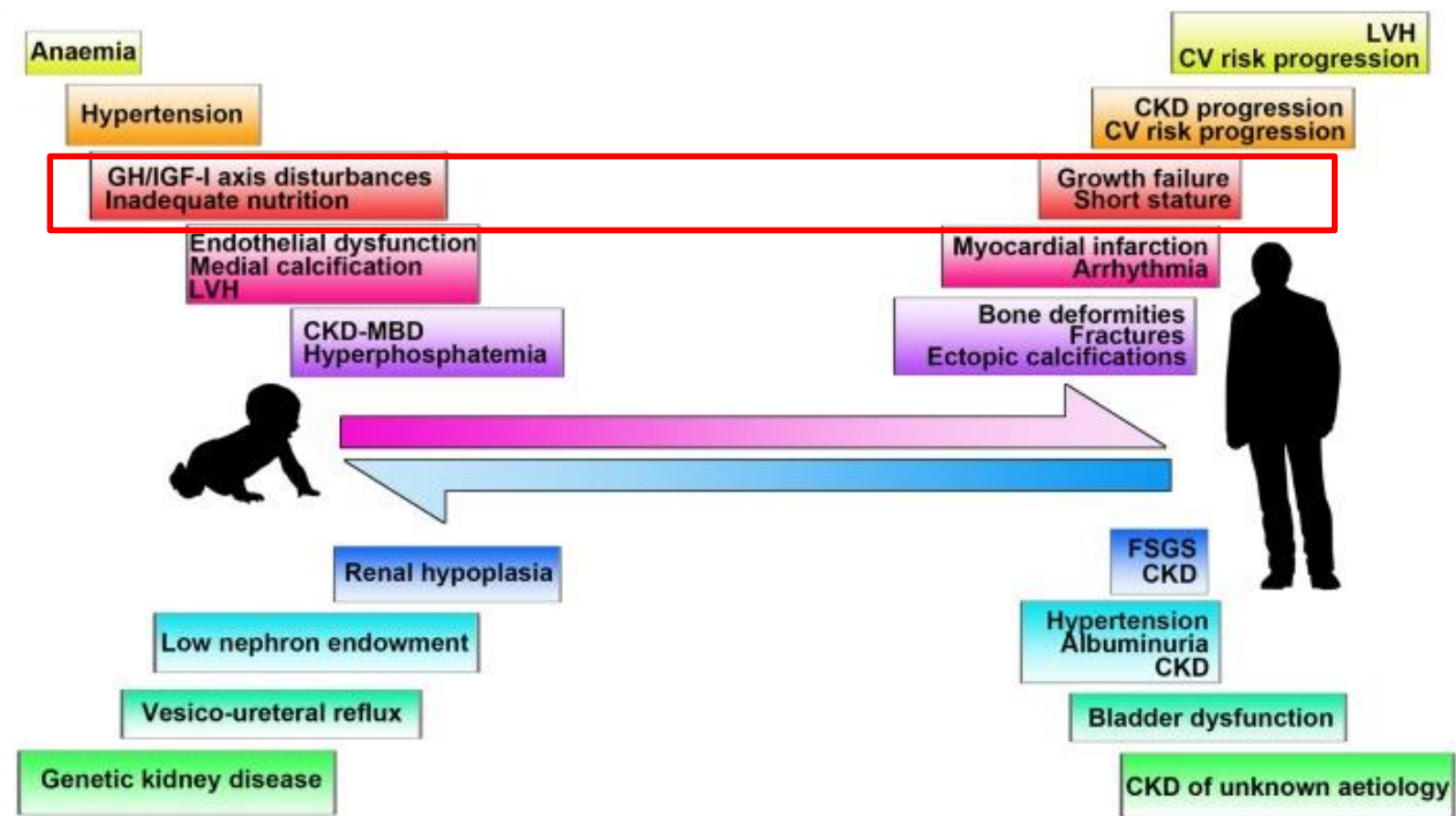
Childhood CKD – Effects in Adulthood



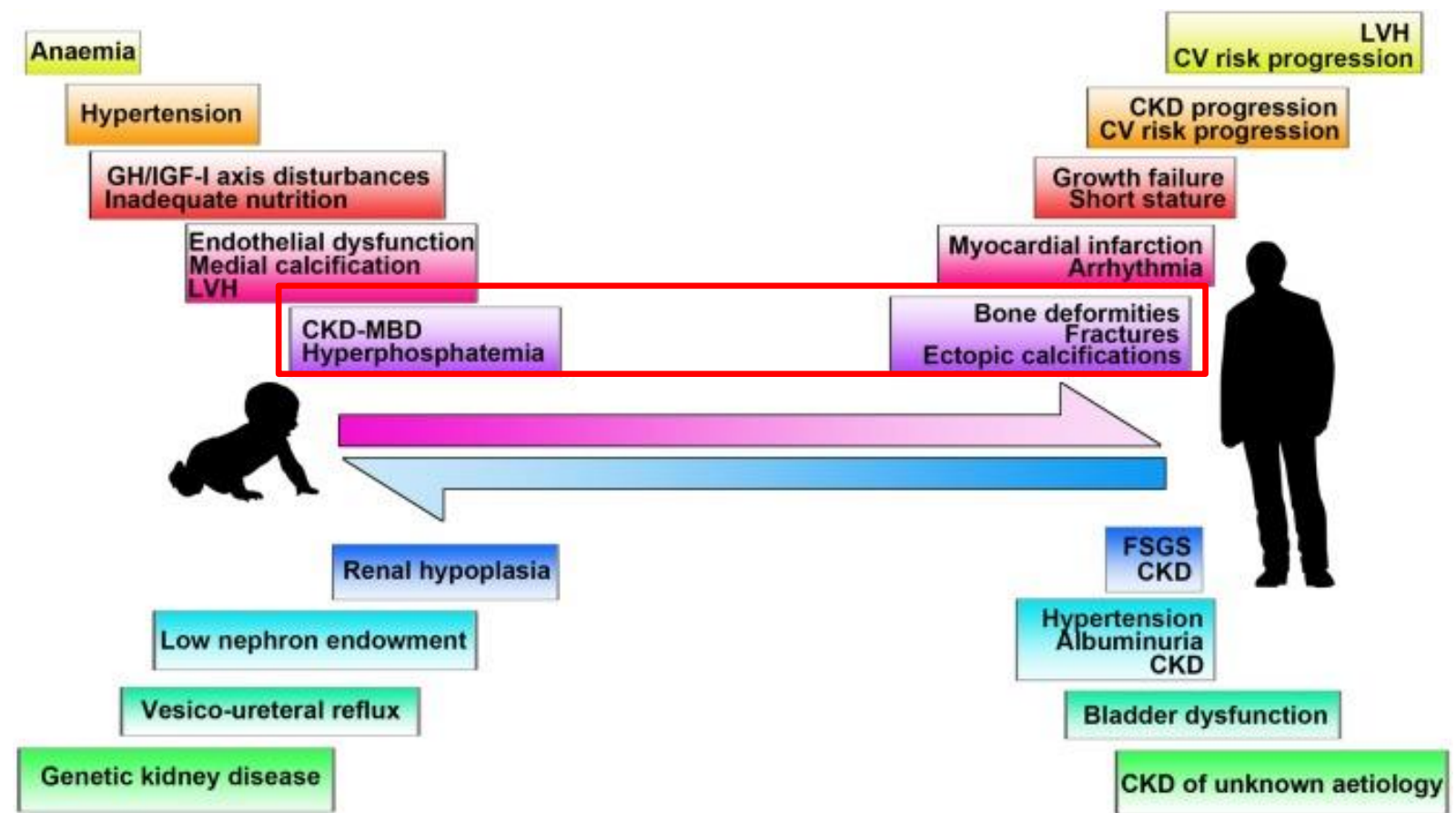
Childhood CKD – Effects in Adulthood



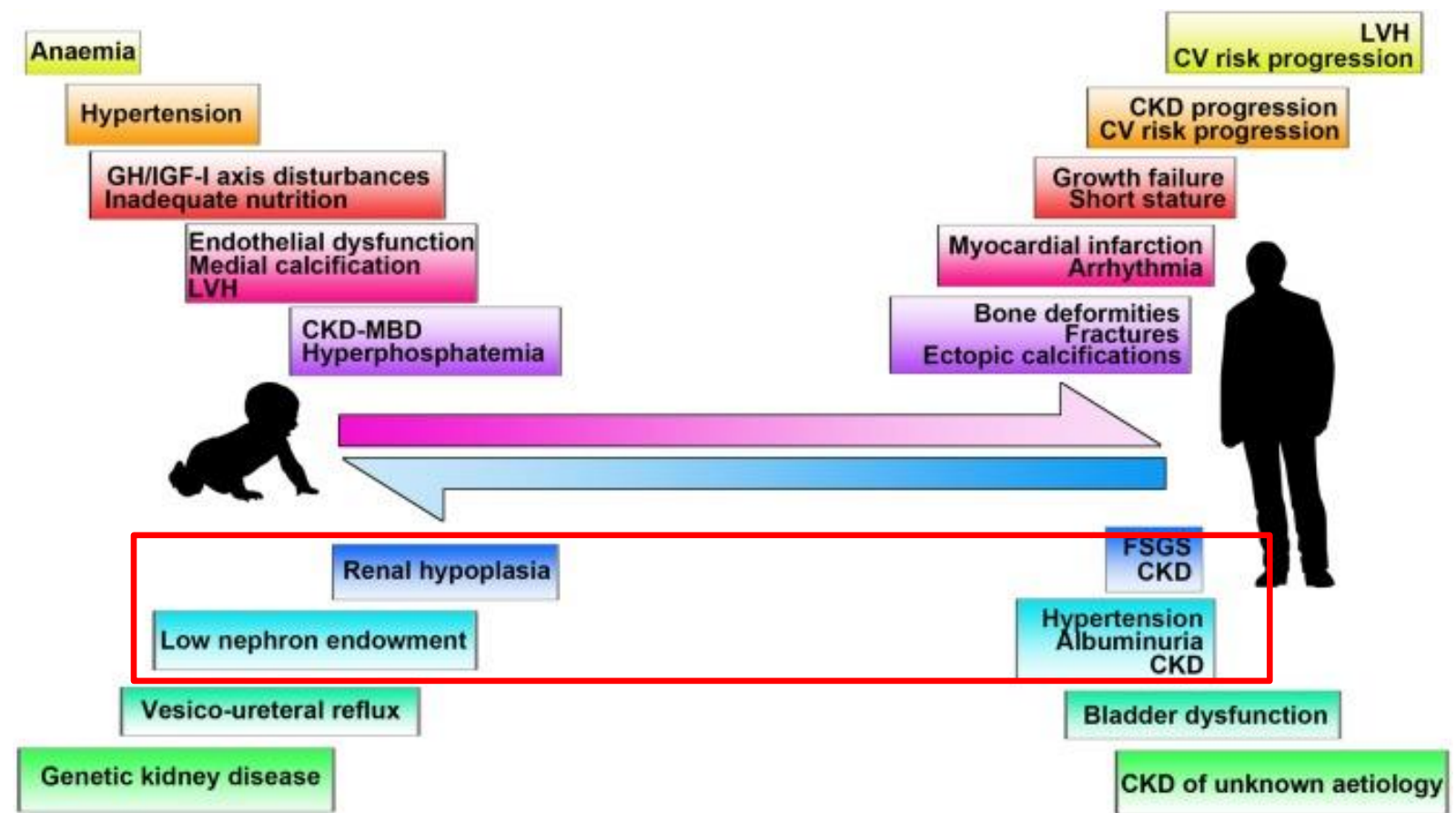
Childhood CKD – Effects in Adulthood



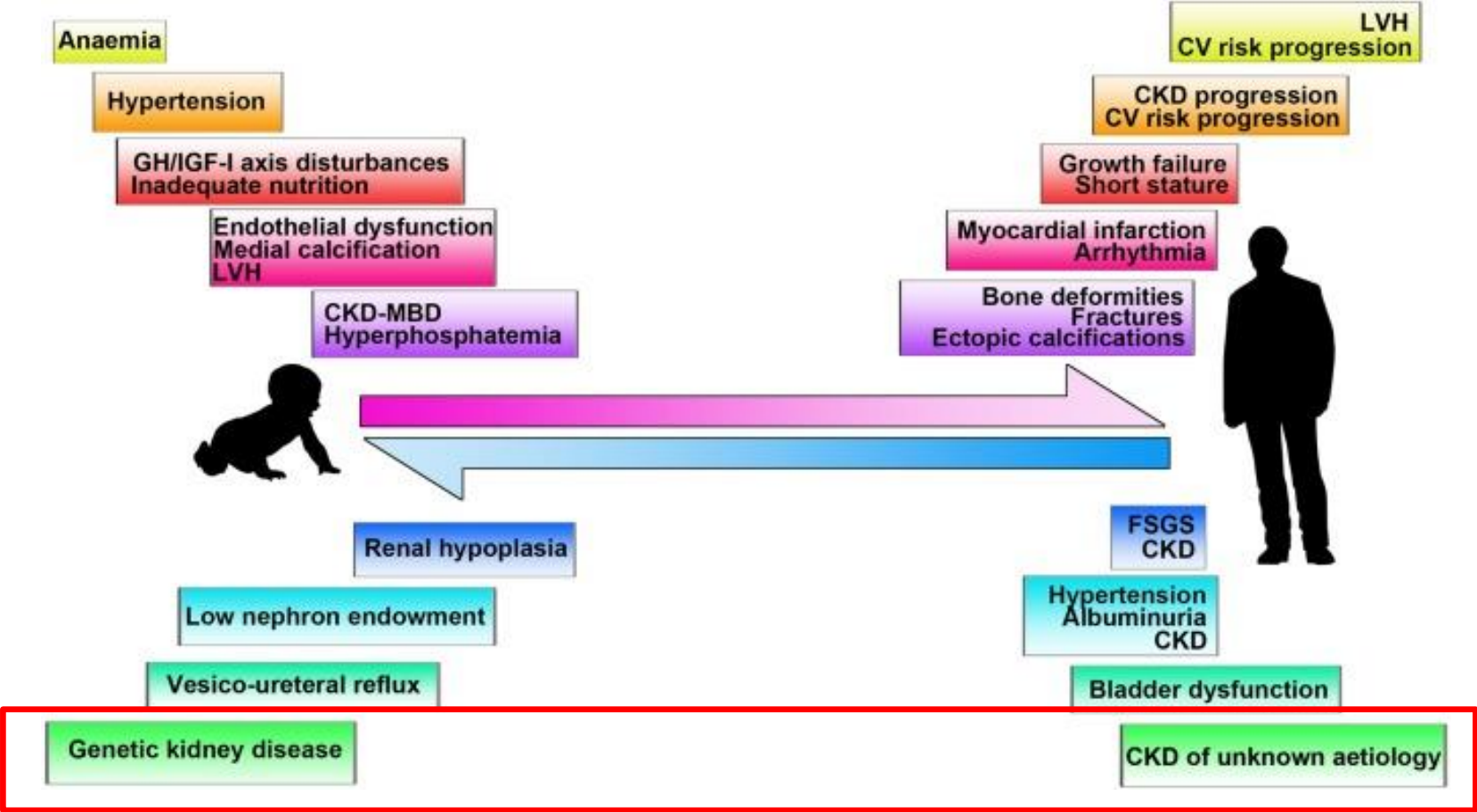
Childhood CKD – Effects in Adulthood



Childhood CKD – Effects in Adulthood



Childhood CKD – Effects in Adulthood



Difficulties in Treating Pediatric CKD



Difficulty Treating Pediatric CKD

Class of Drugs	Number Approved in Pediatrics	Number Approved in Adults	Percent Approved in Pediatrics
ESAs	3	3	100%
Iron Agents	2	7	28.5%
Genetic Disorders with Renal Manifestations	8	9	89%
Growth Failure	2	2	100%
Hyperkalemia	1	3	33%
Hyperphosphatemia	1	7	14%
Hypertension	14	33	42%
Secondary Hyperparathyroidism	3	9	33%



Difficulty Treating Pediatric CKD

- In addition to fewer approved therapies, many patients experience a more rapid progression of CKD during adolescence
- This is due to a variety of factors including compliance with therapy but additionally a rapid change in body composition and increase in mass without ability to compensate



Transitions of Care



Transfer vs Transition

Transfer of Care

- Discrete event
- When a patient moves to the adult clinic/care team
- Often due to age, insurance, geography, program policy, or clinical status (need to start dialysis)
- Can happen without transition

Transition of Care

- Planned structural process based on transitions developmental milestones
- Slowly builds autonomy, knowledge, and self management skills over time
- Includes the changing role of the family and increasing autonomy/need for confidentiality
- Requires handoff between teams and follow-up to ensure successful transition



Transitions of Care – History Taking

- Should have a detailed understanding of nephrology history: anatomy, imaging, prior procedures, labs, genetics, biopsy results, trajectory
- Determine what the adult is able to manage independently and what barriers exist to independent management
- Review reproductive health and teratogenic medications
- Ensure you know about any urologic issues
- Understand treatment history including why prior adult standard of care agents were discontinued or not attempted (intolerance, therapy failure, not approved in pediatrics, etc) – make no assumptions
- Patients should have early follow up rather than default adult timing



Importance of Successful Transitions

- Limited data exists on the progression of CKD at the time of transitions
- However, from transplant data, we know that compared with individuals with the same time since transplant age 25-29 years, death-censored graft failure rates are highest in those ages 17-24 (HR 1.2 95% CI 1.13-1.27)
- Roughly 1/3 of the graft failure in the adolescent age group and at the time of transition is considered unexpected
- 30% failure rate of transplant within the first 36 months of transfer to adult care
- Transplant transition clinic model in Canada demonstrated both decreased incidence of death or graft loss with transition clinic as well as significant cost reduction



Transitions – Pediatric Team Tasks

Verbal and written summary of:

- Demographics
- relevant clinical information
- most recent notes and labs
- Medication list
- Problem list
- Pharmacy and lab numbers
- PCP
- Insurance status
- Date of transfer



Transitions – Adult Team Tasks

- Orientation to adult care
- Review of medical records and discussion of distinctions between pediatric and adult care
- Strengthening self care skills
- Discussing confidentiality and access to information
- Discussing best methods of communication with adolescent/young adult
- Ongoing communication with pediatric provider during time of transition



Post Transition Monitoring

- Pediatric team remains available for support but adult team is primary team
- Ongoing assessments of competencies in self care
- Assessments of adherence as well as documentation of reasons for non adherence and addressing of these issues (willful, forgetfulness, socio-economic factors)
- Monitoring of long term outcomes



TAKE HOME MESSAGES

Nephrotic syndrome:

- Most children can be empirically treated with glucocorticoids without kidney biopsy
- Response to steroids is usually rapid, but frequent relapses and steroid dependency are common
- MMF, rituximab, and CNi are all appropriate second line agents
- Many children enter long periods of remission post puberty but relapses as an adult can also be expected
- Steroid resistance should prompt kidney biopsy, genetic evaluation, and consideration of FSGS



TAKE HOME MESSAGES

Hypertension:

- Pre-adolescent is based on age, sex, and height
- First step is always manual BP with appropriate cuff
- Obesity is a rising cause of hypertension in children, but underlying parenchymal disease should be considered
- Treatment should be based on underlying etiology



TAKE HOME MESSAGES

Transitions:

- Structured process with ongoing communication between pediatric and adult providers
- Can improve outcomes for adolescents with CKD and transplant
- Important considerations including masking of baseline cognitive dysfunction and normal prolonged adolescence in those with chronic disease
- Set expectations for adult care at the first visit
- More frequent follow up initially
- Gain an understanding of pediatric team's rationale to help guide changes in care into adulthood



REFERENCES

AJKDblog. #NephMadness 2023: Transitions of Care Region. AJKD Blog. Published March 1, 2023. Accessed August 17, 2023. <https://ajkdblog.org/2023/03/01/nephmadness-2023-transitions-of-care-region/>

Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. *Clin Kidney J*. 2016;9(4):583-591. doi:10.1093/ckj/sfw047

CDC Surveillance System: Diagnosed CKD Among Medicare Beneficiaries Aged ≥ 65 Years, by U.S. State and County. Accessed August 17, 2023. <https://nccd.cdc.gov/CKD/detail.aspx?Qnum=Q705&topic=1#refreshPosition>

Chronic Kidney Disease Basics | Chronic Kidney Disease Initiative | CDC. Published February 28, 2022. Accessed August 15, 2023. <https://www.cdc.gov/kidneydisease/basics.html>

Chronic Kidney Disease in the United States, 2023. Published June 26, 2023. Accessed August 15, 2023. <https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html>

Etiology of Chronic Kidney Disease in Children. ResearchGate. Accessed August 17, 2023. https://www.researchgate.net/figure/Etiology-of-Chronic-Kidney-Disease-in-Children_tbl2_298856436

Falkner B, Gidding SS, Baker-Smith CM, Brady TM, Flynn JT, Malle LM, South AM, Tran AH, Urbina EM. Pediatric Primary Hypertension: An Underrecognized Condition: A Scientific Statement From the American Heart Association. *Hypertension*. 2023; 80:e101-e111. PMID: 36994715.

Ferguson MA and Flynn JT. Rational use of antihypertensive medications in children. *Pediatr Nephrol*. 2014; 29:979-88. PMID: 23715784.



REFERENCES

- Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2017;140(3):e20171904. PMID: 28827377.
- Foster BJ, Dahhou M, Zhang X, Platt RW, Samuel SM, Hanley JA. Association between age and graft failure rates in young kidney transplant recipients. *Transplantation*. 2011;92(11):1237-1243. doi:10.1097/TP.0b013e31823411d7
- Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol*. 2012;27(3):363-373. doi:10.1007/s00467-011-1939-1
- Ingelfinger JR, Kalantar-Zadeh K, Schaefer F, World Kidney Day Steering Committee. World Kidney Day 2016: Averting the legacy of kidney disease-focus on childhood. *Pediatr Nephrol*. 2016;31(3):343-348. doi:10.1007/s00467-015-3255-7
- Kaspar CDW, Bholah R, Bunchman TE. A Review of Pediatric Chronic Kidney Disease. *Blood Purification*. 2016;41(1-3):211-217. doi:10.1159/000441737
- Khurana M, Egger GF, Yao L, et al. Overcoming Barriers to Drug Development in Children with CKD. *Clinical Journal of the American Society of Nephrology*. 2023;18(8):1101. doi:10.2215/CJN.0000000000000167
- Kidney Disease in Children - NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed August 17, 2023. <https://www.niddk.nih.gov/health-information/kidney-disease/children>
- Malloy MH, Wang LK. The limits of viability of extremely preterm infants. *Proc (Bayl Univ Med Cent)*. 35(5):731-735. doi:10.1080/08998280.2022.207107



REFERENCES

- Masalskienė J, Rudaitis Š, Vitkevič R, Čerkauskienė R, Dobilienė D, Jankauskienė A. Epidemiology of Chronic Kidney Disease in Children: A Report from Lithuania. *Medicina (Kaunas)*. 2021;57(2):112. doi:10.3390/medicina57020112
- Mattoo TK, Sanjad S. Current Understanding of Nephrotic Syndrome in Children. *Pediatr Clin North Am*. 2022; 69:1079-1098. PMID: 36880923.
- Pepper RJ, Trompeter RS. The causes and consequences of paediatric kidney disease on adult nephrology care. *Pediatr Nephrol*. 2022;37(6):1245-1261. doi:10.1007/s00467-021-05182-w
- Raina R, Wang J, Krishnappa V, Ferris M. Pediatric Renal Transplantation: Focus on Current Transition Care and Proposal of the “RISE to Transition” Protocol. *Ann Transplant*. 2018;23:45-60. doi:10.12659/AOT.906279
- Rheault MN and Gbadegesin RA. The genetics of nephrotic syndrome. *J Pediatr Genet*. 2016; 5:15-24. PMID: 27617138.
- Steiner MS, Morton RA, Marshall FF. Vitamin B12 deficiency in patients with ileocolic neobladders. *J Urol*. 1993;149(2):255-257. doi:10.1016/s0022-5347(17)36049-4
- Szczech LA, Stewart RC, Su HL, et al. Primary Care Detection of Chronic Kidney Disease in Adults with Type-2 Diabetes: The ADD-CKD Study (Awareness, Detection and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease). *PLOS ONE*. 2014;9(11):e110535. doi:10.1371/journal.pone.0110535
- Watson AR. Non-compliance and transfer from paediatric to adult transplant unit. *Pediatr Nephrol*. 2000;14(6):469-472. doi:10.1007/s004670050794
- World Kidney Day 2016: Averting the legacy of kidney disease. Focus on childhood. Accessed August 17, 2023. https://core.ac.uk/reader/82662491?utm_source=linkout



REFERENCES

Trautmann A, Boyer O, Hodson E, et al for International Pediatric Nephrology Association. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome. *Pediatr Nephrol*. 2023;38:877-919. PMID: 36269406.

Trautmann A, Vivarelli M, Samuel S, et al for International Pediatric Nephrology Association. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 2020;35:1529-1561. PMID: 32382828.

