Paediatric Nephrology Workshop– 18 June 2023

PERITONEAL DIALYSIS: EXPERIENCE FROM NIGERIAN CENTRES

Dr. Asinobi O. Adanze. FMCPaed, MSc, ISN Fellow, MD (NPMCN)

Disclosure

- I have no disclosure to make.

Objectives

To describe the following:

1. Summarise the burden of Paediatric Acute Kidney Injury & CKD
2. Aetiology of AKI in Low resource setting and outcomes Challenges with management of paediatric AKI in low resource setting
3. Historic Perspectives of Available Treatment modalities for AKI
4. Experience from Nigeria
5. Opportunities, hopes, and way forward in the management of paediatric disorders in Nigeria

University of Ibadan

University of Ibadan Established 1948 : Administrative Block

The College

The First College of Medicine in Nigeria and a Foundation Faculty of the University of Ibadan, then a College of the University of London

AFRICA: SAHARA AND SUB-SAHARA

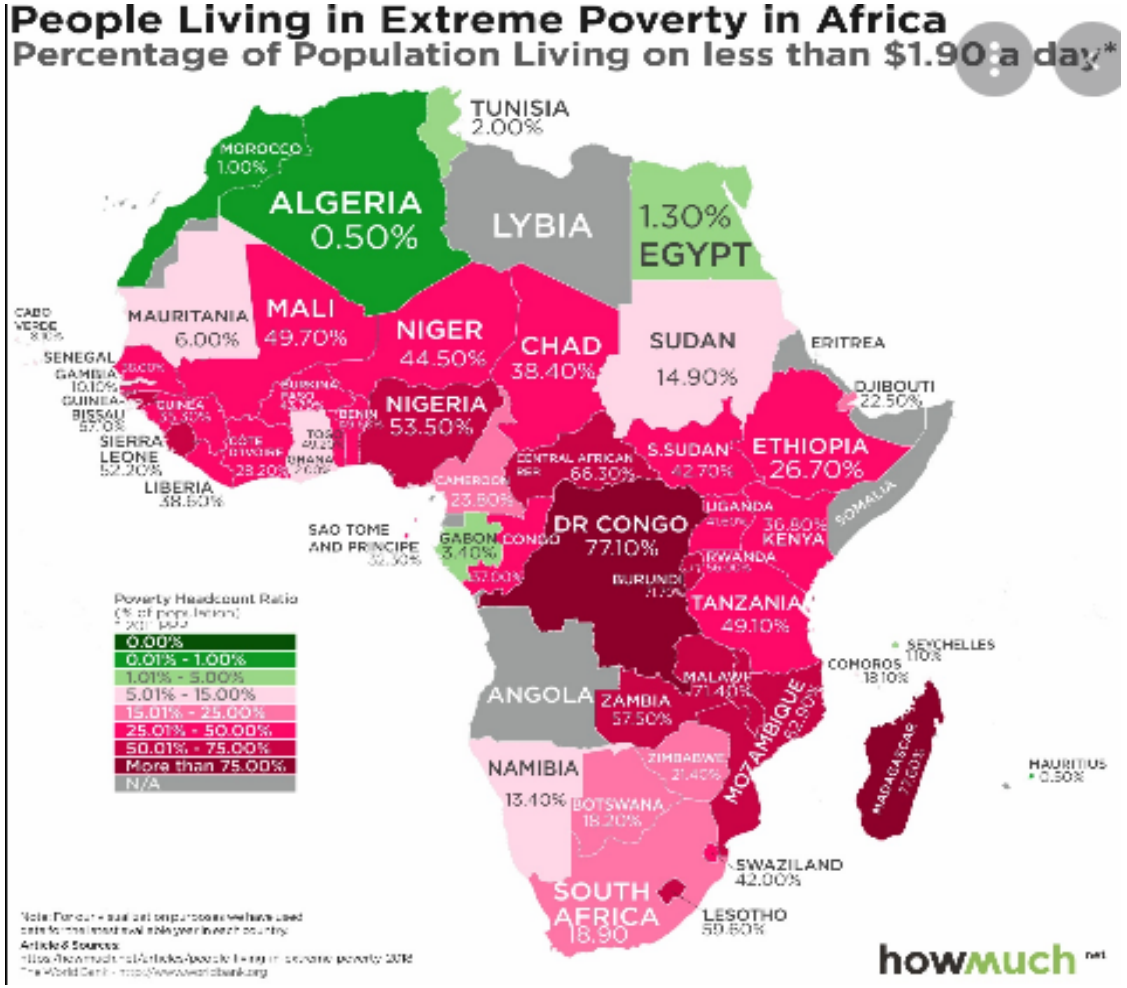
Introduction cont'd

- Nigeria is the most densely populated Country in Africa and Africa is the continent with most extreme levels of poverty.

- Majority live on less than $1.90/day and most of those affected live in Sub-Saharan Africa(SSA)

- Nigeria harbours over 217 million of the 1.4 billion Africans and 1.1 Billion people in Sub-Saharan Africa with 67% of Nigerians living in poverty.

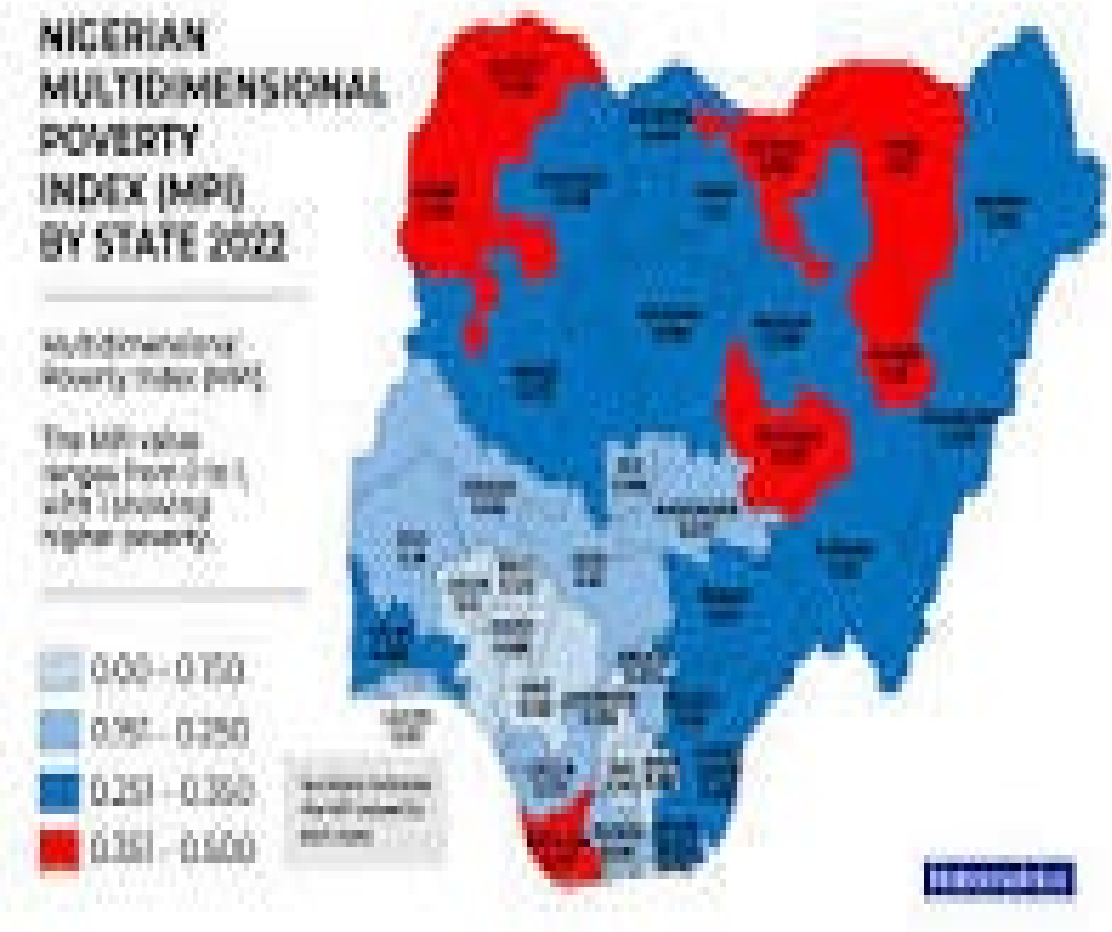
- Provision of KRT in any form has remained a Big challenge in Nigeria.



Available from: https://data.worldbank.org/indicator

NIGERIA

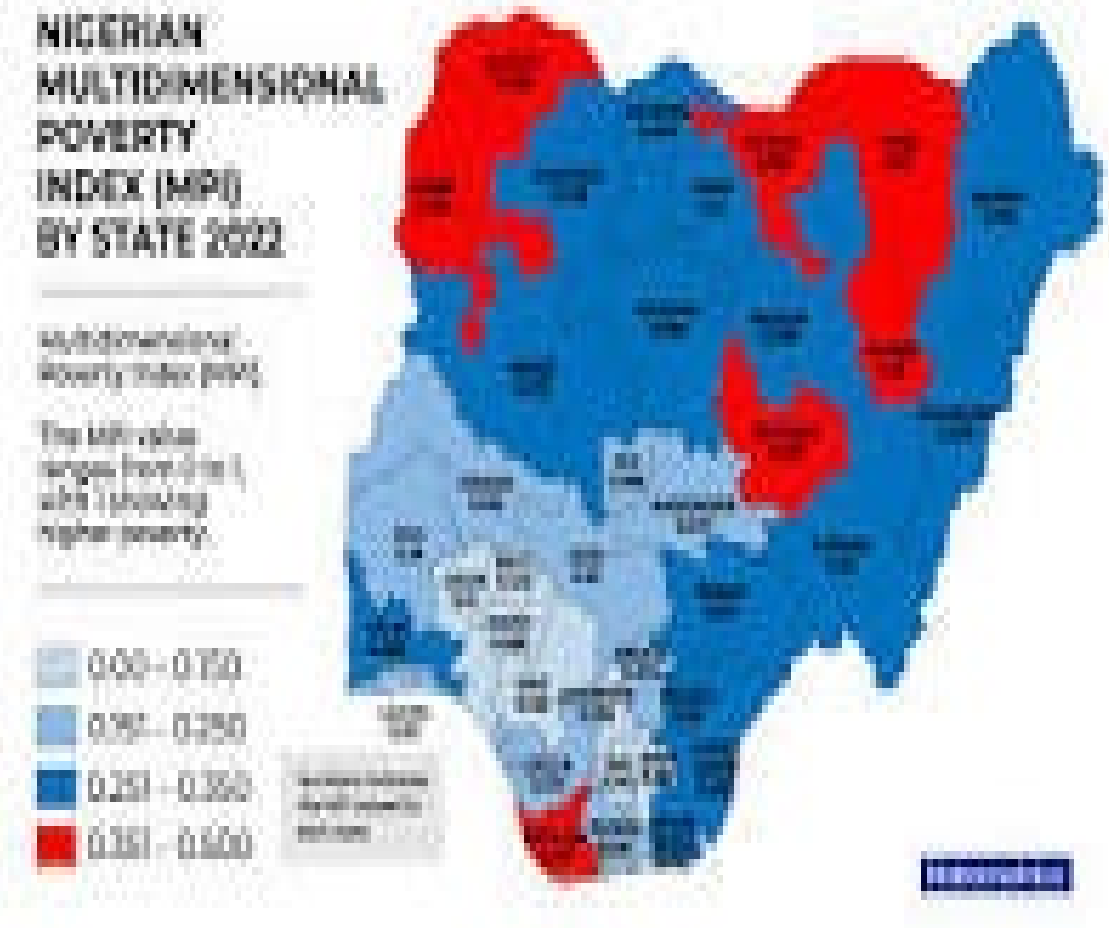
- Nigeria is the most populous black nation in the world
- One out of every four Africans and one out of every five persons of African origin is a Nigerian
- Nigeria, the Giant of Africa, with a very robust economy in the 1970s to early 1980s and the largest economy in Africa is now said to be the Poverty Capital of the world, in spite of her resources



NIGERIA

- Unfortunately, RRT Therapy is generally not compatible with poverty unless deliberate efforts are made by a people to make provision for it

- It costs the developed countries a significant proportion of their GDP



Acute Kidney Disease (AKI)in Children: A Silent Killer in Nigeria (PNAN)

- AKI is a significant public health problem, particularly in low-and middle-income countries (LMICs), where almost 90 percent of the cases occur yearly

- Children and young adults in LMICs are disproportionately affected by AKI and die silently from its largely preventable causes

- The most common causes of AKI requiring acute KRT in Nigeria are infection-related, namely: Sepsis, Malaria and Acute Glomerulonephritis.
- About 70% of our population live in rural areas that are underserved generally and KRT are not being offered

AKI in Children contd

- AKI incidence in children is high (ranging from 10 to 82%, depending on the hospital diagnostic populations studied)
- AKI is associated with increased hospital mortality (especially dialysis-requiring AKI in children which may exceed 50%
- AKI is associated with longer length of stay and ventilation, and with higher total health care costs
- Instituting sustainable treatment programmes for patients with kidney failure has remained a daunting task to most nephrologists in Sub-Saharan Africa
- I feel very unhappy discussing these issues for over 3 decades with minimum achievements but it would have been worse without the efforts of you and I
- However we need to keep up the advocacy and keep hope alive.

Global Burden of AKI

Population	Age	Incidence (range)	RRT requirement (%)	Mortality (%)
Non-ICU hospitalized patients	Adult	<1 in 5 patients	<10	10–20
Critically ill patients	Adult	1 in 3 to 2 in 3 patients	5–11	NR
	Paediatric	1 in 4 patients (10–82%)	1–2	11
Patients undergoing cardiac surgery	Adult	1 in 5 patients (2–50%)	<5	10
	Paediatric	1 in 3 to 1 in 2 patients	NR	6
Patients with sepsis	Adult	1 in 20 to 1 in 2 patients	15	30–60

Hoste et al: Nature Reviews in Nephrology 2018 https://doi.org/10.1038/ s41581-018-0052-0

Aetiology of AKI in Low resource setting

	Children (n=1643)*	Adults (n=993)†
Infection	380 (23%)	274 (28%)
Septicaemia	370	232
HIV	6	0
Tetanus	4	1
Pyelonephritis	0	12
Typhoid	0	7
Cholera	0	22
Glomerular disease	350 (21%)	76 (8%)
Acute glomerulonephritis	183	57
Nephrotic syndrome	115	10
Rapidly progressive acute glomerulonephritis	46	4
Lupus nephritis	5	5
Membranoproliferative acute	1	0

	Children (n=1643)*	Adults (n=993)†
(Continued from previous column)		
Congenital anomaly of the kidney and the urinary tract		
Posterior urethral valves	32	0
Renal agenesis	4	0
Prune belly syndrome	1	0
Prostate	0	9
Malignancy	0	2
Schistosoma	0	2
Unspecified	49	17
Vascular disease or haemolysis	116 (7%)	11 (1%)
Haemolytic uraemic syndrome	111	1
Thrombotic thrombocytopenic purpura	2	0
Purpura fulminans	1	0

Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review Wasiu A Olowu*, Abdou Niang*, Charlotte Osafo, Gloria Ashuntantang, Fatiu A Arogundade, John Porter, Saraladevi Naicker, Valerie A Luyckx

Malaria-Associated Acute Kidney Injury in African Children: Prevalence, Pathophysiology, Impact, and Management Challenges_ A review by Batte et al 2021

Part of the Abstract:

- Acute kidney injury (AKI) is emerging as a complication of increasing clinical importance associated with substantial morbidity and mortality in African children with severe malaria
- Using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI, an estimated 24–59% of African children with severe malaria have AKI with most AKI community-acquired
- AKI is a risk factor for mortality in pediatric severe malaria with a stepwise increase in mortality across AKI stages. AKI is also a risk factor for postdischarge mortality and is associated with increased long-term risk of neurocognitive impairment and behavioral problems in survivors
- In this review, we outline the KDIGO bundle of care and highlight how this could be applied in the context of severe malaria to improve kidney perfusion, reduce AKI progression, and improve survival.
- With increased recognition that AKI in severe malaria is associated with substantial post-discharge morbidity and long-term risk of chronic kidney disease, there is a need to increase AKI recognition through enhanced access to creatinine-based and nextgeneration biomarker diagnostics.
- Long-term studies to assess severe malaria-associated AKI's impact on long-term health in malaria-endemic areas are urgently needed

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Original paper

OXFORD

Acute Kidney Injury in Children with Severe Malaria Is Common and Associated with Adverse Hospital Outcomes

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ABSTRACT

Background: The prevalence of acute kidney injury (AKI) in children with severe malaria in sub-Saharan African may have been underestimated. The study aimed to determine the prevalence of

Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review - *Wasiu A Olowu*, Abdou Niang*, Charlotte Osafo, Gloria Ashuntantang, Fatiu A Arogundade, John Porter, Saraladevi Naicker, Valerie A Luyckx*

- **Findings:** The authors identified 3881 records, of which 41 met inclusion criteria, including 1403 adult patients and 1937 paediatric patients.

Acute kidney injury in sub-Saharan Africa is severe, with 1042 (66%) of 1572 children and 178 (70%) 253 of adults needing dialysis in studies reporting dialysis need

- Only 666 (64%) of 1042 children (across 11 studies) and 58 (33%) of 178 adults (across four studies) received dialysis when needed

- Overall mortality was 34% in children and 32% in adults, but rose to 73% in children and 86% in adults when dialysis was needed but not received

- Major barriers to access to care were out-of-pocket costs, erratic hospital resources, late presentation, and female sex

Burden of ESKD

- End-stage kidney disease (ESKD) is a rapidly increasing global health and health care burden.

- The inability to care for many patients at risk for and in need of treatment for ESKD disproportionately impacts low- and middle-income countries (LMICs).

- The true burden of end-stage kidney disease (ESKD) in children is largely unknown and infrequently reported in Africa.

- Worldwide, prevalence of CKD is between 11 to 13% compared to 13.9% in sub-Saharan Africa (SSA) with a prevalence between 17% in Ghana and 30% in Zimbabwe.
- *[Thurlow et al. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy Am J Nephrol 2021;52:98–107*;

Burden of ESKD

- Most times the available data underestimates true incidence and prevalence of ESKD due to unrecognized ESKD and limited access to kidney replacement therapy (KRT) in many countries

- Unfortunately, national ESKD data are not available in many LMICs in Africa and the 2 most populous developing nations – China and India

Burden of ESKD

- RRTs are indeed lifesaving but very expensive to deliver, even in developed countries and up to the present times
- Kidney transplantation, the best/preferred treatment for ESKD is not available in most African countries. Situation worse for children
- Theses facilities have been available for the management of ESKD for several decades in the developed world and accessible to the generality of their patients but same not happening in LMICs

Peritoneal Dialysis in Children

HISTORICAL PRSPECTIVES

- 1st Reports of use of PD in children with renal failure -
  -1948 by Bloxsum and Powell
  -1949 by Swan and Gordon

- During the 1950s – development of disposable, nylon catheters & commercially prepared dialysis solutions

- Adaptation of the technique of Acute Intermittent PD for use in infants & children with ARF – Segar et al. 1961
  - Etteldorf et al. 1962

History of PD contd

- Development of permanent P.D catheters, 1st proposed by Palmer et al. & later perfected by Tenckhoff & Schecter 1966

- Boen ST (1964) & Tenckhoff (1972) devised an automated dialysate delivery system

- 1978, PD fluids became available in plastic bags courtesy Dimitrios Oreopoulos

HISTORICAL PERSPECTIVES CONTD:

- **1959**: Ist use of PD in ESKD pts.
- **1968**: Introduction of Tenckhoff Catheter (brought a paradigm shift in the use of PD for ESKD pts).
- **1978**: Introduction of PD Cycler machines

  Popovich and Moncrief described a continuous form of PD known as potable/wearable equilibrium technique.
- **Published 1967:** First PD in Nigeria by Akinkugbe OO at the University College Hospital, Ibadan
- **1968-1969**: Ist cases of Paediatric acute PD reported by Seriki et al. at UCH Ibadan
- **1992 (Sept):** Ist CAPD Services in Nigeria: OAUTH Complex Ile Ife by Akinsola et al

AJKD
World Kidney Forum

Fifty Years of Dialysis in Africa: Challenges and Progress

Rashad S. Barsoum, MD, FRCP, FRCPE,[1] Soha S. Khalil, BPharmSc,[1] and Fatiu A. Arogundade, MD[2]

This review addresses the development of dialysis services in Africa in the face of past and contemporary challenges. Maintenance dialysis treatment programs developed in 29 countries over the past 50 years, usually many years after their independence and the end of subsequent territorial and civil wars. Eight countries had the resources to launch national dialysis programs, conventionally defined as those accommodating at least 100 patients per million population. Additionally, based on information obtained from international and local publications, conference proceedings, and personal communications, it appears that limited short-term dialysis therapy currently is available in most African countries. Currently, the prevalence of and outcomes associated with dialysis in Africa are influenced significantly by the following: (1) local health indexes, including the prevalence of undernutrition and chronic infections; (2) per capita gross domestic product; (3) national expenditures on health and growth of these expenditures with incremental demand; (4) availability and adequate training of health care providers; and (5) literacy. In an attempt to reduce the socioeconomic burden of maintenance dialysis treatment, 12 countries have adopted active transplantation programs and 5 are striving to develop screening and prevention programs. Our recommendations based on these observations include optimizing dialysis treatment initiatives and integrating them with other health strategies, as well as training and motivating local health care providers. These steps should be taken in collaboration with regulatory authorities and the public.
Am J Kidney Dis. 65(3):502-512.

Research

Challenges and possible solutions to peritoneal dialysis use in Nigeria

Samuel Ajayi[1,&], Yemi Raji[1], Temitope Bello[2], Ayodeji Arije[1]

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Key words: Peritoneal dialysis, challenges, solutions, Nigeria

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Abstract

Introduction: peritoneal dialysis is a form of renal replacement therapy that is both effective and relatively affordable. Peritoneal dialysis (PD) was first used in Nigeria as a treatment option for renal failure. Its use was first reported in Nigeria in 1969 and became more widespread in the 80s and 90s. Haemodialysis, which is capital intensive to set up and requires infrastructures and facilities such as electricity, intense water consumption and buildings, seems to have upstaged peritoneal dialysis both in demand and supply. **Methods:** this cross-sectional study is a convenient survey of nephrologists, renal technicians and nurses in Nigeria. We used a structured, self-administered questionnaire on a cross-section of members and associate members attending a national nephrology association meeting. **Results:** there were 68(54.4%) doctors, 43(27.2%) nurses, and 14(11.2%) renal technicians, all from medical institutions with renal treatment programs who participated in the study. The most common problems encountered with PD use are financial constraints (51.7%), inadequate fluid supply (50%), frequent line blockage (22.4%) and frequent infections (17.2%). Reasons attributed to the stoppage of PD in the centres included lack of PD fluids (50.8%), unavailability of PD catheters (22.8%), lack of expert personnel to train (15.8%). **Conclusion:** main challenges to peritoneal dialysis use in Nigeria include limited experience and training and availability and cost of consumables. Effort to overcome the factors militating against its use should be positively pursued so that peritoneal dialysis will be re-integrated into the mainstream of renal replacement therapy once more.

Pan African Medical Journal. 2020;35:138. doi:10.11604/pamj.2020.35.138.21066

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R.M. Akuse

Review Article

Paediatric Peritoneal Dialysis in a Developing Country: Practice, Challenges and Opportunities

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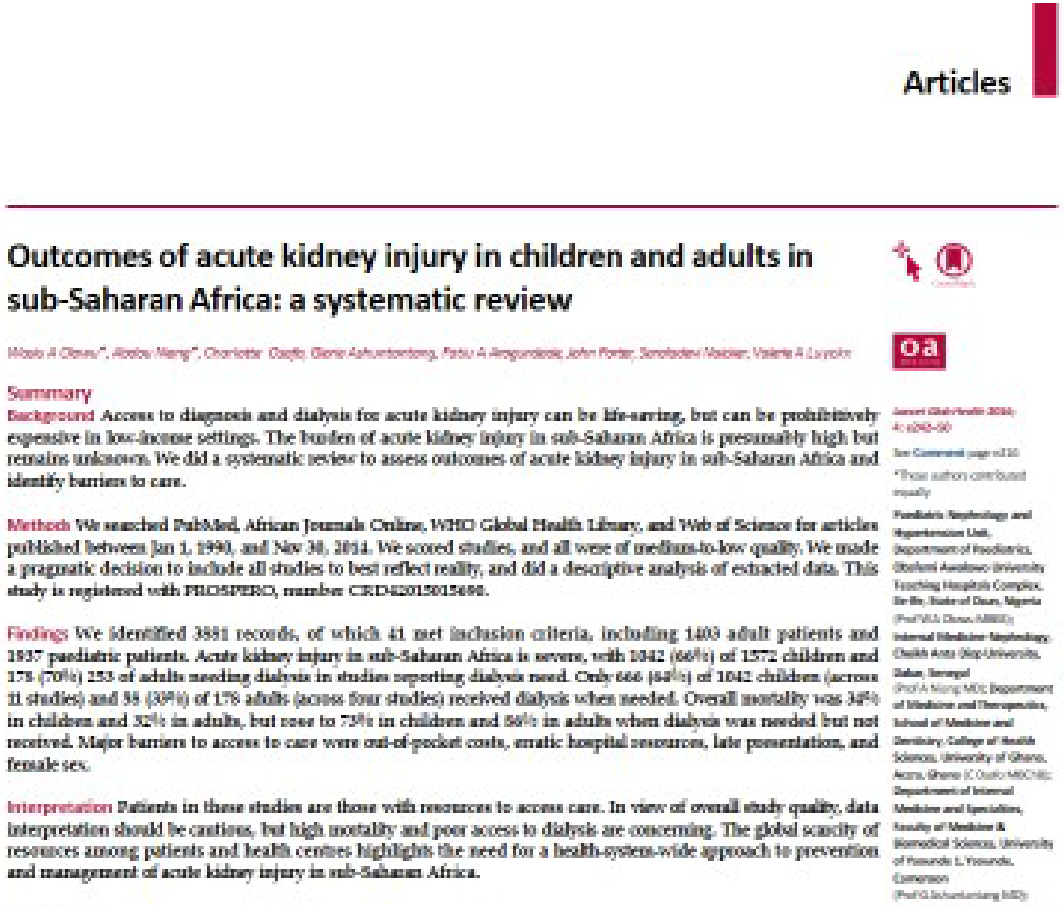
Abstract

Background: The practice and challenges of peritoneal dialysis (PD) in a developing country may be uniquely different from what obtains in developed countries.
Method: A review of the practice and challenges of PD in Nigeria as a case study and documentation of opportunities for improvement
Review: There has been renewed interest in the provision of PD to children in acute kidney injury in Nigeria and this has led to adaptations such as use of nasogastric tubes as PD catheters and use of constituted PD fluid. The use of adaptations is lifesaving but complication rates may be higher than with the use of standard gadgets. Other challenges include limited availability and high cost of PD catheters and PD fluid. There are also challenges with the availability of expertise for the insertion of PD catheters and the PD procedure.
Opportunities to advance paediatric PD include sustained efforts to provide PD with the use of adaptations, collection of data on outcomes of PD, advocacy for more support from government, non-governmental organisations and industry in the forms of insurance coverage, access to consumables and/or training in paediatric PD.
Conclusion: Sustained provision of PD with adaptations, documentation of outcomes, and advocacy may lead to improvement in paediatric PD services.
Key words: Peritoneal dialysis, children, developing countries, sub-Saharan Africa, Nigeria, acute kidney injury, end-stage renal disease.

Challenges with management of paediatric AKI in low resource setting



Articles

Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review

Moses A Olowu*, Abdou Niang*, Charlotte Osafo, Elena Ashuntantang, Fatiu A Arogundade, John Porter, Sonoladeni Naicker, Valerie A Luyckx

Summary

Background Access to diagnosis and dialysis for acute kidney injury can be life-saving, but can be prohibitively expensive in low-income settings. The burden of acute kidney injury in sub-Saharan Africa is presumably high but remains unknown. We did a systematic review to assess outcomes of acute kidney injury in sub-Saharan Africa and identify barriers to care.

Methods We searched PubMed, African Journals Online, WHO Global Health Library, and Web of Science for articles published between Jan 1, 1990, and Nov 30, 2014. We scored studies, and all were of medium-to-low quality. We made a pragmatic decision to include all studies to best reflect reality, and did a descriptive analysis of extracted data. This study is registered with PROSPERO, number CRD42015015680.

Findings We identified 3881 records, of which 41 met inclusion criteria, including 1403 adult patients and 1837 paediatric patients. Acute kidney injury in sub-Saharan Africa is severe, with 1042 (66%) of 1572 children and 178 (70%) 253 of adults needing dialysis in studies reporting dialysis need. Only 666 (64%) of 1042 children (across 11 studies) and 58 (33%) of 178 adults (across four studies) received dialysis when needed. Overall mortality was 34% in children and 32% in adults, but rose to 75% in children and 86% in adults when dialysis was needed but not received. Major barriers to access to care were out-of-pocket costs, erratic hospital resources, late presentation, and female sex.

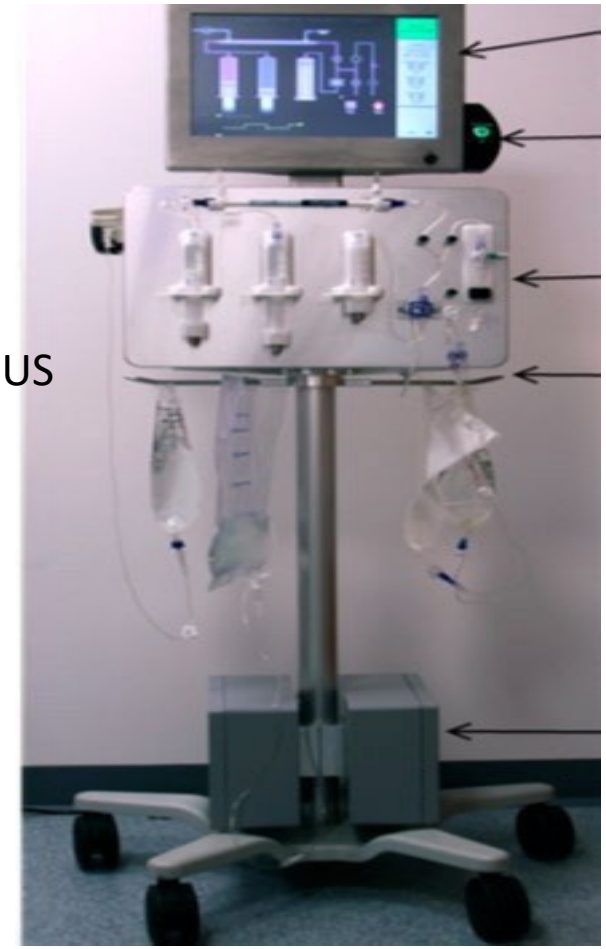
Interpretation Patients in these studies are those with resources to access care. In view of overall study quality, data interpretation should be cautious, but high mortality and poor access to dialysis are concerning. The global scarcity of resources among patients and health centres highlights the need for a health-system-wide approach to prevention and management of acute kidney injury in sub-Saharan Africa.

- Poor socioeconomic conditions
- Limited coverage health insurance
- Illiteracy
- Late presentation to the hospital
- Erratic power supply

Challenges with patient management

- Shortages skilled manpower and brain drain
- Limited treatment facilities/Inaccessible/Cities
-
- Poor health seeking behaviour
- Limited treatment options (CRRT)

NIDUS



- Nigerian Context

Kidney Replacement Therapy (KRT): Historic Perspectives

- The management of AKI in children in Nigeria has gone through phases
- Availability of RRT in the form of acute PD commenced in Ibadan in the adult population in 1967 by Prof. OO Akinkugbe
- 1st Paper on the PD in children published in 1969 titled "Acute Uraemia" by Seriki
- PD continued at the UCH using: Rigid PD catheters and Bottled PD fluids manufactured in our Hospital Pharmacy till mid 1980s.

- Haemodialysis became available in Nigeria at LUTH Lagos in 1981 and UCH Ibadan in 1990
- HD became available to children <15 years at UCH from 1996
- Due to non-availability of appropriate sized dialyzers and blood lines many children below the age of 5years do not have access to HD
- The non-availability of HD contributed to the poor outcome of an epidemic of Diethylene Glycol poisoning in Nigerian toddlers in Year 2008

Late Emeritus Professor OO Akinkugbe of Ibadan, Performer of 1st PD in Nigeria, published 1967

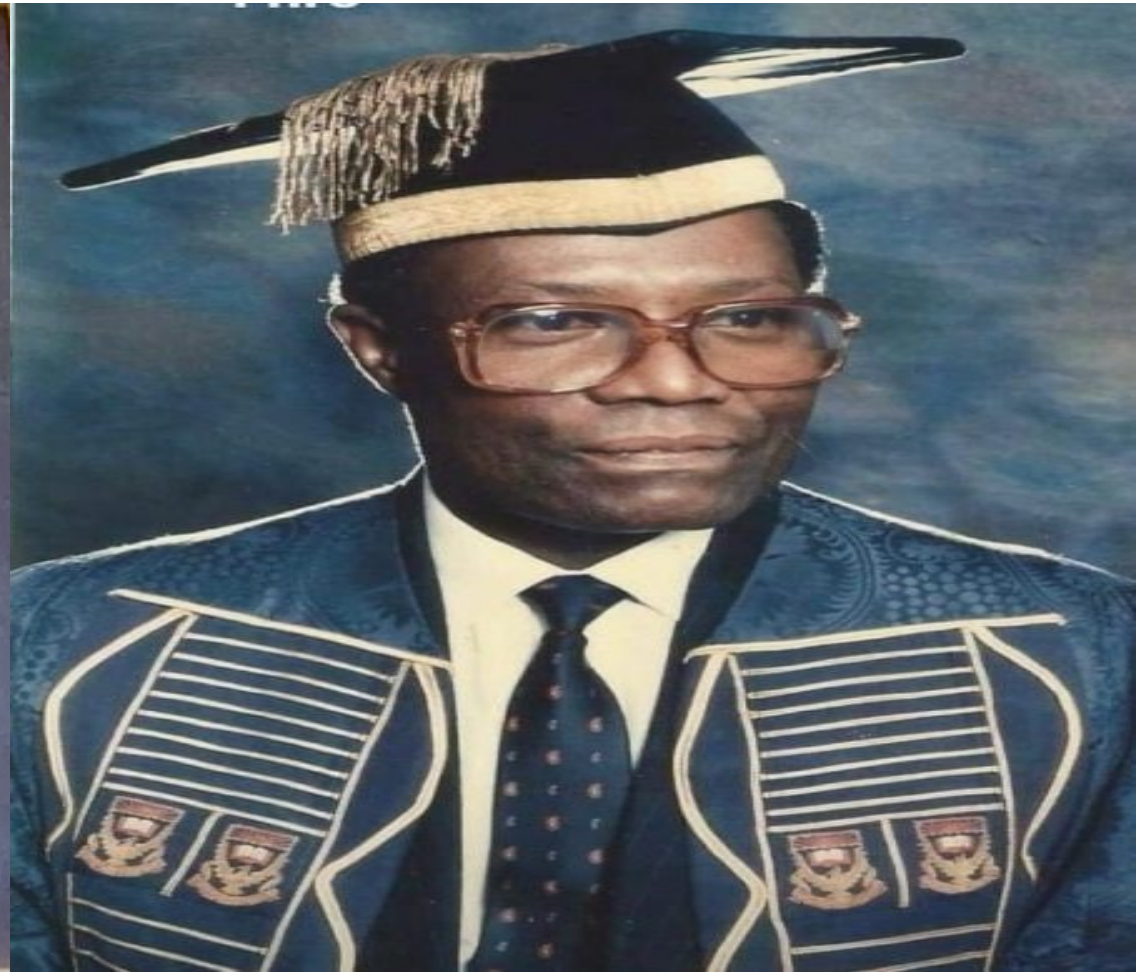
- In addition to initiating PD in Nigeria, worked in the Field of Childhood Hypertension and trained generations of Nigerians in Nephrology

- Foundation President of the Nigerian Association of Nephrology and the Nigerian Soociety of Hypertension

Foundation Paediatric Nephrologists in Ibadan and Nigeria

Late Professor Ralph Hendrickse, Ist HOD Paed Dept. UCH Ibadan

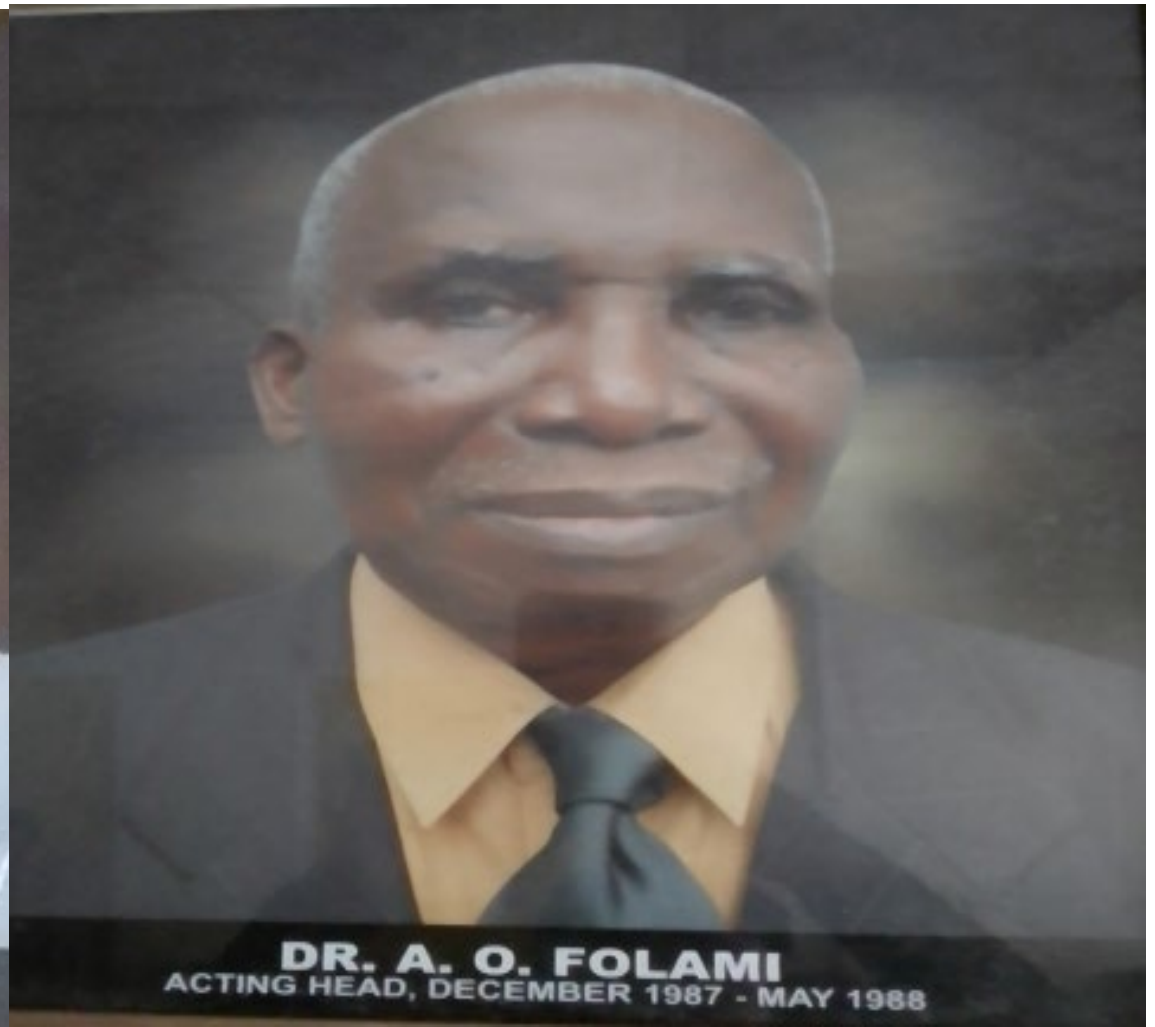
Late Emeritus Professor Adeoye Adeniyi, Former VC Unillorin



2nd Generation Paediatric Nephrologists in Ibadan

First Initiated Paediatric PD in Ibadan

Late Prof. Ayo Folami, Fellowship at Hosp for Sick Children, Toronto Canada



Indigenous Pioneers of Paediatric Nephrology in Northern Nigeria

Prof. MB Abdurrahman, ABU Zaria/Overseas: 2nd Generation

Prof. Henry Aikhionbare, ABU Zaria/ UBTH Benin: 3rd Generation

Pioneers of Paediatric Nephrology in Eastern Nigeria, 3rd Generation

Late Professor AB Okoro, UNTH Enugu

Prof. Felicia Eke, UPTH Port Harcourt

Our Current Leaders in PNAN

PNAN President, Prof. Henrietta Uche Okafor, UNTH Enugu

Prof. Ifeoma Anochie UPTH, PNAN Rep. at IPNA

Subsequent Generation of Paediatric Nephrologists

Other Members of the 3rd Generation

- Dr. Ogunlaja - UCH Ibadan/ Premier Hospital, Lagos. Fellowship at Hospital for Sick Children Toronto, Canada.
- Dr. Oyemade - UCH Ibadan/Overseas
- Etc
- FROM MIDDLE 1980s CAME THE DOWNTURN OF NIGERIAN ECONOMY WITH EXODUS OF SPECIALISTS AND LACK OF FACILITIES!!!
- The 4TH & 5TH GENERATIONS trained by the few remaining Paediatric and Adult Nephrologists took over training of our younger Colleagues in the Nation.
- Faced with the Huge burden of poverty, lack of materials (not being imported) and shortage of manpower.
- Then came the BIRTH OF IMPROVISATION in Ibadan and other parts of Nigeria

Members of the 4th & 5th Generation : 1990-2000

4th Generation:

- Prof. Uche Okafor – UNTH Enugu* (President PNAN)
- Prof. Rosamund Akuse – ABU Zaria
- Dr. Adanze Asinobi – UCH Ibadan, Ibadan*
- Dr. Liza Onifade – LUTH Lagos/Overseas*
- Prof. Michael Ibadin - University of Benin, Benin (Former CMD)
- Prof. Wasiu Olowu- OAU Ile-IfeProf. Wasiu Olowu- OAU Ile-Ife

*Present at the Inauguration of AFPNA in London with Late Prof. AB Okoro & Prof. Felicia Eke.

5th Generation of Paediatric Nephrologists in Nigeria

- Prof. Ifeoma Anochie – UPTH Port Harcourt, Former IPNA Councillor
- Dr. Franca Ikimalo – Private Practice, Port Harcourt
- Prof. Rasheed Gbadegesin – UCH Ibadan/Overseas
- Prof. Adedoyin – Provost COM UniIlorin, Ilorin
- Prof. Isaac Ocheke – University of Jos, Jos
- Dr. Seyi Oniyangi – National Hospital, Abuja
- Prof. Joy Ebenebe – Nnamdi Azikiwe University, Nnewi
- Prof. IS Etuk – University of Calabar, Calabar
- Prof. Enobong Ikpeme - University of Uyo, Uyo
- Prof. Samuel Uwaezuoke – UNTH Enugu
- Dr. Gbelee – UniIlorin/LASUTH
- Prof. Adekambi – OSUTH, Sagamu

Present Active Generation: ≥ Year 2000; >70 in number

- Paediatric Nephrology Association of Nigeria (PNAN) has a Vibrant Team of Young and Dedicated men and women who despite all odds are out to fight for the kidneys and lives of Nigerian children and by extension those of the Adults

- Permit me not to mention names one by one in other not to fall into error, all their labours are appreciated

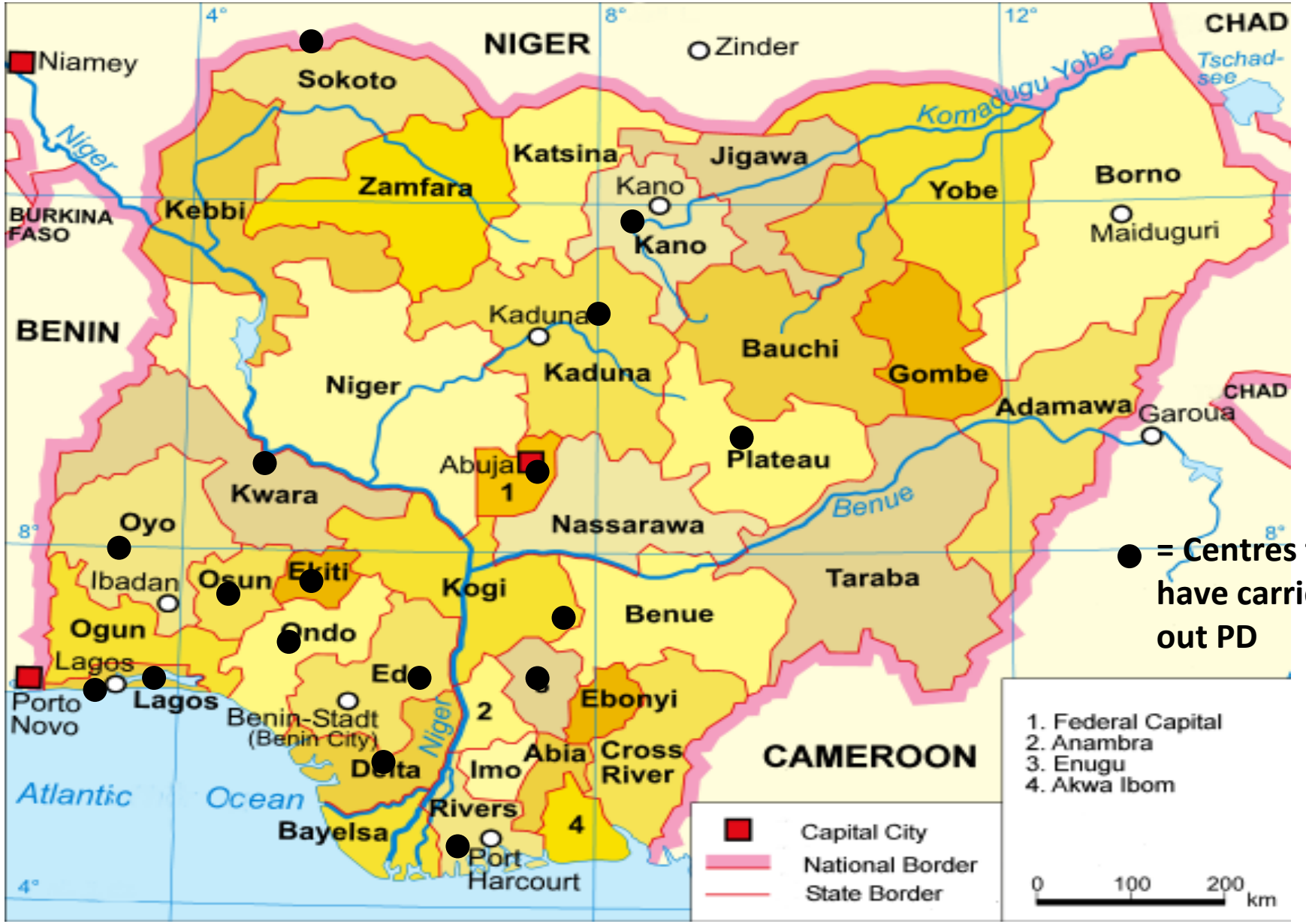
- There are about 100 Paediatric Nephrologists looking after approximately 100 million Nigerian children aged <19 years i.e approx. 1 per million children

- Many have undergone Fellowship training by IPNA and ISN, for which we are grateful, but we are still very short of Experts

Available Treatment modalities for AKI

RRT Modalities	Number of centres
HD	More commonly available but inadequate & expensive
PD	Only Acute PD for Children . Dr. Oguntade has rekindled the fire on Chronic PD at the Zenith Kidney & Medical Centres. Will address participants
CRRT	A very few centres
Others	

Centres that have carried out Paediatric PD



Modality of renal replacement therapy

S/N	PLACE	TYPE OF RRT	CHALLENGES
1	FMC Umuahia	HD, PD	Limited resources- improvisation of PD
2	University of Uyo Teaching Hospital	HD, PD	Use of improvised PD catheter and fluid
3	Abubakar Tafawa Balewa University Teaching Hospital Bauchi	HD	High cost of HD
4	University of Calabar Teaching Hospital	HD	High cost of HD
5	FMC, Asaba	HD	High cost of HD
6	ISTH, Irrua	HD	High cost of HD, few HD machines
7	UBTH, Benin	HD	Inadequate facility
8	UNN Teaching Hospital	HD, PD	High cost of HD
9	Zenith Medical and Centre, Abuja	HD	-
10	University of Abuja Teaching Hospital	HD, PD	High cost of HD
11	Garki Hospital, Abuja	HD	-

Modality of renal replacement therapy

12	National Hospital Abuja	HD, PD	Challenges
13	ABU Teaching Hospital, Zaria	HD	Poor funding of HD
14	Amino Kano Teaching Hospital, Kano	HD, PD	PD better because of cost
15	UITH, Ilorin	HD, PD	High cost of HD
16	LUTH	HD, PD	High cost of HD
17	LASUTH, Ikeja	HD, PD	High cost of HD
18	OOUTH, Ogunn state	HD	High cost of HD
19	LAUTECH, Osogbo	HD	High cost of HD
20	OAUTHC, Ile-Ife	HD	High cost of HD
21	Bowen University Teaching Hospital, Ogbomoso	PD	Improvised PD catheter
22	UCH, Ibadan	HD, PD	Poor funding and support
23	UPTH	HD, PD	High cost of HD
24	Usman Dan Fodio University Teaching Hospital, Sokoto	HD, PD	Improvised PD, complications from PD
25	Sani Yariman Bakura specialist Teaching Hospital, Gusau	HD	Inadequate facility for HD and lack of PD

On-line Survey on Dialysis Availability for Paed AKI in Nigeria by Dr. Briggs and Dr. Asinobi (Unpublished) on PNAN Platform 2023

- Only 11 Respondents (LUTH & LASUTH Lagos did not participate)
- All from tertiary institutions
- All public institutions (further clarifications may be needed)
- Geopolitical locations:

5 - South-South (Benin & Uyo did not respond)

1- South-East

3- South-West (There should be at least 7 Centres from SW ? Issues)

2 - North-Central (UniABUJA did not participate)

1-- North-East

0- North-West (There should be I that ?failed to respond)

On-line Survey on Dialysis Availability for Paed AKI in Nigeria by Dr. Briggs and Dr. Asinobi (Unpublished) on PNAN Platform 2023 _2

- Dialysis offered mainly to children from 1/12 to <18yrs but majorly to between 5 &18 years
- Causes_ Sepsis, Malaria, Acute watery diarrhoea & AGN
- Type of Dialysis- 66.7% of the institutions
- Outcome- Good generally
- Cost of E/U/Cr – B/w N3000 & N8000
- 75% do not use Tenckhoff catheters
- 58.4% use improvised catheters, 25% do not
- If no Tenckhoff _ Majority use Rigid catheter, NG Tube, Foley's Catheter
- Improvised fluid for PD in over 50%, Cost of 2L PD fluid N2000 –N45000
- All manual PD
- Catheter insertion by Paediatricians, Paed Nephrologists & Surgeons majorly
- Average no. of cycles of PD to restore kidney function- 20-40
- Constraints: Financial constraints, lack of consumables and lack of human resources

Overcoming Kidney Disease Challenges in Low-income settings

- PREVENTION CHEAPER
  Primary prevention _ Adequate maternal nutrition and Immunization & Use of Folic acid prenatally

- Prevention of Preterm births, Exclusive Breast feeding, childhood immunisations and adequate nutrition, preventing malaria in our setting

- Early diagnosis and appropriate intervention

- Secondary prevention
- Tertiary Prevention
- Indeed , All levels of Prevention required

Over coming the barrier

Pragmatic Approach

RESULTS The median age was 7 years (range 3–12). 23 patients (70%) were males. Of the 33 patients that required RRT, 29 had PD. The children had an access rate of 88% (95% CI = 76.77–99.03). The access rate was not related to gender (p = 1.000), age group (p = 0.240), or socioeconomic status (p = 0.755). Complications were pericatheter leakage of fluid (n = 7, 24%), catheter malfunction (n = 5, 17%), abdominal wall edema (n = 3, 10%), scrotal edema (n = 2, 7%), and peritonitis (n = 1, 3%). In-hospital mortality was 3/29 (10%; 95% CI = 2.2–27.3). Cost analysis revealed that the cost of consumables was reduced by 88.5%.

Over coming the barrier

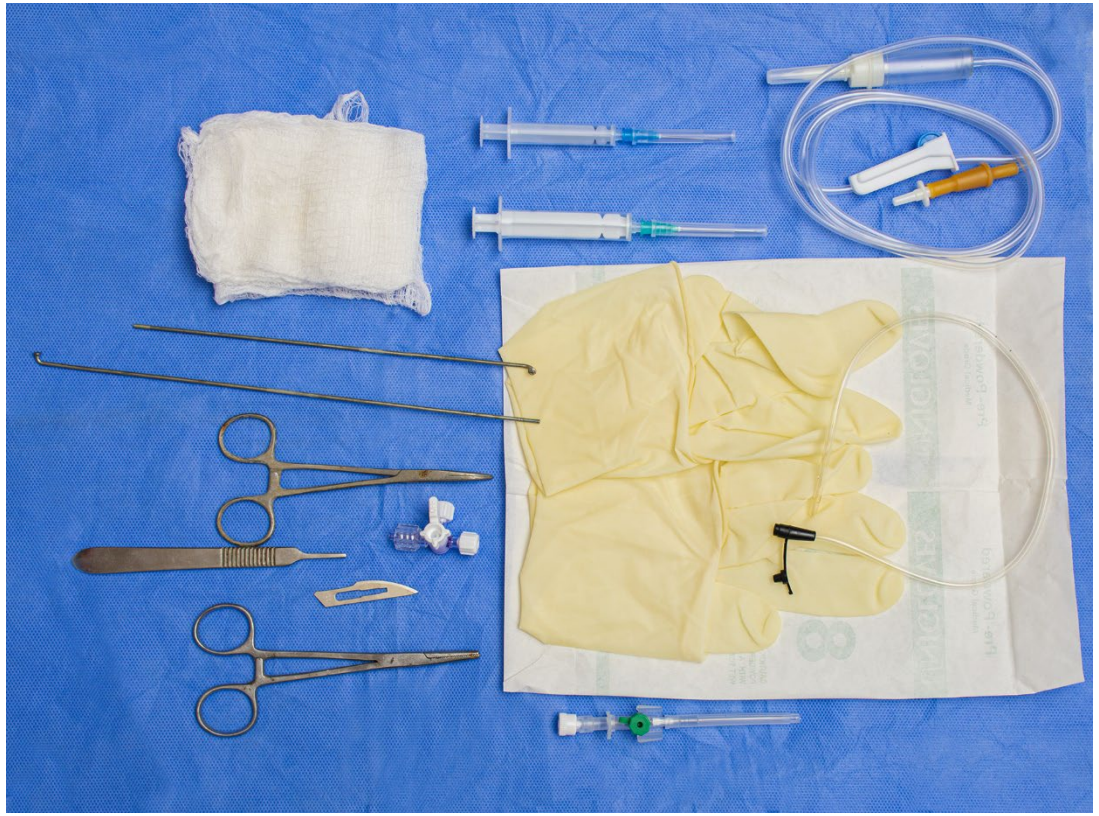
Adaptation to available resources

Bicycle spokes

Nasogastric tubes

Locally prepared PD fluid

Local production of consumable

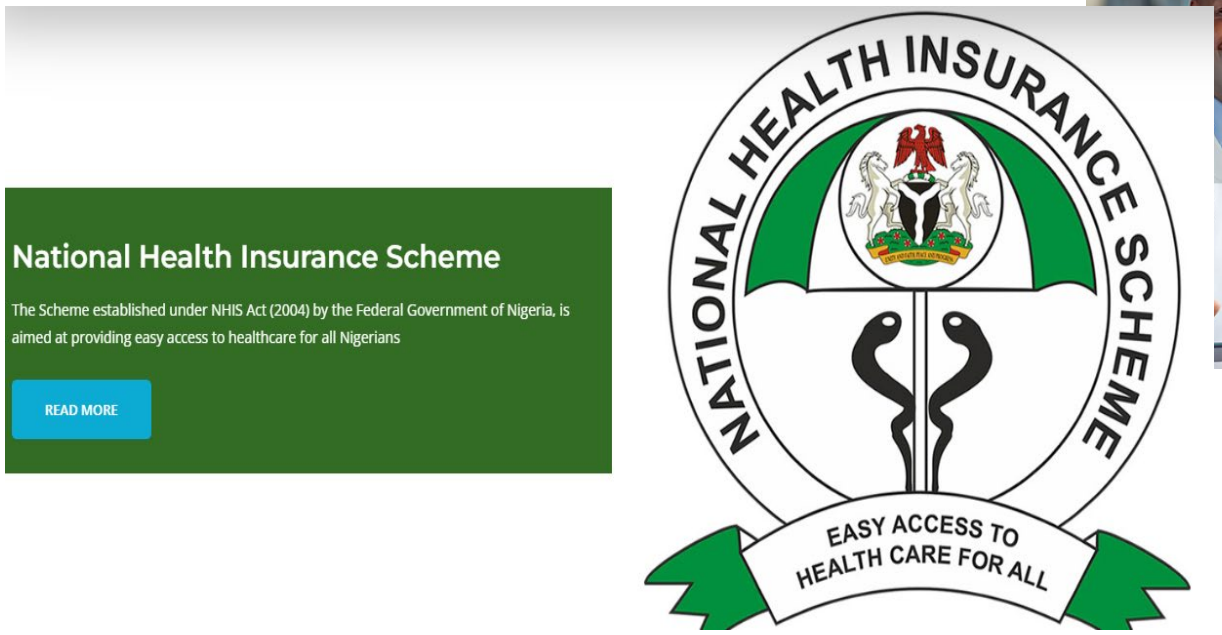


Over coming the barrier

- Disease surveillance
- Cohort studies
- Functional National Renal Registry
- Advocacy
- Training and Re-training

Over coming the barrier

Increased Uptake of Health Insurance Scheme ($25/enrollee)



Concluding remarks

At Ibadan and in many Centres across Nigeria, the challenges are similar and linked to poverty, ignorance, misplaced priorities, lack of infrastructure, limited access to medical care and lack of political will to fund healthcare

- Although accessibility to kidney care has improved in Nigeria due to training opportunities provided by international professional organisations (ISN, IPNA, IPTA), most children still face significant barriers to kidney care because they live in rural areas or cannot afford the care

Concluding remarks

As a consequence, late presentation becomes the norm with avoidable consequences such as AKI, Death and long – term complications such as Hypertension and CKD

- The African continent has the least density of healthcare practitioners and Nephrology trainees which are being further drained by the current economic and security challenges, especially in Nigeria. Brain drain has become a major issue with both young and older doctors, nurses and other healthcare personnel
- Preventive Nephrology should be enhanced at all levels

- THANK YOU

Acknowledgements

- All my Colleagues in the Department of Paediatrics, UCH Ibadan especially, Dr. Debo Ademola, Dr. Michael Alao, Prof. Toyin Ogunkunle and Prof. IkeOluwa Lagunju
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- Our Renal Sister Center Program Partners at the Children's Hospital Alberta, Canada, headed by Prof. Julian Midgley – You have been Amazing!!!
- All members of PNAN and NAN, I am proud of you all!!!
- Thank you All.

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Fluid Management in the Paediatric Patient

Ibadan

19 June 2023

Julian Midgley

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

Objectives

What are the indications for fluid management?

Are there (relative) contraindications for certain fluid managements?

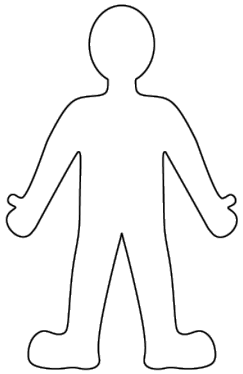
Why looking at urine can guide (and potentially mislead)

Outline

Fluids

Cases

Final thoughts



Fluids (in)

By mouth

- Breast milk
- Water
- Tea/Coffee
- Soda/pop

Intravenously

- 5% Dextrose
- 0.9% Saline

Fluids (in)

By mouth

- Breast milk
- Water
- Tea/Coffee
- Soda/pop

Intravenously

- 5% Dextrose
- 0.9% Saline
- 3% saline
- Balanced crystalloids (eg Plasmalyte, Ringers)

Alternatives to 0.9% Saline - Balanced Crystalloids

Table 2. Characteristics of Commonly Available Crystalloid Infusion Fluids in Comparison to Human Plasma

	Human Plasma	Normal Saline	Lactated Ringer's	Plasma-Lyte[a]	Sterofundin[b] ISO	Sodium Bicarbonate in D5W[c]
Sodium (mmol/L)	142	154	130	140	145	130
Chloride (mmol/L)	103	154	109	98	127	0
Potassium (mmol/L)	4.5	0	4	5	4	0
Calcium (mmol/L)	2.5	0	2.7	0	2.5	0
Magnesium (mmol/L)	1.25	0	0	1.5	1	0
Bicarbonate (mmol/L)	24	0	0	0	0	130
Glucose (mmol/L)	0	0	0	0	0	241
Gluconate (mmol/L)	0	0	0	23	0	0
Maleate (mmol/L)	0	0	0	0	5	0
Lactate (mmol/L)	1	0	28	0	0	0
Acetate (mmol/L)	1	0	0	27	24	0
Osmolality (mOsm/kg)	288	286	254	NK	290	470[d]
Relative cost	$$$$$	$	$	$	$	$

Note: Conversion factors for units: magnesium in mmol/L to mEq/L, ×2; glucose in mmol/L to mg/dL, ×18.01; lactate in mmol/L to mg/dL, ×9.01. Based in part on information compiled in Severs et al.[5]

Abbreviations: D5W, dextrose 5% in water; NK, not known.

[a]Baxter, Deerfield, IL.

[b]B Braun, Melsungen, Germany (used more frequently in Europe).

[c]Based on the addition of three 50-mL ampules of sodium bicarbonate 8.4% to 1 L of D5W.

[d]Glucose is rapidly metabolized and easily crosses cell membranes, hence it is osmotically mostly inactive.

Severs et al Am J Kid Dis 66:147 (2015)

Urine (out)

Volume	(water) Osmolality
Cations	(Sodium, Potassium, Ammonium, Calcium and Magnesium)
Anions	(Chloride, Bicarbonate, Sulphate, Phosphate, Organic)
Other	Urea, creatinine, protein etc

Homeostasis

Stability

Maintained by control mechanisms

receptor, “control center”, effector

For body fluids

volume

composition

Kidneys are an “effector” (but also one of the “receptors”)

(but the brain and endocrine systems play their part)

Indications for (iv) Fluid Management

When the usual homeostatic mechanisms have not been sufficient

Indications for (iv) Fluid Management

When the usual homeostatic mechanisms have not been sufficient

0.9% Saline (only one)

Hypovolaemia

5% Dextrose (can give two)

Hypoglycaemia

Hypernatraemia

Indications for (iv) Fluid Management

When the usual homeostatic mechanisms have not been sufficient

0.9% Saline (only one)

Hypovolaemia

5% Dextrose (can give two)

Hypoglycaemia

Hypernatraemia

Also, hypokalaemia, hypocalcaemia, hypophosphataemia, acidosis

Case 1

18 months old girl post-op after craniosynostosis surgery

Intubated, morphine infusion, in PICU

serum Na^+ 138 mmol/L

iv fluid 70% "maintenance" D5% 0.45% NaCl, 20 mmol K^+/L

8 hrs later serum Na^+ 130 mmol/L

(the correct response to a low value is often to add more eg oxygen, haemoglobin so ….with a low sodium level add more sodium…)

iv fluid changed to D5% 0.9% NaCl, 20 mmol K^+/L

8 hrs later serum Na^+ 125 mmol/L

Case 1 - Diagnosis

Iatrogenic hyponatraemia (with 0.9% [“normal”] saline!)

Resident - it is “SIADH”

Fellow - no it isn’t “SIADH”……. because

- the urine output is > 1 mL/kg/hr
- the urine output is increasing over the last 8 hours

Is there SIADH?

What could have prevented the hyponatraemia?

Case 1 - Diagnosis

Look at the urine!

Urine Na	125 mmol/L
Urine osmolality	900 mosmol/kg

No lab reference ranges – but what does this tell us?

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Urinary excretion of sodium is not low, so

no drive for sodium retention and likely no hypovolaemia

(unless sodium wasting was causing hypovolaemia)

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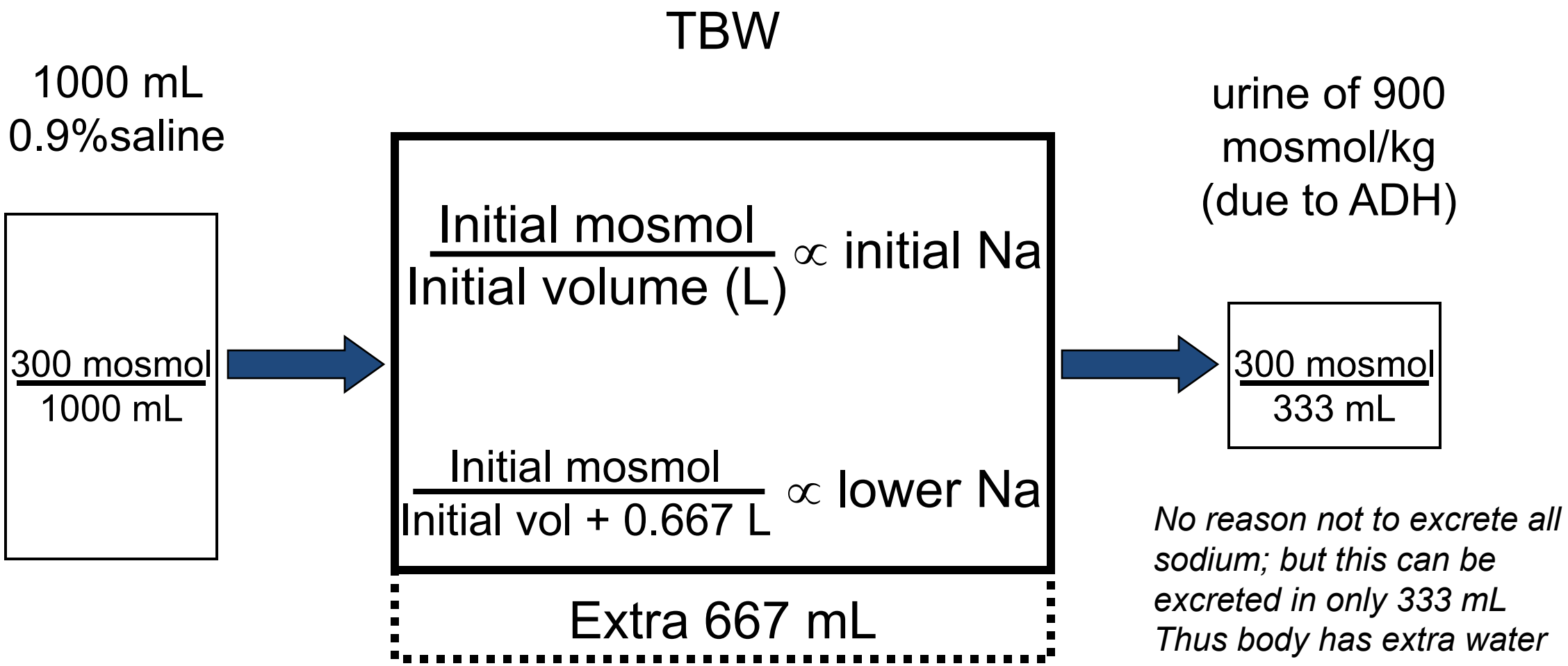
Water excretion is low (there is an ADH effect on the kidney)

not homeostatic, with hyponatraemia expect a dilute urine

Case 1 – explanation of why Na decreases



Case 1 – whey did the urine output increase?

Ordinarily urine volume increase with water excretion

Drink water, increased urination (urine with low osmolality)

Homeostasis - ADH excretion is inhibited

In SIADH ADH is fixed and high

Urine output is usually low and the urine is concentrated

But if the number of osmols given is doubled the urine flow doubles

Case 1 – Take home messages

Increased ADH limits the ability to excrete water

(and there are many reasons for non-physiological ADH)

When urine output is low think ?actually due to decreased EABV

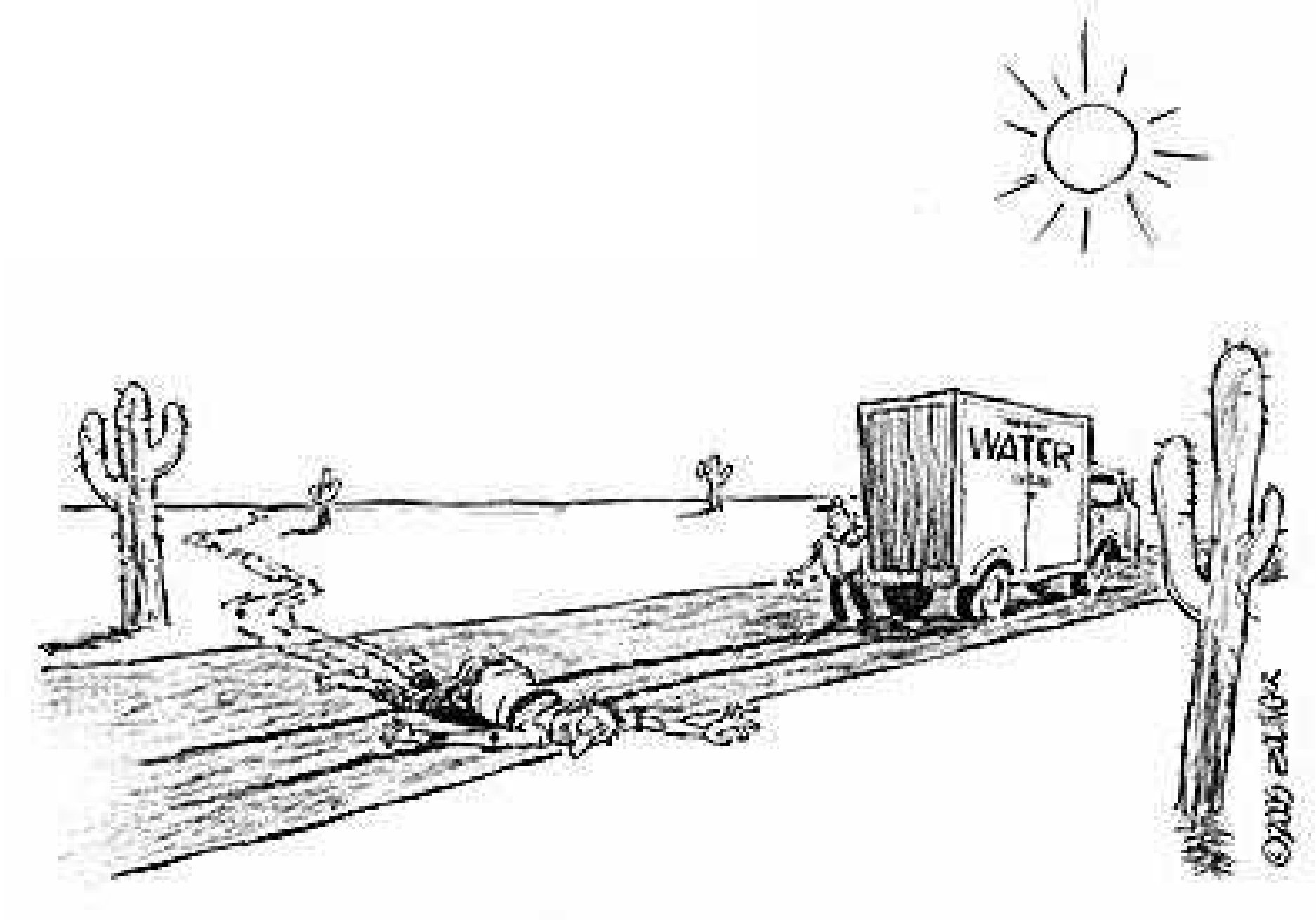
If no history or exam findings to suggest – no bolus of saline

A liter of any fluid contains a liter of water

0.9% saline can still lead to iatrogenic hyponatraemia

Only iv fluid with an osmolality greater than urine doesn't!

A "maintenance" rate of any iv fluid is contraindicated in SIADH


WATER

Case 2

A 6-month-old infant comes to the ED

- Mother knows something is not “right”
- Fussy, not feeding so well (usually has a good intake)

PMH – not very good weight gain

- (recently changed from breast milk to formula)

Examination

- Low grade fever
- Not hypovolaemic

Case 2

Labs drawn

10 mL/kg of 0.9% saline bolus and then “maintenance” rate

Case 2

Labs drawn

10 mL/kg of 0.9% saline bolus and then “maintenance” rate

Na 161 mmol/L

Case 2

Labs drawn

10 mL/kg of 0.9% saline bolus and then “maintenance” rate

Na 161 mmol/L

Repeat labs
Na 169 mmol/L

Case 2

What is going on?

Look at the urine….

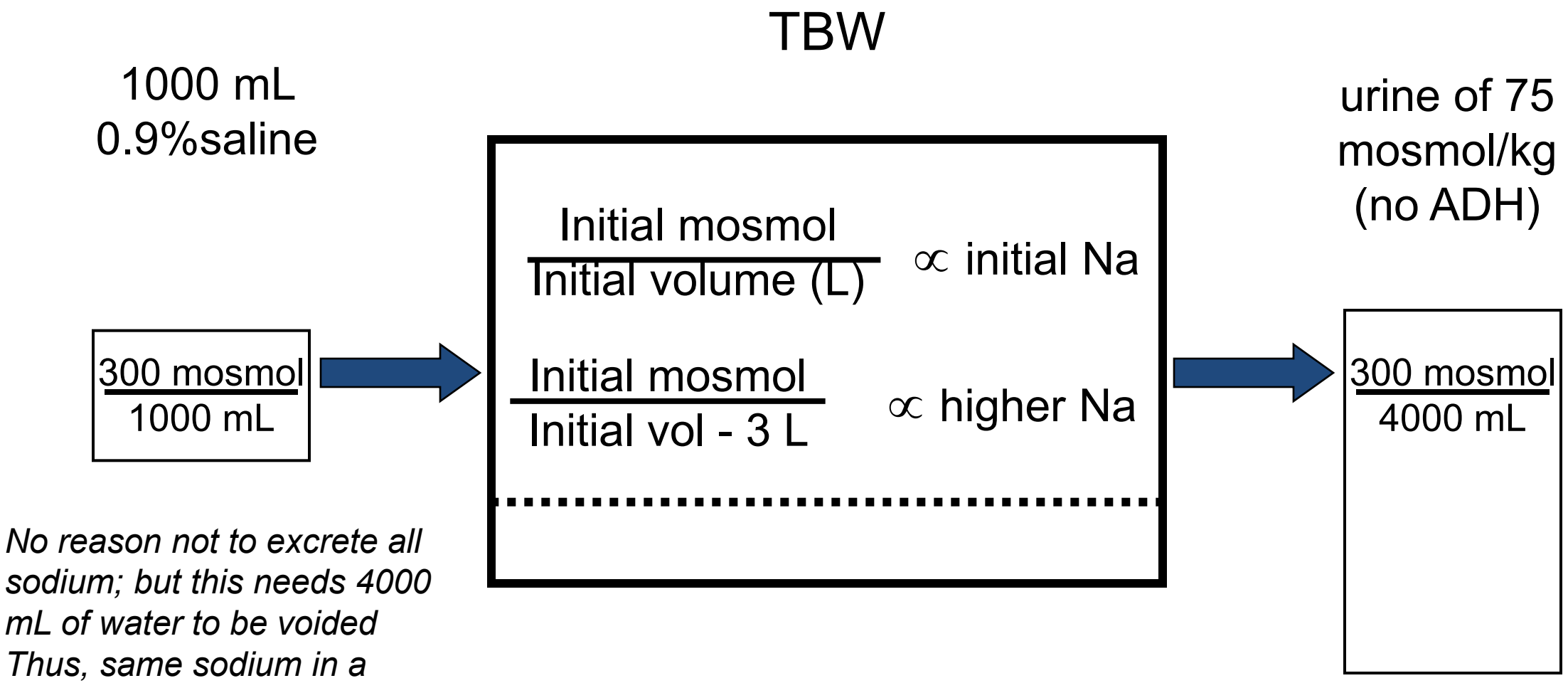
Urine osmolality 75 mosomol/kg

No lab reference range (or if there is: 50 – 1200 mosmol/kg)

With hypernatraemia expect “no” water excretion (ADH+++)

(0.9% saline not indicated as no hypovolaemia, but 5% dextrose is)

Case 2 – explanation of why Na increased



No reason not to excrete all sodium; but this needs 4000 mL of water to be voided
Thus, same sodium in a smaller amount of water

Osmolal Balance

Intravenous fluids that are iso-osmolar to serum
may still cause a decrease or increase in serum Na^+

The osmolality of intravenous fluids should be compared to (anticipated) urine osmolality to determine whether there will be a change in serum Na^+

If iv fluid is hypo-osmolar to the urine there will be a fall in Na^+

If iv fluid is hyperosmolar to the urine there will be an increase in Na^+

Carlotti AP Int Care Med 27:921 (2001)

How to treat SIADH

Since there is an inability to excrete water – don't give water!

(0.9% saline is not indicated
there is no hypovolaemia and 1 L of 0.9% saline has 1 L of water)

3% saline is indicated in *symptomatic* hyponatraemia (3 to 5 mL/kg)
the fluid osmolality is about 1000 mosmol/kg
and, so
usually higher than the urine osmolality
(will increase the serum Na^+)

Brenkert et al Pediatr Emer Care 29:71-73 (2013)

How to treat Nephrogenic Diabetes Insipidus

Inability to stop excretion of water

Give water

Excreting salt is difficult

Reduce salt intake

(never give 0.9% saline – unless there is definite hypovolaemia!)

Look at the Urine!

In disease states affecting fluid and electrolyte balance

Urine studies inform on

1) the appropriateness of the kidneys' response

2) a "renal" cause of disease (if inappropriate response)

Urine osmolality is relatively straight forward to interpret

Urine sodium concentration less so

Urinary Na^+ Concentration - U[Na^+]

Ordinarily U[Na^+] is related to sodium intake *and* water intake

U[Na^+] may not be of clinical utility

Unless there is an expected renal homeostatic Na excretion response (or evidence for a renal cause of disease)

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Tubular handling of Na^+ is described by the fractional excretion of Na

$$FE_{Na} = \frac{\text{Excreted Na}}{\text{Filtered Na}} = \frac{U[Na^+] \times V}{[Na^+] \times GFR}$$

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Note: a decrease in GFR increases the FE_{Na}

an increase in dietary Na increases the FE_{Na}

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Tubular handling of Na^+ is described by the fractional excretion of Na

$$FE_{Na} = \frac{\text{Excreted Na}}{\text{Filtered Na}} = \frac{U[Na^+] \times V}{[Na^+] \times GFR} = \frac{U[Na^+] \times [Creat]}{[Na^+] \times U[Creat]}$$

Note: a decrease in GFR increases the FE_{Na}

an increase in dietary Na increases the FE_{Na}

Utility of FE_{Na}

If hypovolaemia (decreased EABV) is clinically suspected
a low (usually < 0.3%) FE_{Na} is supportive

If there is a high (usually >> 0.3%) FE_{Na} with hypovolaemia
(decreased EABV) renal wasting may be the cause

In hyponatraemia a low FE_{Na} goes against the diagnosis of SIADH
(there may be appropriate ADH)

In nephritic syndrome a low FE_{Na} is expected and can be <0.1%
(clearly giving iv 0.9% saline is contraindicated!)

Fluid Management in Kidney Transplant Recipients

Pre surgery

- Hold ACE inhibitors/other antihypertensives

Intra-operatively

- IV 0.9% saline/5% albumin/inotropes to maintain BP
  - (especially at time of un-clamping)
- Mannitol, furosemide just prior to perfusion of organ

Post-operatively

- Use a balanced crystalloid mL for mL replacing urine output
- Urine electrolytes to assist in composition of iv fluid

Kidney Transplant

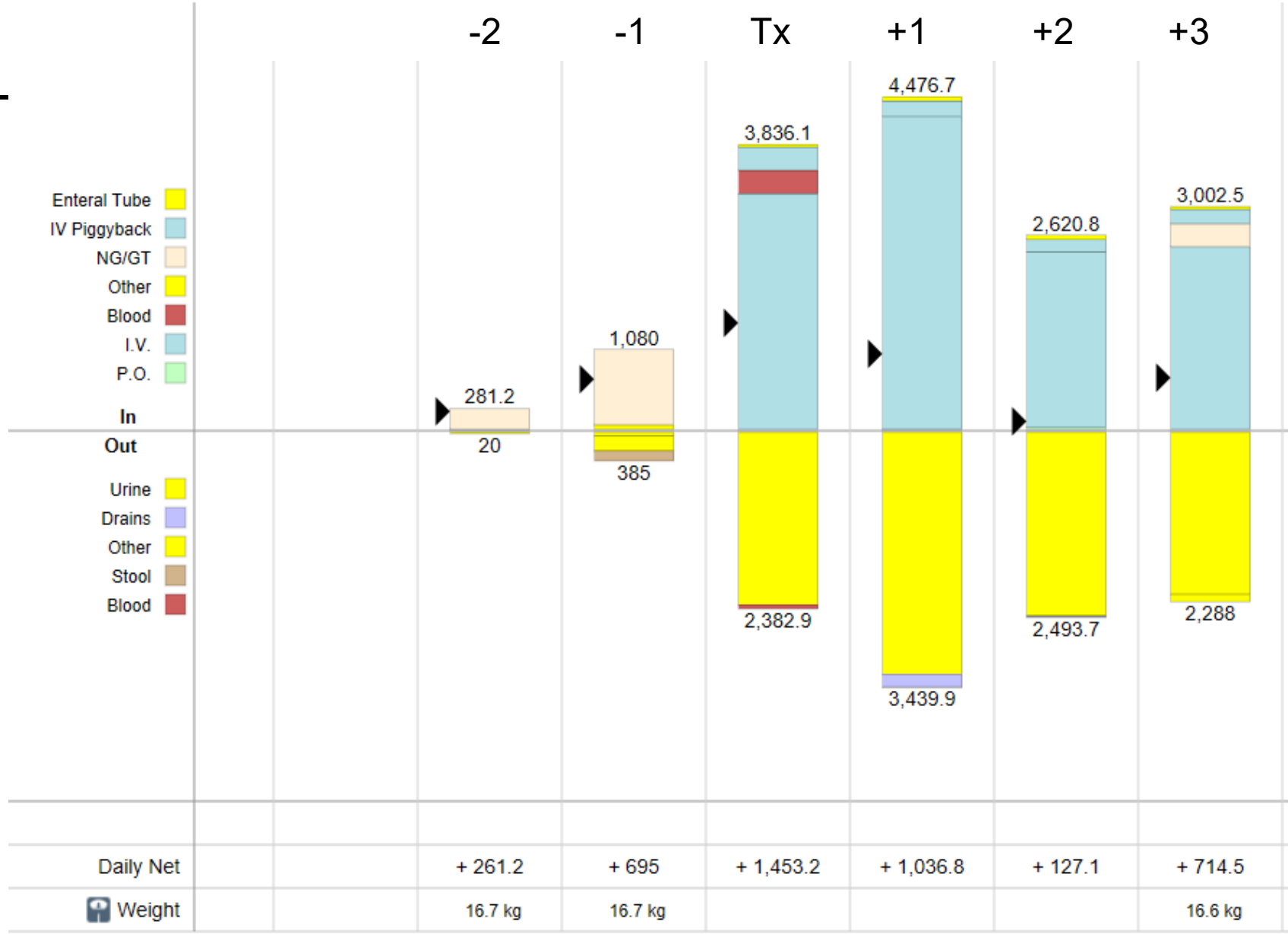
4 year old boy

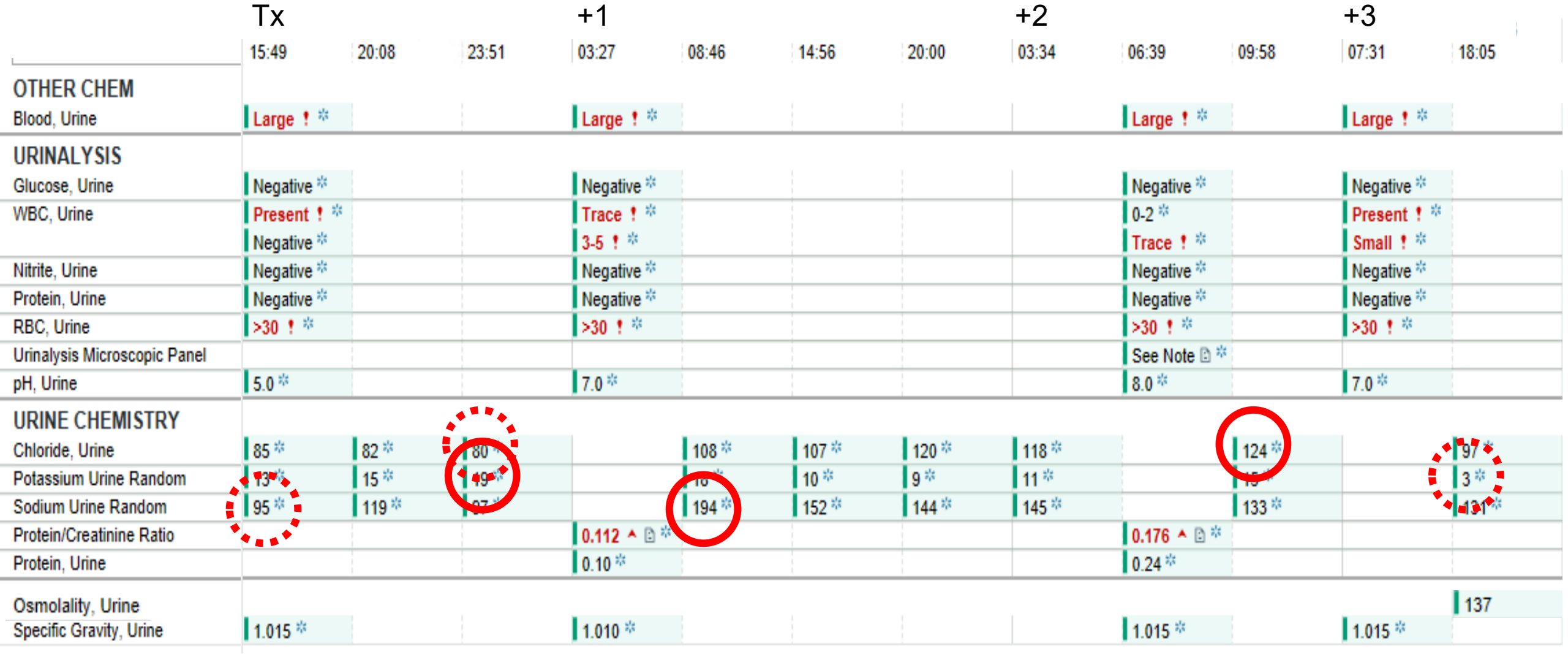
16.7 kg

Post transplant

Day of 230 mL/kg

Day +1 268 mL/kg





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	15:49	20:08	23:51	03:27	08:46	14:56	20:00	03:34	06:39	09:58	07:31	18:05
OTHER CHEM												
Blood, Urine	Large !			Large !					Large !		Large !	
URINALYSIS												
Glucose, Urine	Negative			Negative					Negative		Negative	
WBC, Urine	Present !			Trace !					0-2		Present !	
	Negative			3-5 !					Trace !		Small !	
Nitrite, Urine	Negative			Negative					Negative		Negative	
Protein, Urine	Negative			Negative					Negative		Negative	
RBC, Urine	>30 !			>30 !					>30 !		>30 !	
Urinalysis Microscopic Panel									See Note			
pH, Urine	5.0			7.0					8.0		7.0	
URINE CHEMISTRY												
Chloride, Urine	85	82	80		108	107	120	118		124		97
Potassium Urine Random	13	15	19		18	10	9	11		15		3
Sodium Urine Random	95	119	97		194	152	144	145		133		131
Protein/Creatinine Ratio				0.112 ▲					0.176 ▲			
Protein, Urine				0.10					0.24			
Osmolality, Urine												137
Specific Gravity, Urine	1.015			1.010					1.015		1.015	

Urine haematuria and proteinuria (dip negative but protein to creatinine ratio 112 mg/mmol and 176 mg/mmol)

Urine Cl	minimum 80 mmol/L	max 124 mmol/L
Urine K	minimum 3 mmol/L	max 19 mmol/L
Urine Na	minimum 95 mmol/L	max 194 mmol/L
Urine Osm	137 mosmol/kg	

Kidney Transplant

Good kidney perfusion essential
- Maintain BP (near donor BP)
- iv fluids
- Inotropes

Large volumes often used (more if native kidneys in situ)
- Mannitol and furosemide
- Reduced homeostatic ability

Matching input electrolytes to those in urine
- As well as matching volume

https://hospitalpharmacyeurope.com/news/iv-fluid-therapy-nutrition/paracetamol-infusion-dosage-for-babies-labelled-ten-times-correct-amount-on-patient-information-leaflet/

Final thoughts on Fluid Management

What data is needed

- History
- Examination (includes weight)
- Initial labwork

Fluid management

- Repeat examination
- Ins & Outs
- Daily weight (order it and preferably graph it)
- Repeat labwork (preferably graph values)
  significant changes within reference range…

Clinicians often think that low Na^+ is treated with IV Na^+

Why? Perhaps it is because of what they (apparently) observe!

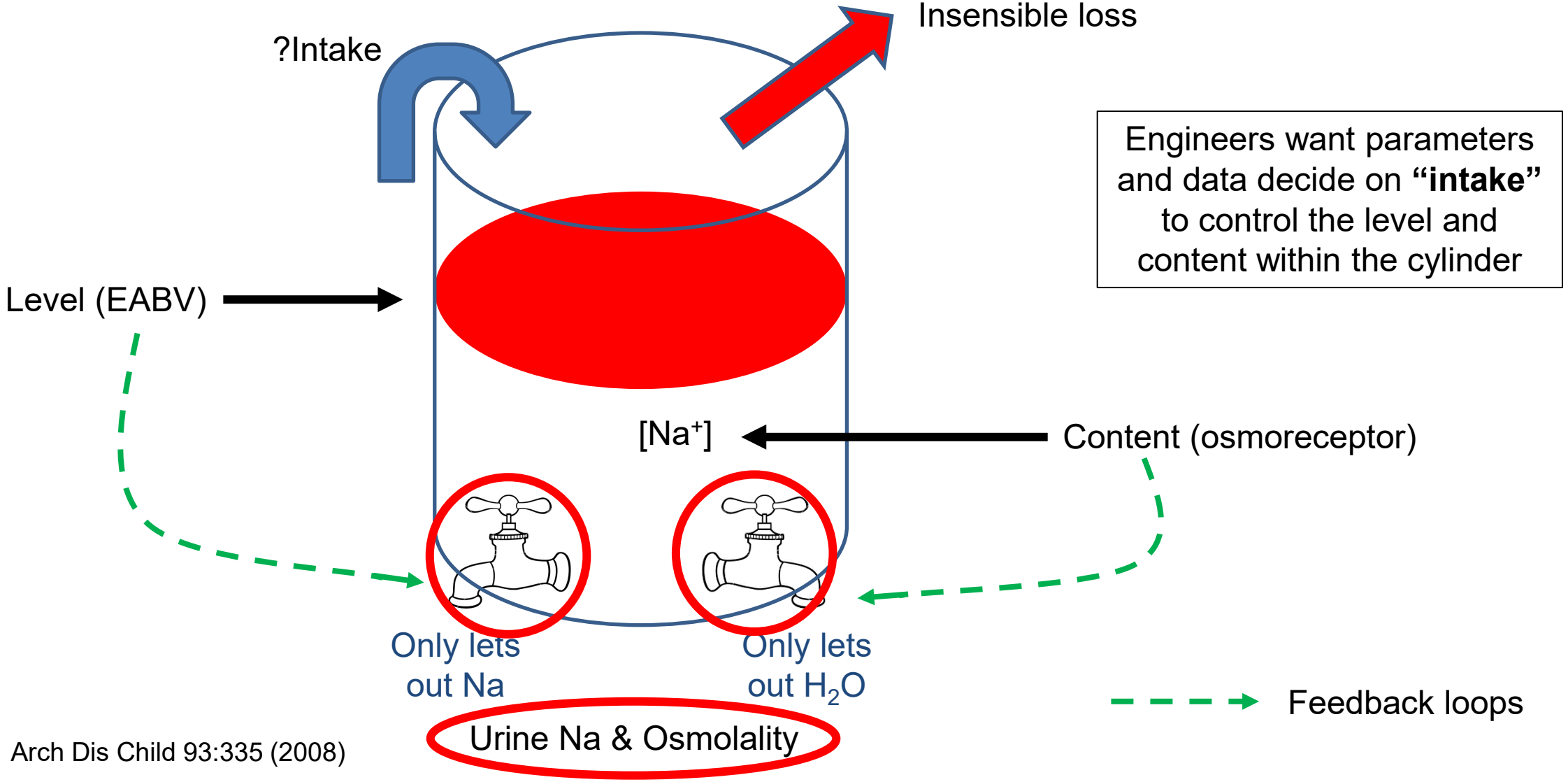
Patients with dehydration often have hyponatraemia
(hypotonic dehydration) – kidneys can't excrete xs water as ADH is present

Patients with dehydration often have hypovolaemia
IV saline is an appropriate treatment for hypovolaemia
resolution of hypovolaemia means that ADH is no longer high

With much less ADH present the kidneys are able to excrete water
The hyponatraemia resolves…..

(the excretion of water resolved the hyponatraemia and not the addition of sodium; at least from a kidney point of view)

An Engineer's Perspective on Fluid Management



Coulthard M Arch Dis Child 93:335 (2008)

Exceptions to “Maintenance” Requirements

“Maintenance” fluids maintains usual intake
(replace usual losses, insensible & renal)

A good way to think about this is “maintaining urine output”

THUS! Maintenance fluids is inappropriate with

Osmotic diuresis	eg glycosuria
Abnormal kidney function	eg CKD, DI, PIGN
ADH secretion……	
Anephric state	

and increased insensible losses eg burns, extreme prematurity

Getting Fluid Management “Right”

Not difficult with normal functioning kidneys

too much/little water, Na or K – kidneys deal with that

Really important with abnormal kidney function

abnormal kidneys eg dysplasia

no kidneys

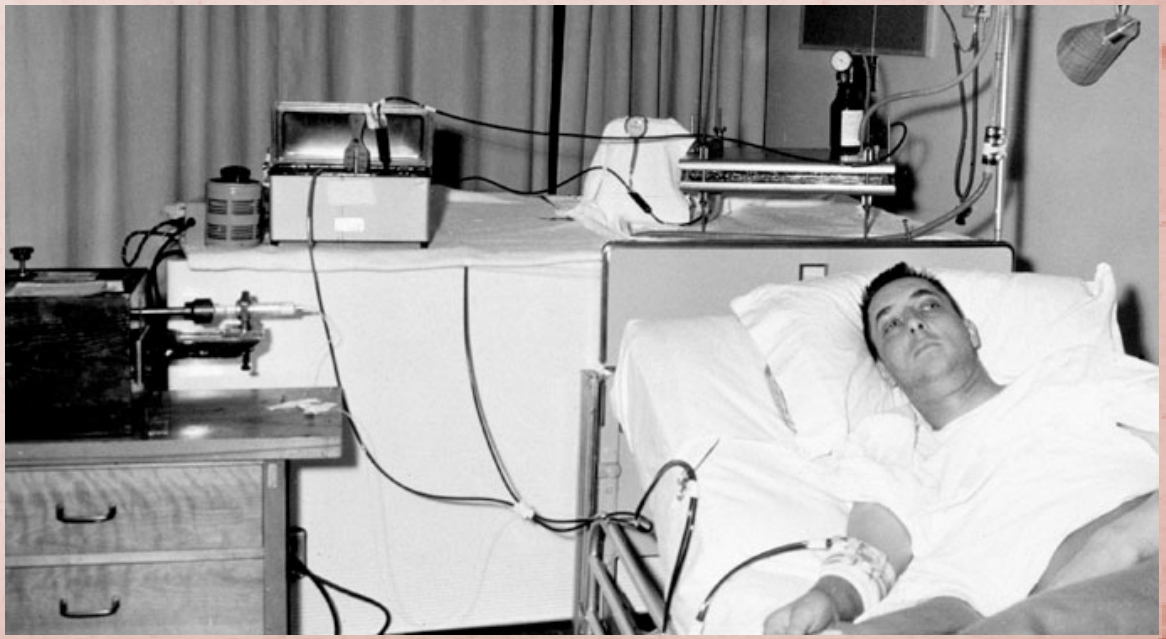
abnormal function eg nephritis, ATN, AKI, SIADH etc


Alberta Children's Hospital

Prescribing haemodialysis in children

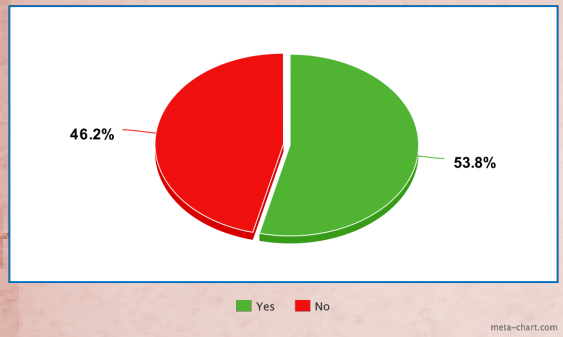
Malcolm A. Lewis

Consultant Paediatric Nephrologist

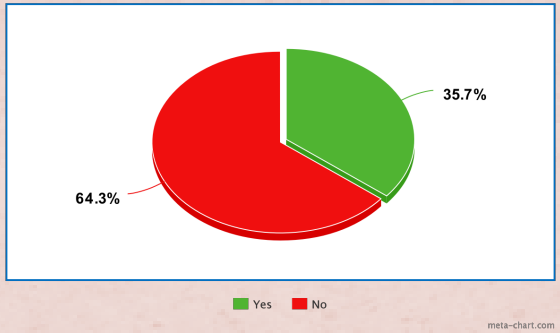


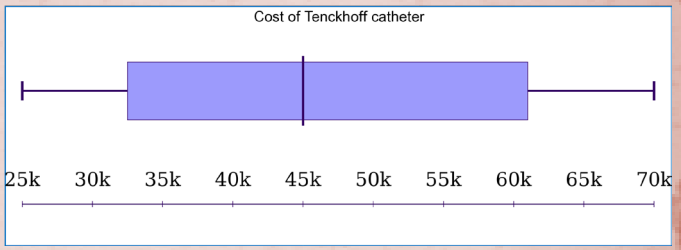
Why haemodialysis? – PD availability and cost

Units undertaking PD

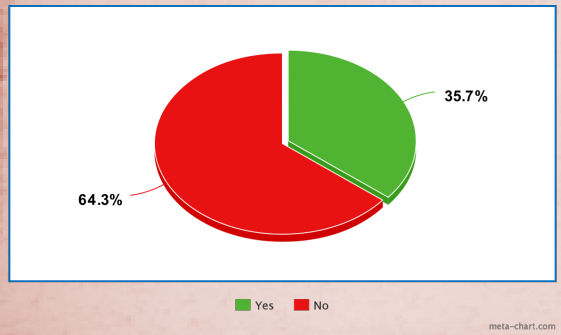


Are Tenckhoff catheters available

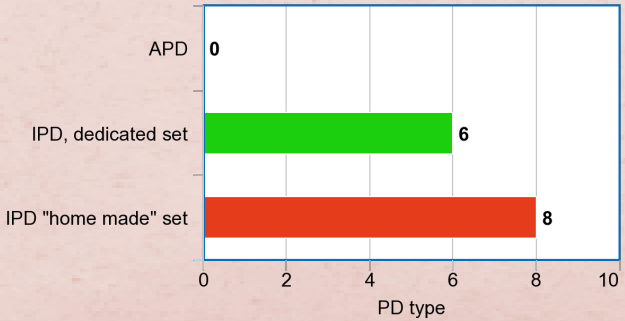


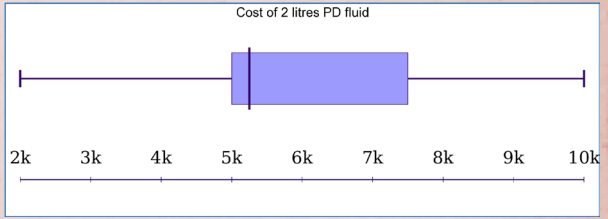


Commercial PD fluid available?

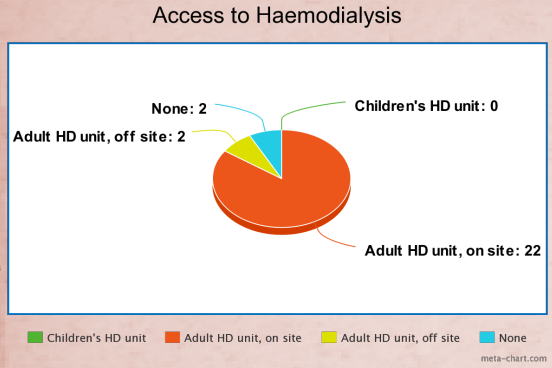


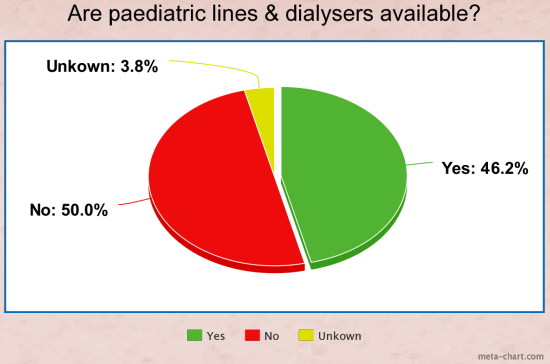
Type of PD used

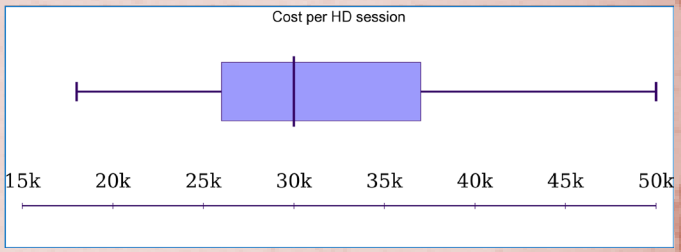




Why haemodialysis? – HD availability and cost



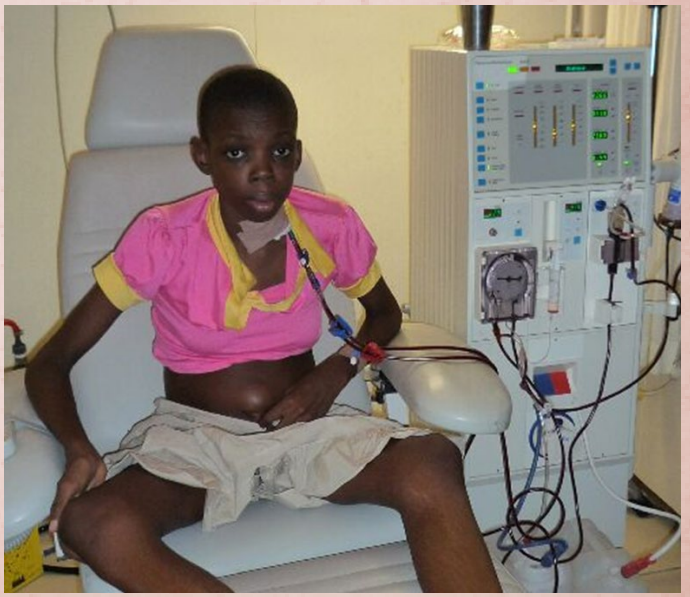




- First day of PD, catheter and fluid 56K, subsequent days 11K, 1 week 122K
- First day of HD 30K, 3 x HD in a week 90K (soft catheter may cost more)
- HD available to more than undertake PD, though through adult units
- PD limited to manual sets and low volumes
- HD using current machines generally
- 1 HD session may take patient from critical to end of an AKI episode

Components of haemodialysis

- Machine and water supply
- Power (NEPA)
- Vascular access
- Single versus double needle dialysis
- Dialyser and dialysis lines - the circuit
- Bleed out or not. Blood flow rate. UF rate.
- Anticoagulation
- Electrolyte settings
- Dialysis nurse(s) and technician(s)

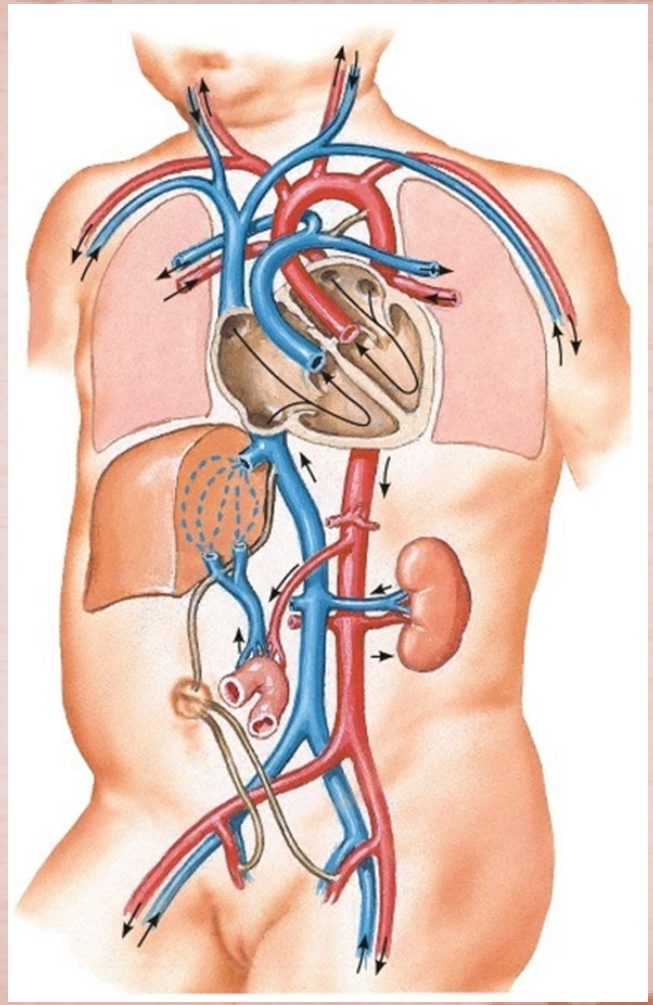


Machine and water supply

- Machines vary by manufacturer
- Need pure water supply
- For HDF needs ultra pure water supply
- Many have fixed water flow rate, others variable and some set to 1.5 x blood flow rate – but may be adjusted
- Need dialysis technicians for adjustment of factors like water flow rate often
- Need nursing staff familiar with the machines and alarms

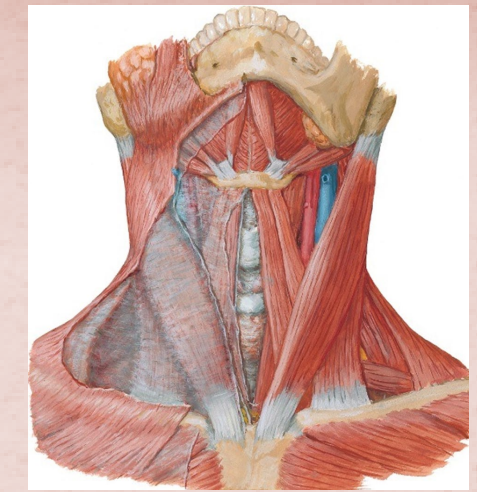
Vascular access

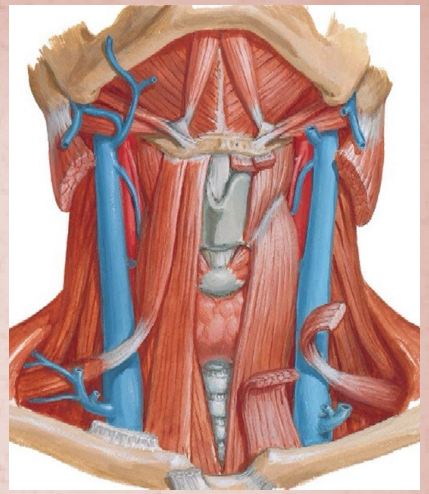
- AV fistula
- Tunnelled CVC
- Percutaneous CVC
  - Jugular
  - Subclavian
  - Femoral

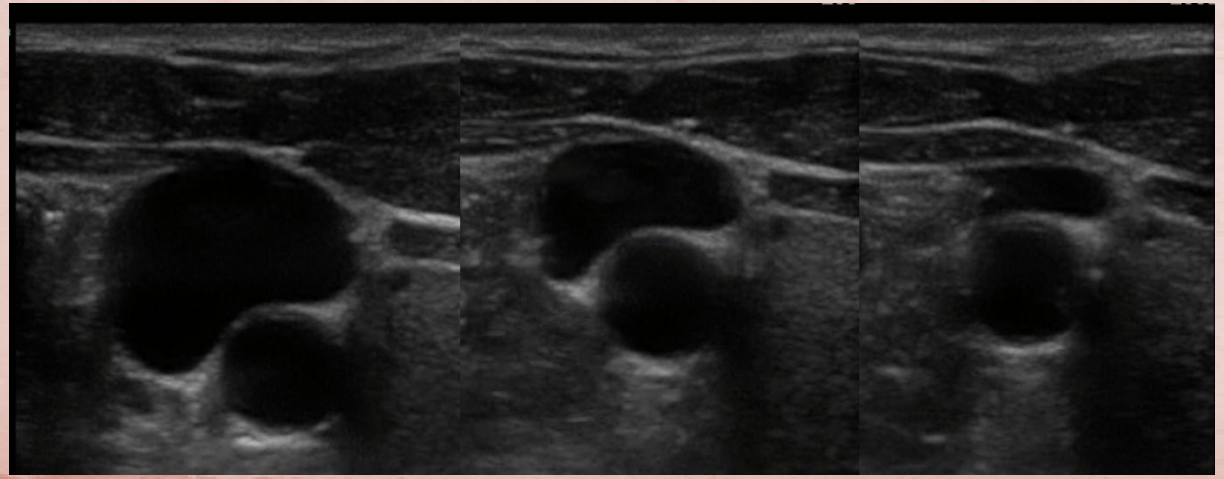


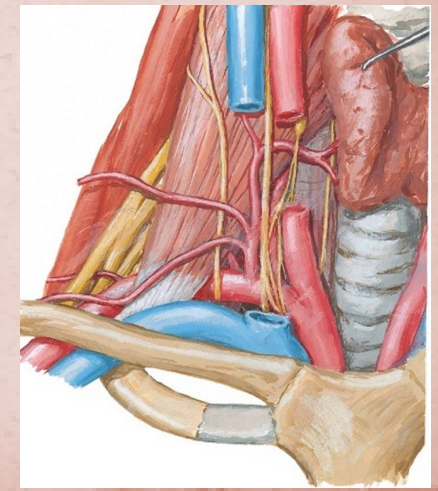
Jugular access

- Best for acute and chronic
- Stiff catheters uncomfortable
- Right better than left
- Vessel compression problem



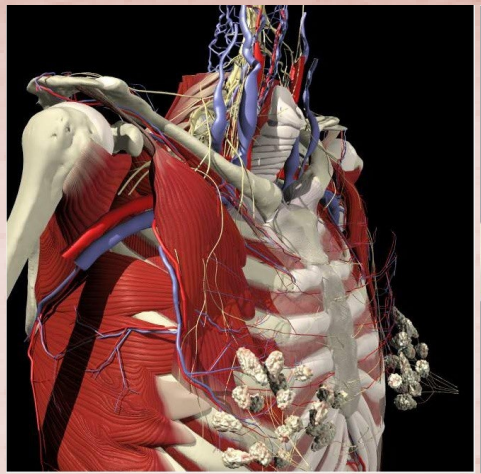


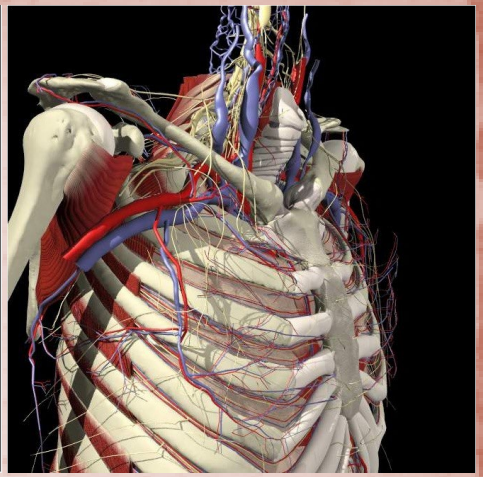


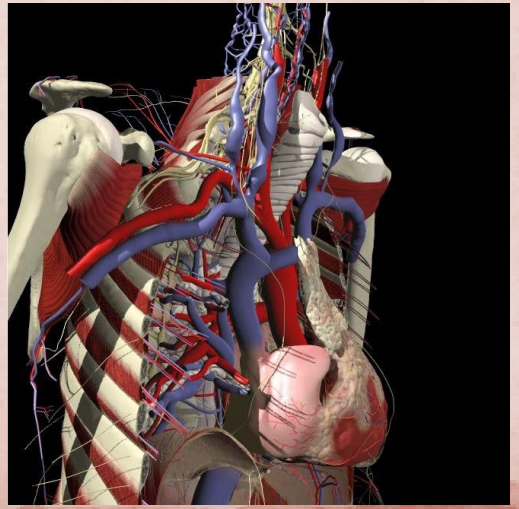


Subclavian access

- More difficult technically
- Risk of pneumo or haemothorax
- Safest insertion is with continuous image intensification
- Stenosis prevents AV fistula creation
- Stable and comfortable if inserted

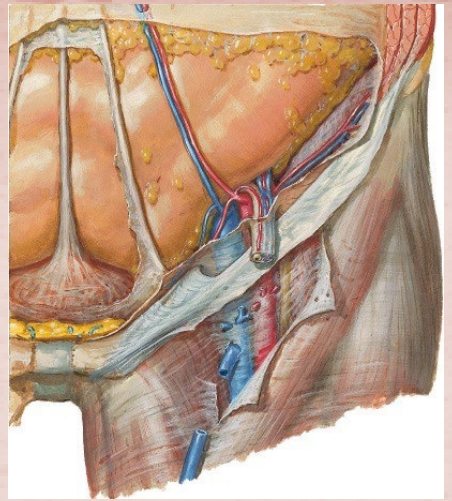


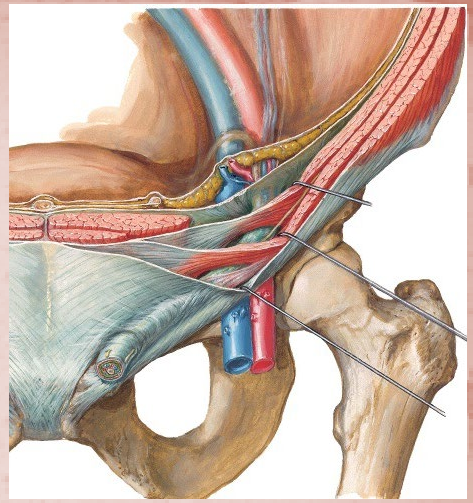


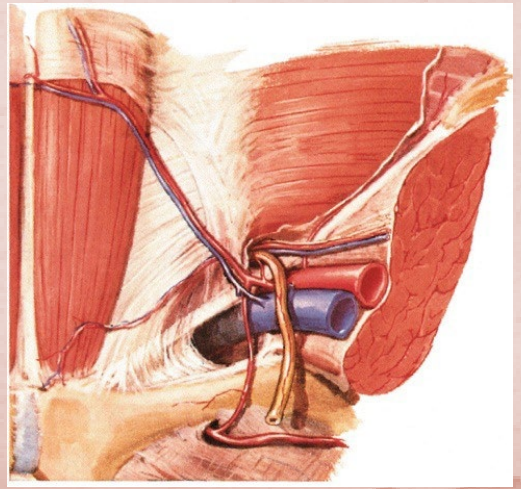


Femoral access

- Fastest and can be easiest
- Lowest risk of wire associated arrhythmia
- Remember the vein dips back to follow posterior wall of pelvis
- Risk of pelvic/IVC thrombosis
- Cannot last for long







Type / size of CVC

- Most CVC's dual lumen
- Can use 2 x single lumen or 1 CVC and large cannula
- Most units define catheter size by weight
  - This relates to flow not size
  - Flow = radius^4

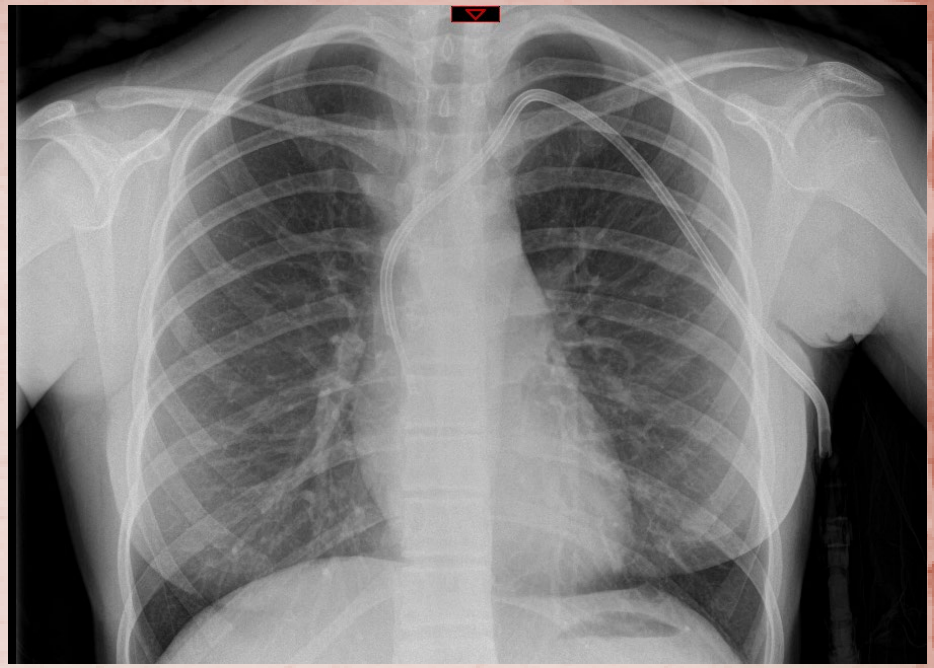
French size	Diameter (mm)
8	2.6
10	3.3
12	4.0
14	4.6
16	5.3

Weight (kg)	Catheter
< 5	8 F Medcomp Hemocath
5 - 19	10 F Medcomp
20 - 34	12 F Medcomp *Pediatric Quinton Permcath*
≥ 35	Palindrome Bioflow Duramax *Adult Quinton Permcath*

Weight	Flow @ 5 ml/kg/min	1 Lumen Fr^4	Derived dual lumen Fr
10	50	600	10
15	75	900	11
20	100	1200	12
25	125	1500	12
30	150	1800	13
35	175	2100	14
40	200	2400	14
45	225	2700	14
50	250	3000	15
55	275	3300	15
60	300	3600	15
65	325	3900	16
70	350	4096	16

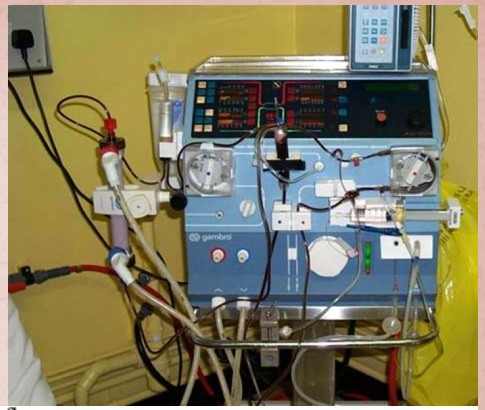
Type / size of CVC

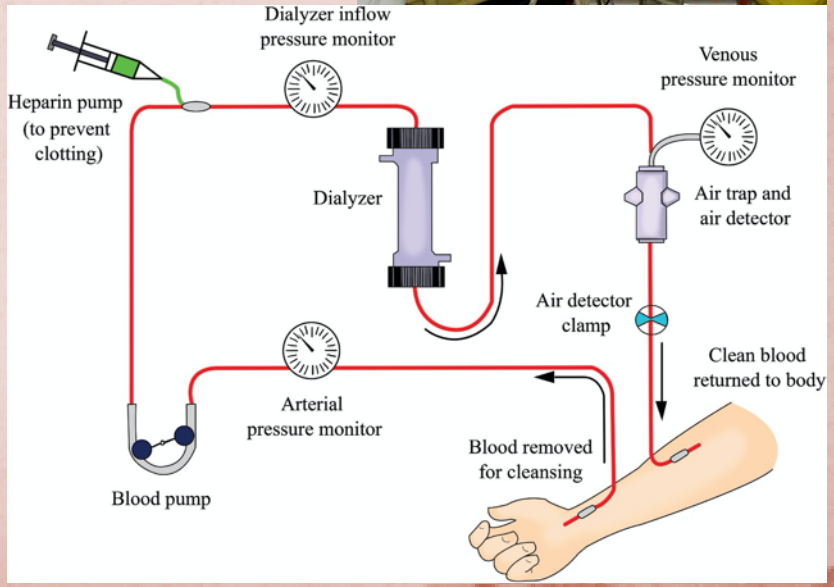
- Important to define catheter by fit:
  - What is the vessel diameter?
  - Need to allow for flow past when “dry”
  - How long is the catheter?
  - Position of side holes
  - Position of “arterial” lumen hole
  - Position of cuff on tunnelled lines
  - Too wide a catheter leads to “low venous pressure” alarms
  - Too narrow will not permit adequate flow



Dialyser and lines – the circuit

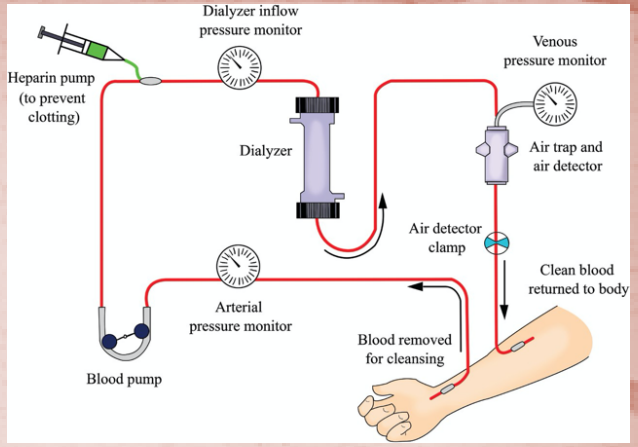
- Circuit comprises 3 parts
  - Arterial line
  - Dialyser
  - Venous line
- "Arterial line" takes from patient
  - Arterial low pressure = poor blood flow
- "Venous line" returns to patient
  - Venous high pressure = occlusion to return
  - Venous low pressure = free return with wide bore catheter and low flow
- Dialyser – SA < patient's BSA





Dialyser choice

- Aim for dialyser SA 0.75 – 1 x BSA
- Lower blood volume the better
- In high urea states use smaller dialyser if possible
- If large SA dialyser used reduce blood flow

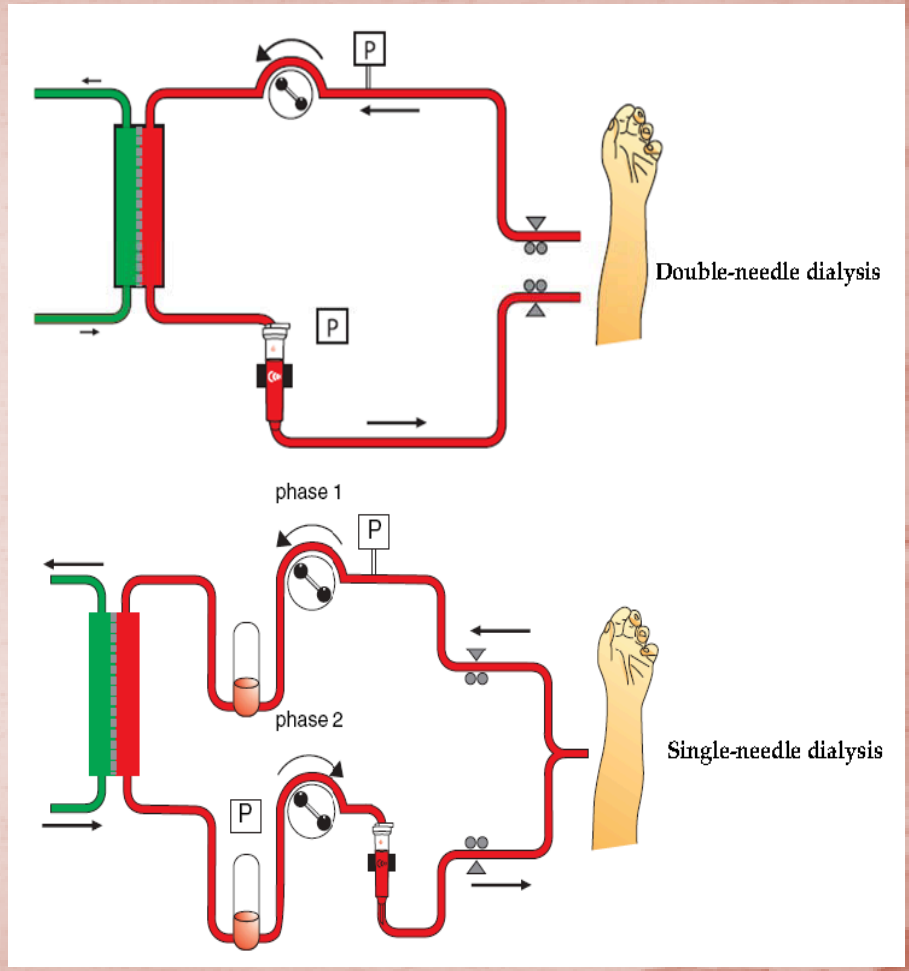


Dialyzer	Priming Volume (mls)	Surface area (m^2)	kUF (ml/hr/ mmHg TMP)	Material
FX 40	32	0.6	20	Helixone (polysulfone)
FX 50	53	1.0	33	"
FX 60	74	1.4	46	"
FX 600	97	1.5	52	"
FX 800	118	1.8	63	"
FX 1000	138	2.2	75	"

Dialyzer	Priming Volume (mls)	Surface area (m^2)	kUF (ml/hr/ mmHg TMP)	Material
FX Paed	18	0.2	7	Helixone (polysulfone)
Polyflux 2H	17	0.2	15	Polymix

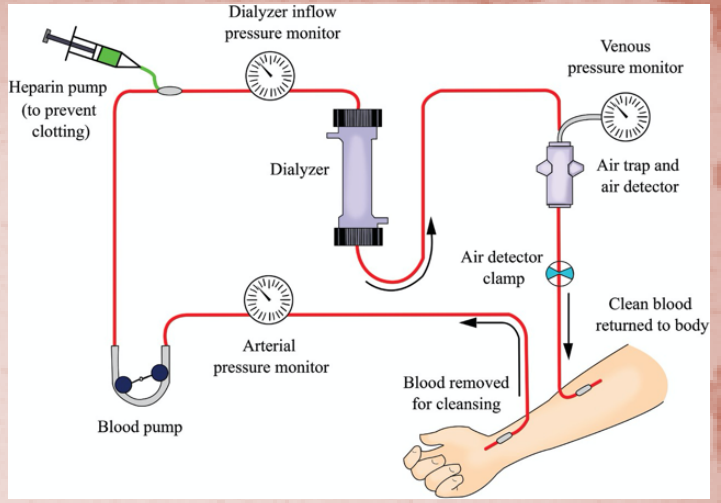
Single or double needle dialysis

- Single needle rarely considered
- Flow = radius^4 (Poiseuille's law)
- If using low flow raises venous pressure
- Needs appropriate circuit with expansion chambers
- Can be useful in small patients



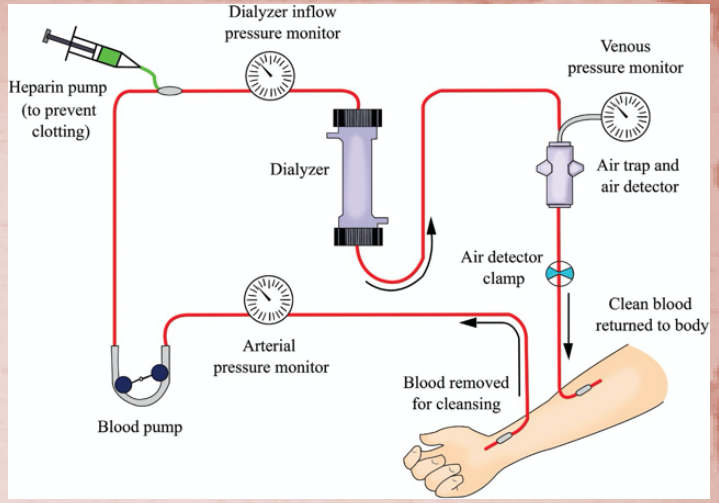
The Circuit – line and dialyser selection

- Lines come in varying sizes
  - *Neonatal*
  - Paediatric
  - Adult
- Aim is to give circuit volume (lines + dialyser) <10% of circulating volume
- Circulating volume = 80 ml/kg
- Problem is not volume per se, it is connection depletion or dilution and disconnection blood bolus
- For circuit too large prime with blood and do not wash back



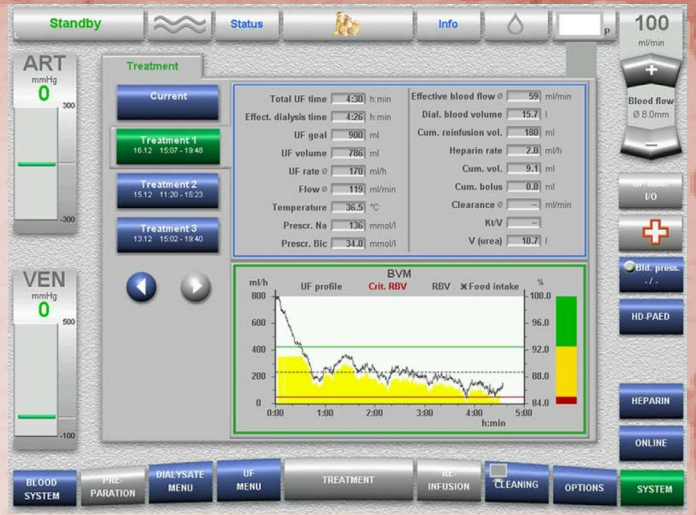
Connection – bleed out or not

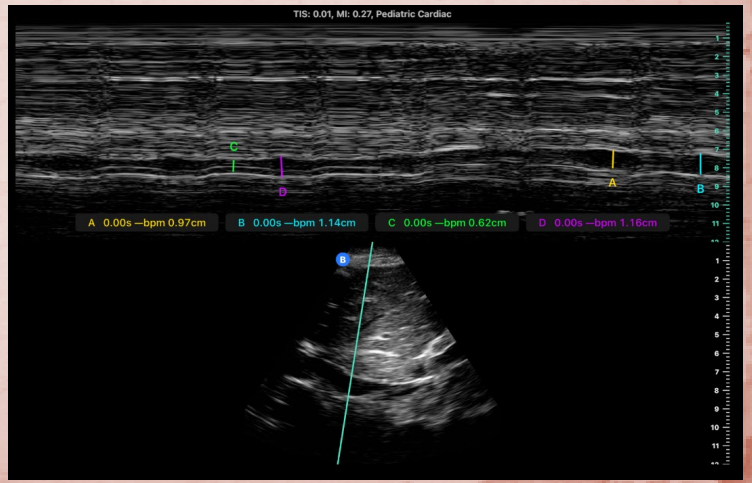
- Connecting circuit primed with blood is a straight connection.
- Connecting saline primed circuit some straight connect some bleed out
- Bleeding out depletes circulating volume, drops BP and makes UF more difficult
- As long as circuit volume <10% patient's blood volume straight connection best even when hypertensive or fluid overloaded
- Add circuit volume on to total UF calculation



Blood flow rate and UF rate

- Blood flow rate usually 5 ml/kg/min
- Vary according to;
  - Desire for clearance, raise to improve, decrease where urea very high or dialyser oversized
  - Decrease if repeated low arterial pressure
  - Increase if repeated low venous pressure
  - Decrease if high venous pressure but no occlusion
- UF rate best <10 ml/kg/hour
  - Weight – ideal weight x 1000 + circuit volume
  - Intravascular overload easy to remove
  - Severe overload use isolated UF
  - Oedema more problematic to remove



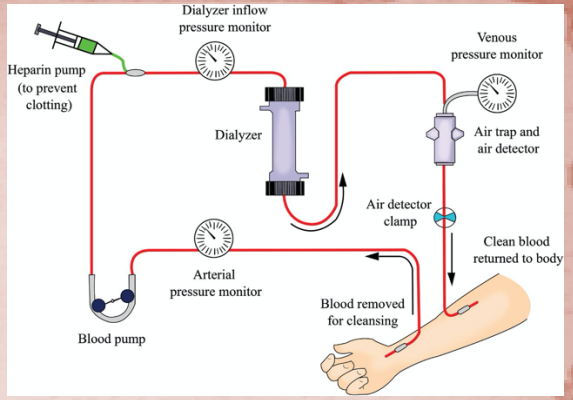


Anticoagulation

- **Infractionated or LMWH**

"Dry" weight (kg)	Tinzaparin units	Volume (ml)*
0 - 5	250	1
5 - 10	500	2
10 - 20	1000	4
20 - 30	1500	6
30 - 40	2000	8
40 - 50	2500	10
* Dilute 2500 units of Tinzaparin to 10 ml with 0.9% sodium chloride (=250 units/ml)		

"Dry" weight (kg)	Tinzaparin units	Volume (ml)*
50 - 60	3000	6
>60	3500	7
	4000	8
	4500	9
	5000	10
* Dilute 5000 units of Tinzaparin to 10 ml with 0.9% sodium chloride (=500 units/ml)		



Standard heparinisation			
"Dry" weight (kg)	Load (units/kg)	Load dose	Infusion (units/kg/hr)
5 - 15	10 - 16	50 - 250	15 - 25
15 - 25	16 - 20	250 - 500	15 - 25
25 - 35	18 - 20	500 -750	15 - 25
35 - 55	18 - 20	750 - 1000	15 - 25
>55	20	1000	15 - 25

Minimal heparinisation			
"Dry" weight (kg)	Load (units/kg)	Load dose	Infusion (units/kg/hr)
5 - 15	5 - 10	25 - 150	5 - 10
15 - 25	5 - 10	75 - 250	5 - 10
25 - 35	5 - 10	125 - 350	5 - 10
35 - 55	5 - 10	175 - 550	5 - 10
>55	5 - 10	275 - 550	5 - 10

Electrolyte settings

- Potassium and calcium determined by the concentrate
- Potassium options 1.0, 2.0 or 3.0 mmol/l
- Calcium options 1.0, 1.25 or 1.5 mmol/l (1.25 standard)
- Magnesium physiological – no options
- Phosphate absent
- Sodium determined by machine, 130 – 160 mmol/l
- Bicarbonate determined by machine 20 -45 mmol/l, default 45 mmol/l

The prescription

Date: ……

Name: …… Hosp No: …… Age: ….. Ht: ….. Dry Wt: ….. BSA: …..

Dialyser: …… Lines: Paediatric [ ] Adult [ ] Dialysate temp: 37.5 or …..

Prime: 0.9% saline [ ] Packed cells [ ] 5% Albumin [ ] 20% Albumin [ ] Bleed out [ ]

Blood flow: ……ml/min Duration of dialysis: ……hr Total UF: ……..ml Isolated UF for 1 hr: Yes / No UF in isolated: ……ml

Potassium: 1 mmol/l [ ] 2 mmol/l [ ] 3 mmol/l [ ] Calcium: 1 mmol/l [ ] 1.25 mmol/l [ ] 1.5 mmol/l [ ]

Sodium: ….. mmol/l or variable [ ] Bicarbonate: 45 mmol/l or ….. Glucose: 0 mmol/l [ ] 1 mmol/l [ ] 2 mmol/l [ ]

Infusion(s) in dialysis: Packed cells [ ] 5% Albumin [ ] 20% Albumin [ ] Volume: ……. ml time ….. hr

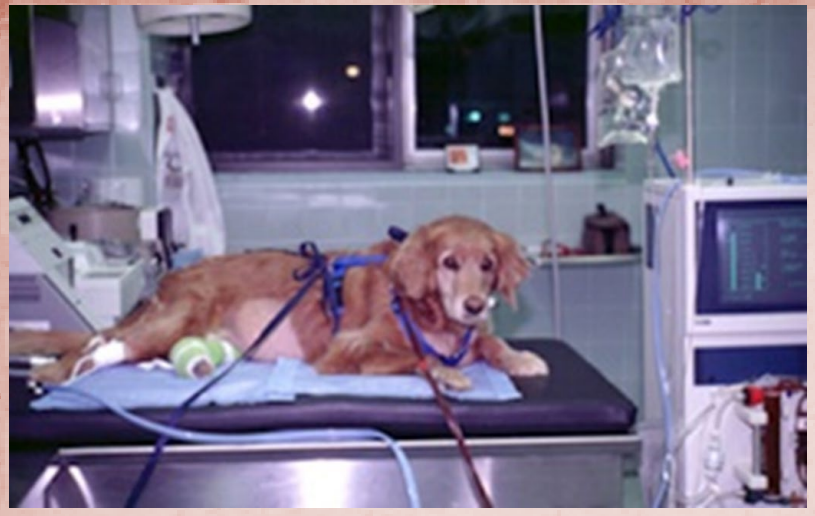
If BP drops below …. mmHg, administer …… ml of 0.9% saline

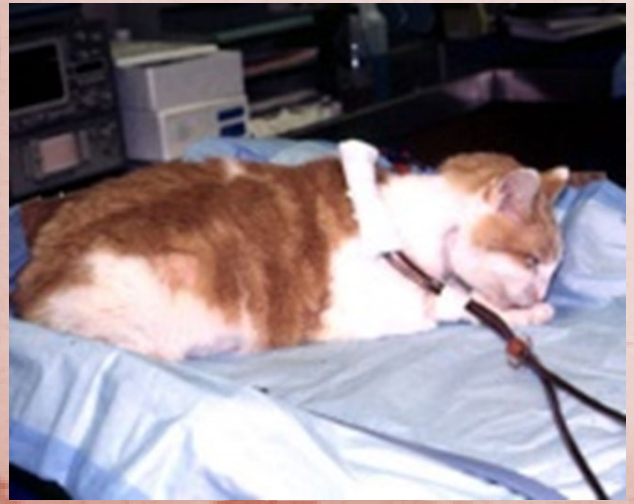
If BP above …. mmHg, administer Nifedipine [ ] Hydrallazine [ ] Captopril [ ], …. mg

Variable Sodium – profiling details if selected:

……

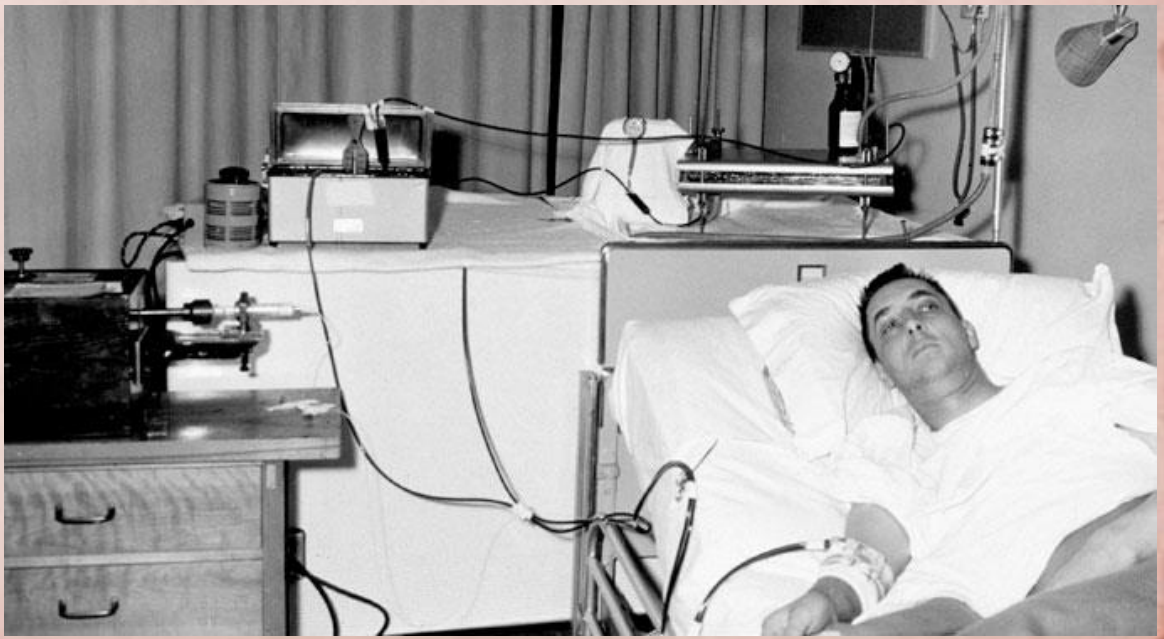
……






24
DEC.
I don't care what day it is.
Four hours is four hours.

Prescribing haemodialysis in children

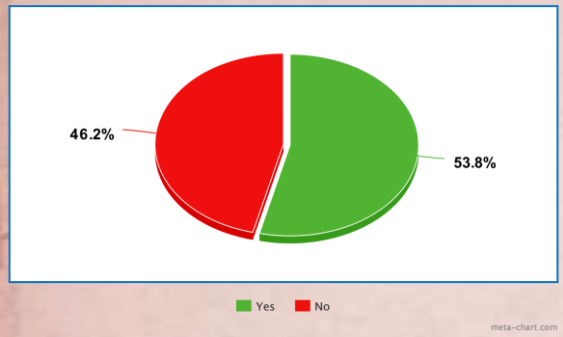


Malcolm A. Lewis

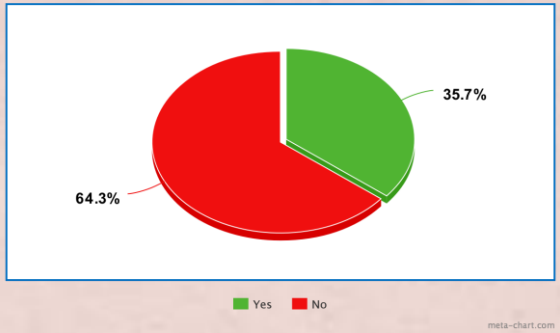
Consultant Paediatric Nephrologist

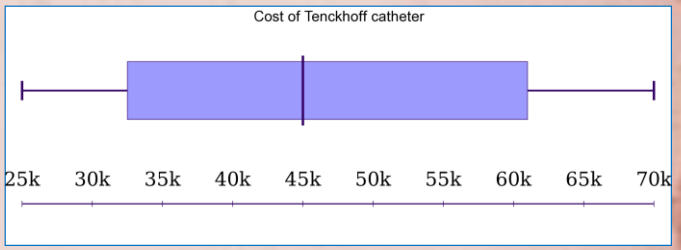
Why haemodialysis? – PD availability and cost

Units undertaking PD

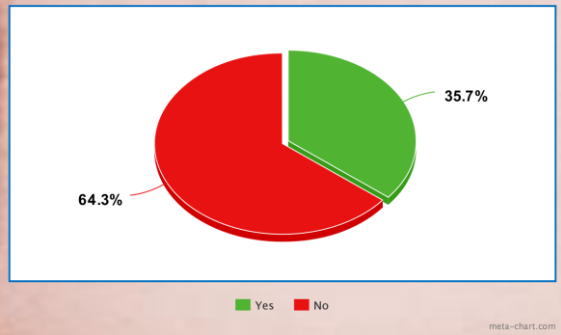


Are Tenckhoff catheters available

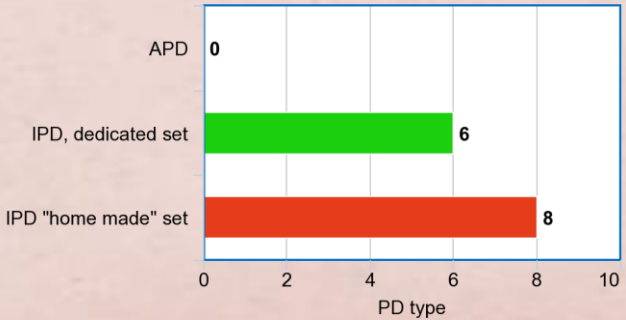


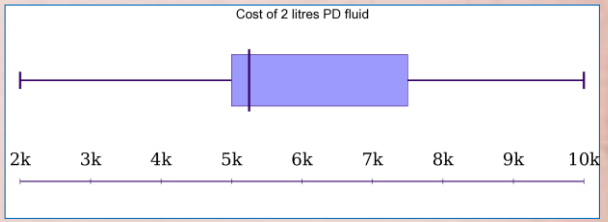


Commercial PD fluid available?

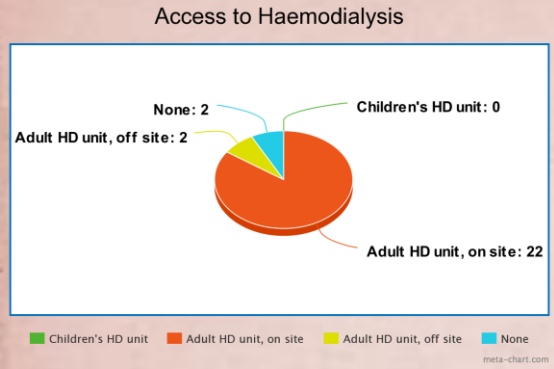


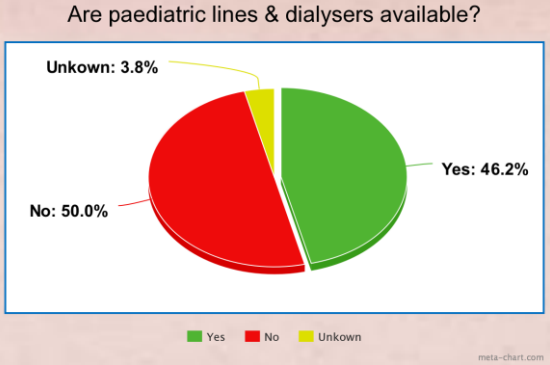
Type of PD used

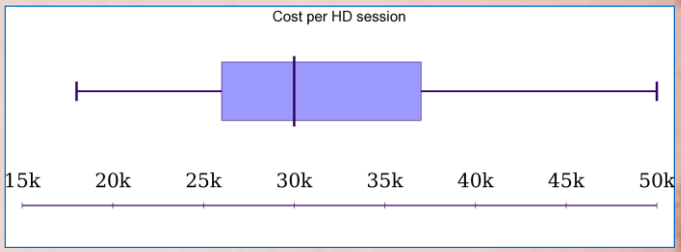




Why haemodialysis? – HD availability and cost



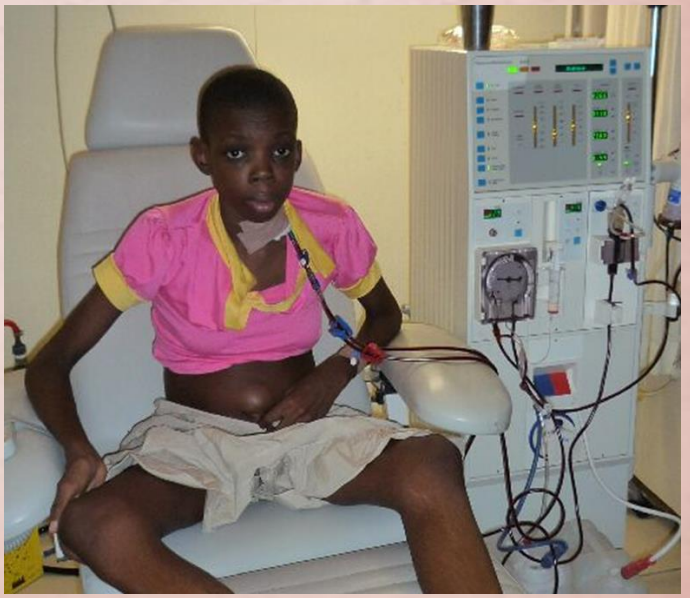




- First day of PD, catheter and fluid 56K, subsequent days 11K, 1 week 122K
- First day of HD 30K, 3 x HD in a week 90K (soft catheter may cost more)
- HD available to more than undertake PD, though through adult units
- PD limited to manual sets and low volumes
- HD using current machines generally
- 1 HD session may take patient from critical to end of an AKI episode

Components of haemodialysis

- Machine and water supply
- Power (NEPA)
- Vascular access
- Single versus double needle dialysis
- Dialyser and dialysis lines - the circuit
- Bleed out or not. Blood flow rate. UF rate.
- Anticoagulation
- Electrolyte settings
- Dialysis nurse(s) and technician(s)

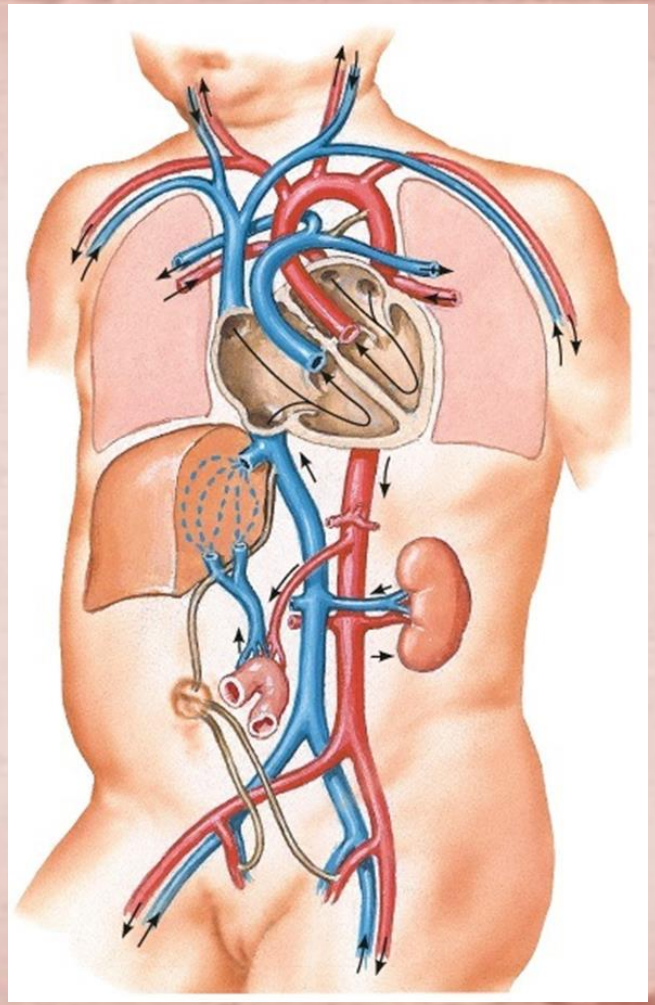


Machine and water supply

- Machines vary by manufacturer
- Need pure water supply
- For HDF needs ultra pure water supply
- Many have fixed water flow rate, others variable and some set to 1.5 x blood flow rate – but may be adjusted
- Need dialysis technicians for adjustment of factors like water flow rate often
- Need nursing staff familiar with the machines and alarms

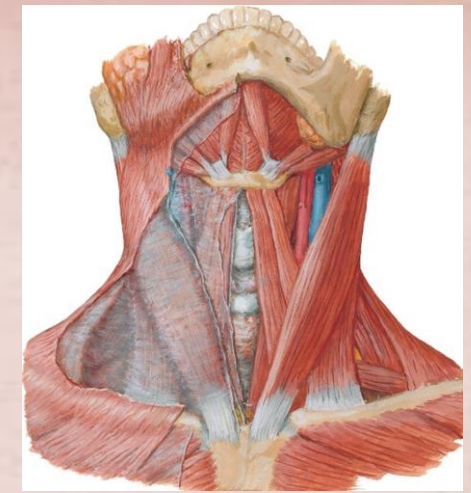
Vascular access

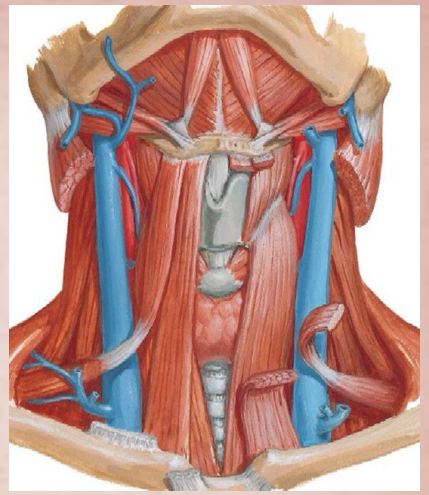
- AV fistula
- Tunnelled CVC
- Percutaneous CVC
  - Jugular
  - Subclavian
  - Femoral

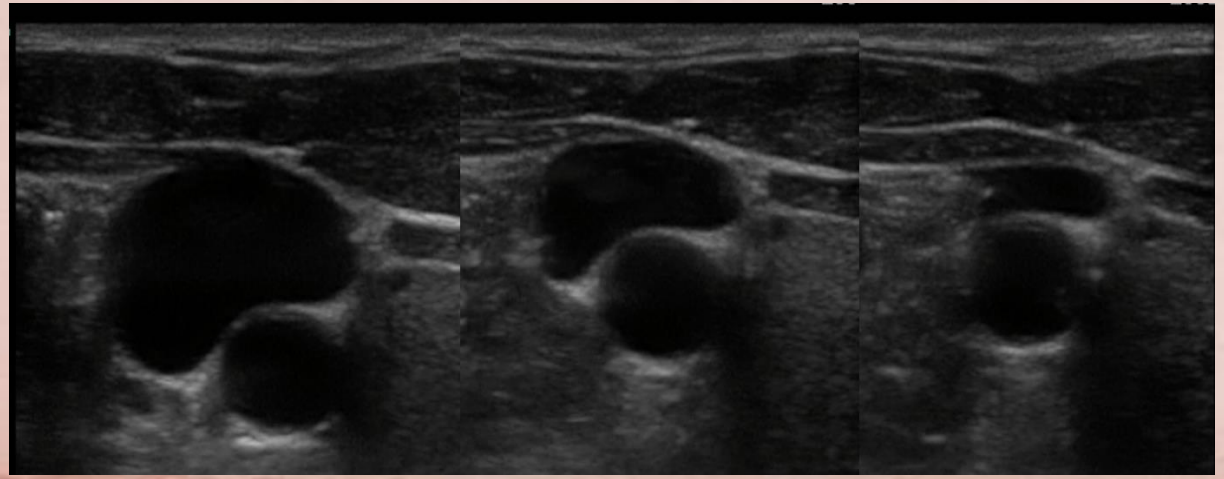


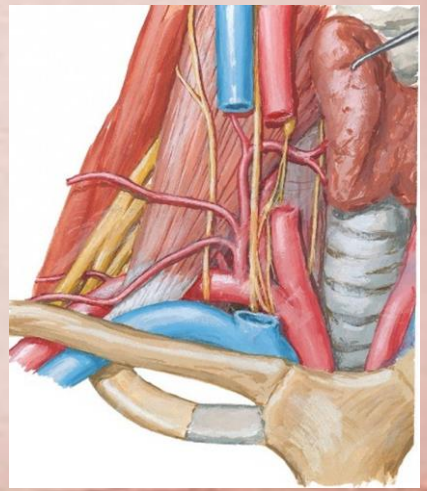
Jugular access

- Best for acute and chronic
- Stiff catheters uncomfortable
- Right better than left
- Vessel compression problem



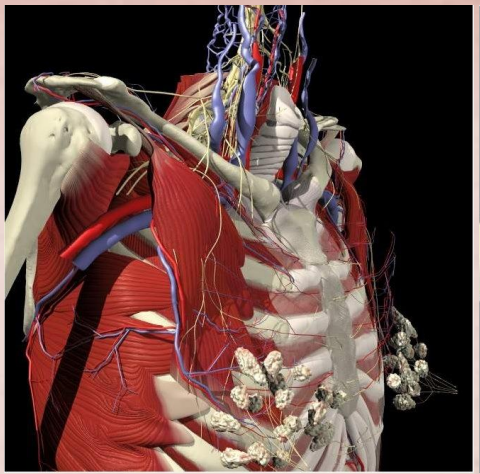


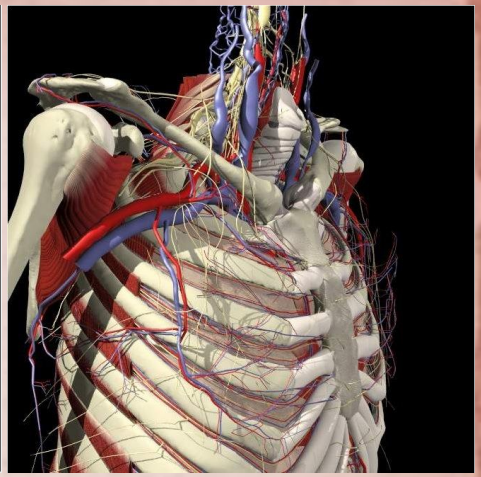


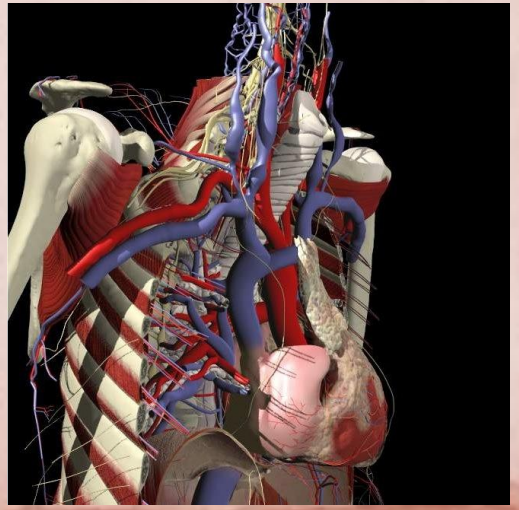


Subclavian access

- More difficult technically
- Risk of pneumo or haemothorax
- Safest insertion is with continuous image intensification
- Stenosis prevents AV fistula creation
- Stable and comfortable if inserted

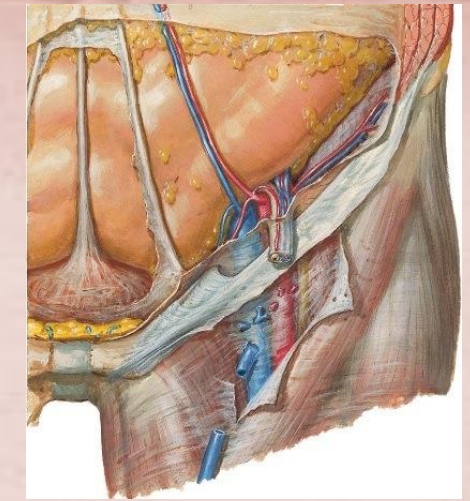


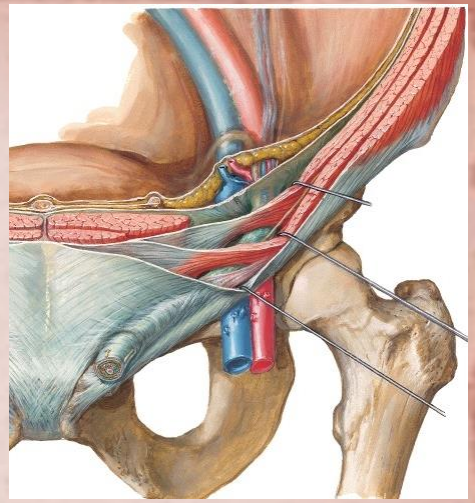


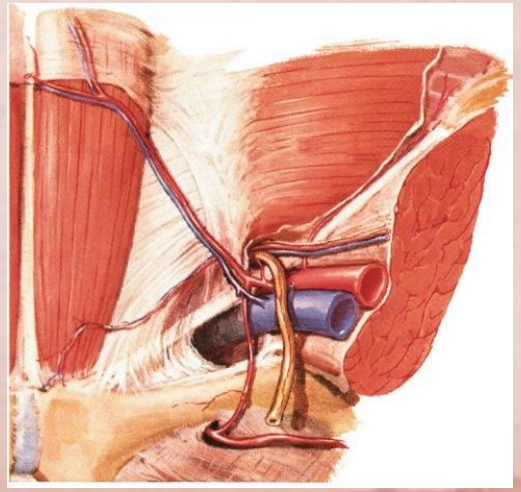


Femoral access

- Fastest and can be easiest
- Lowest risk of wire associated arrhythmia
- Remember the vein dips back to follow posterior wall of pelvis
- Risk of pelvic/IVC thrombosis
- Cannot last for long







Type / size of CVC

- Most CVC's dual lumen
- Can use 2 x single lumen or 1 CVC and large cannula
- Most units define catheter size by weight
  - This relates to flow not size
  - Flow = radius^4

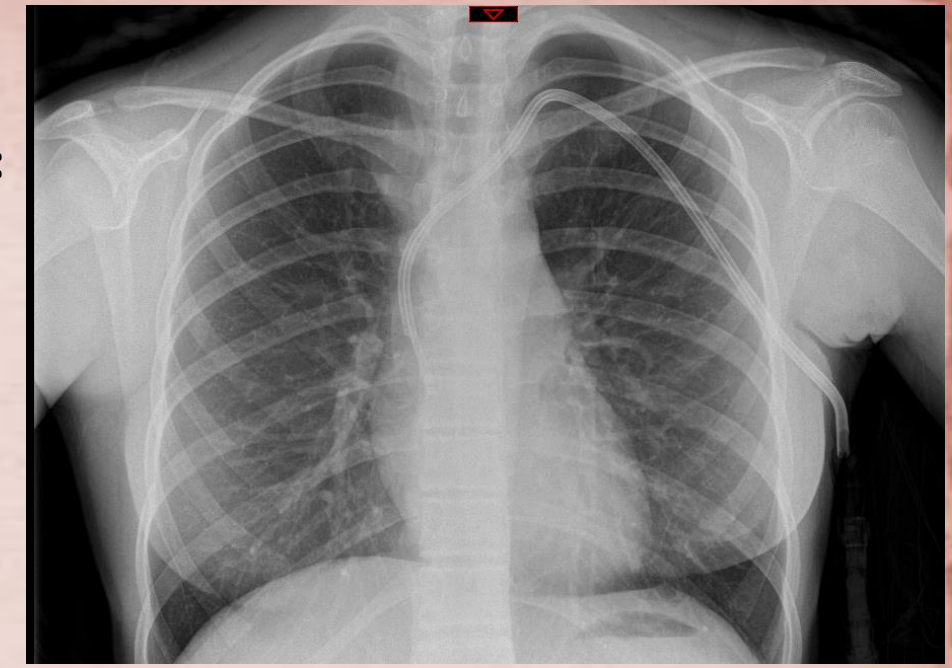
French size	Diameter (mm)
8	2.6
10	3.3
12	4.0
14	4.6
16	5.3

Weight (kg)	Catheter
< 5	8 F Medcomp Hemocath
5 - 19	10 F Medcomp
20 - 34	12 F Medcomp *Pediatric Quinton Permcath*
≥ 35	Palindrome Bioflow Duramax *Adult Quinton Permcath*

Weight	Flow @ 5 ml/kg/min	1 Lumen Fr^4	Derived dual lumen Fr
10	50	600	10
15	75	900	11
20	100	1200	12
25	125	1500	12
30	150	1800	13
35	175	2100	14
40	200	2400	14
45	225	2700	14
50	250	3000	15
55	275	3300	15
60	300	3600	15
65	325	3900	16
70	350	4096	16

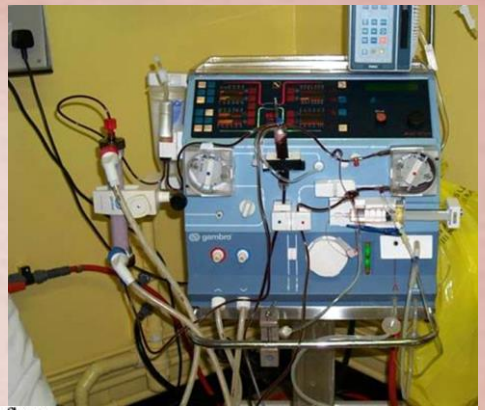
Type / size of CVC

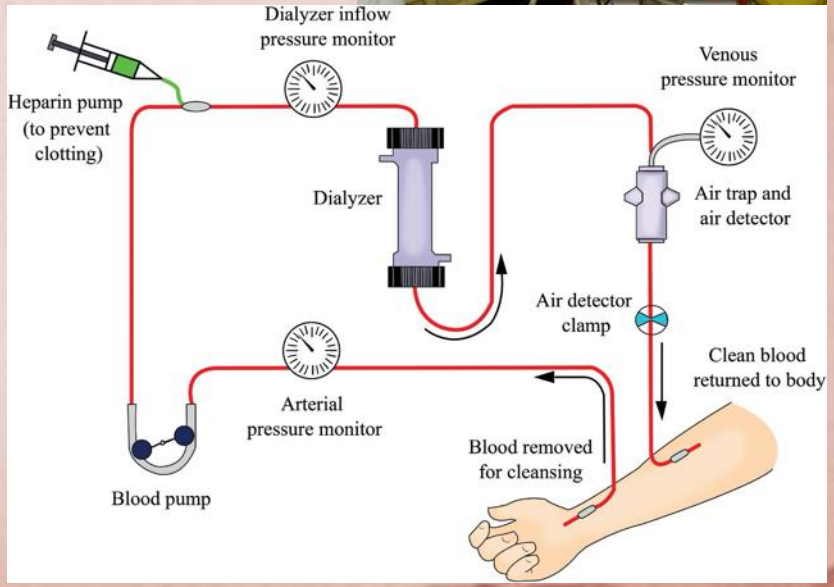
- Important to define catheter by fit:
  - What is the vessel diameter?
  - Need to allow for flow past when “dry”
  - How long is the catheter?
  - Position of side holes
  - Position of “arterial” lumen hole
  - Position of cuff on tunnelled lines
  - Too wide a catheter leads to “low venous pressure” alarms
  - Too narrow will not permit adequate flow



Dialyser and lines – the circuit

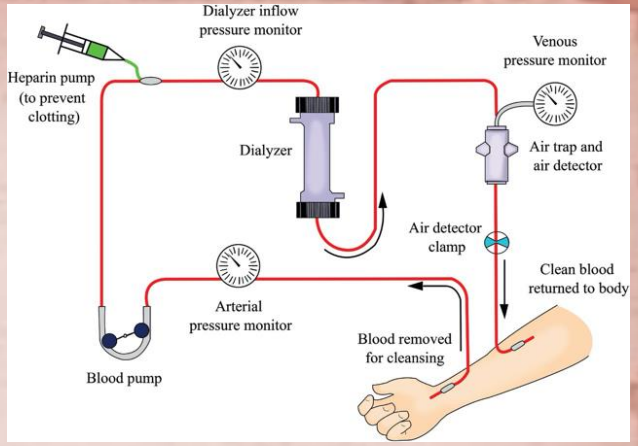
- Circuit comprises 3 parts
  - Arterial line
  - Dialyser
  - Venous line
- "Arterial line" takes from patient
  - Arterial low pressure = poor blood flow
- "Venous line" returns to patient
  - Venous high pressure = occlusion to return
  - Venous low pressure = free return with wide bore catheter and low flow
- Dialyser – SA < patient's BSA





Dialyser choice

- Aim for dialyser SA 0.75 – 1 x BSA
- Lower blood volume the better
- In high urea states use smaller dialyser if possible
- If large SA dialyser used reduce blood flow

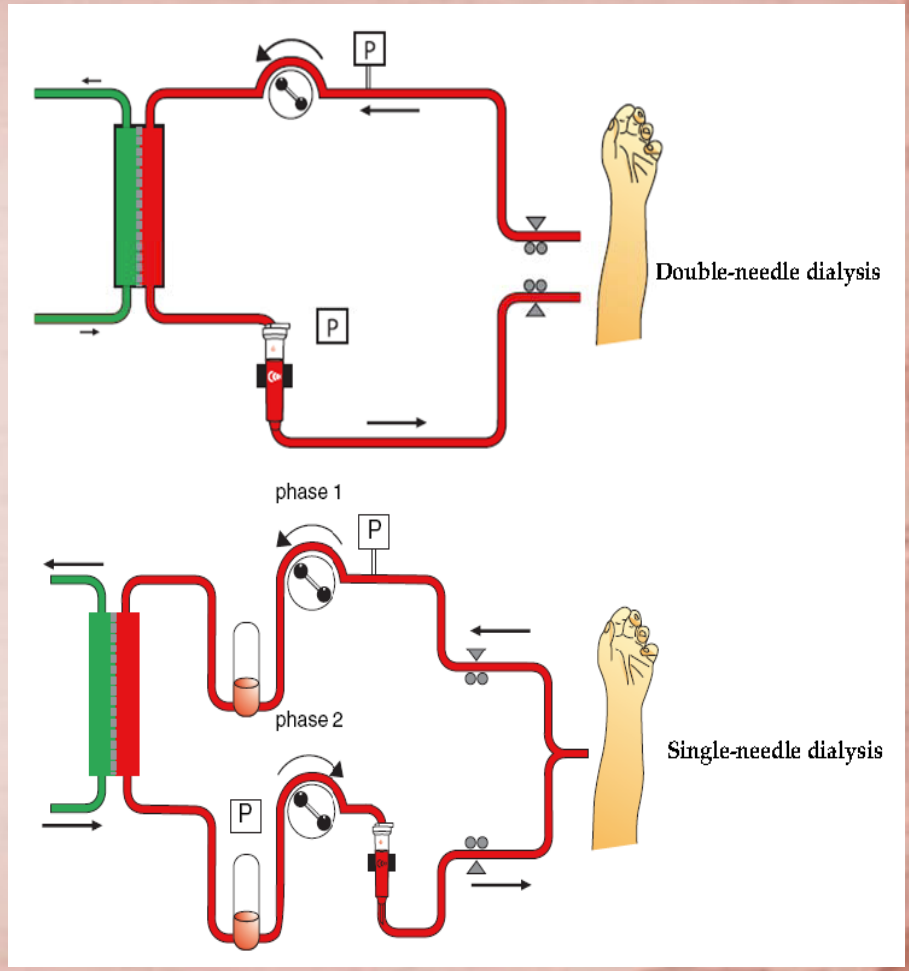


Dialyzer	Priming Volume (mls)	Surface area (m^2)	kUF (ml/hr/ mmHg TMP)	Material
FX 40	32	0.6	20	Helixone (polysulfone)
FX 50	53	1.0	33	"
FX 60	74	1.4	46	"
FX 600	97	1.5	52	"
FX 800	118	1.8	63	"
FX 1000	138	2.2	75	"

Dialyzer	Priming Volume (mls)	Surface area (m^2)	kUF (ml/hr/ mmHg TMP)	Material
FX Paed	18	0.2	7	Helixone (polysulfone)
Polyflux 2H	17	0.2	15	Polymix

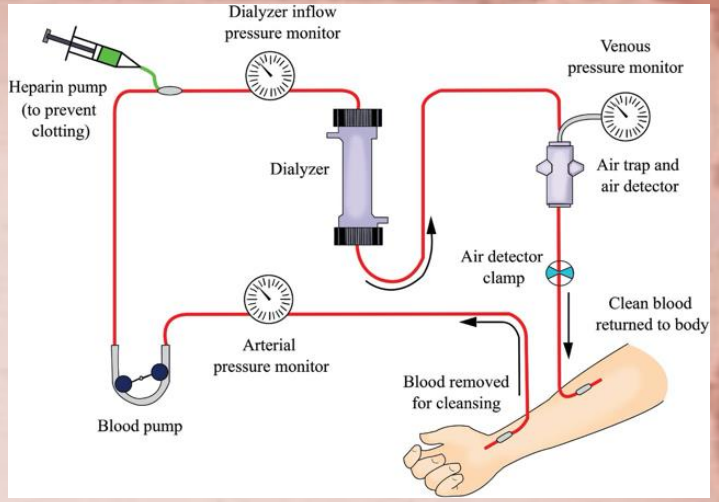
Single or double needle dialysis

- Single needle rarely considered
- Flow = radius^4 (Poiseuille's law)
- If using low flow raises venous pressure
- Needs appropriate circuit with expansion chambers
- Can be useful in small patients



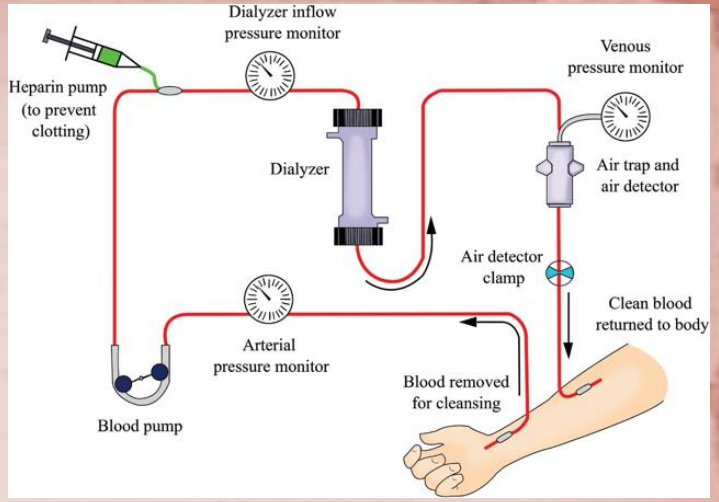
The Circuit – line and dialyser selection

- Lines come in varying sizes
  - *Neonatal*
  - Paediatric
  - Adult
- Aim is to give circuit volume (lines + dialyser) <10% of circulating volume
- Circulating volume = 80 ml/kg
- Problem is not volume per se, it is connection depletion or dilution and disconnection blood bolus
- For circuit too large prime with blood and do not wash back



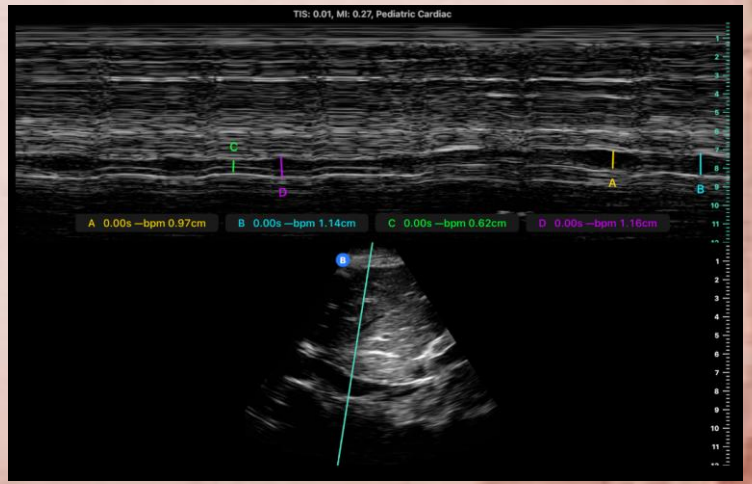
Connection – bleed out or not

- Connecting circuit primed with blood is a straight connection.
- Connecting saline primed circuit some straight connect some bleed out
- Bleeding out depletes circulating volume, drops BP and makes UF more difficult
- As long as circuit volume <10% patient's blood volume straight connection best even when hypertensive or fluid overloaded
- Add circuit volume on to total UF calculation



Blood flow rate and UF rate

- Blood flow rate usually 5 ml/kg/min
- Vary according to;
  - Desire for clearance, raise to improve, decrease where urea very high or dialyser oversized
  - Decrease if repeated low arterial pressure
  - Increase if repeated low venous pressure
  - Decrease if high venous pressure but no occlusion
- UF rate best <10 ml/kg/hour
  - Weight – ideal weight x 1000 + circuit volume
  - Intravascular overload easy to remove
  - Severe overload use isolated UF
  - Oedema more problematic to remove



Anticoagulation

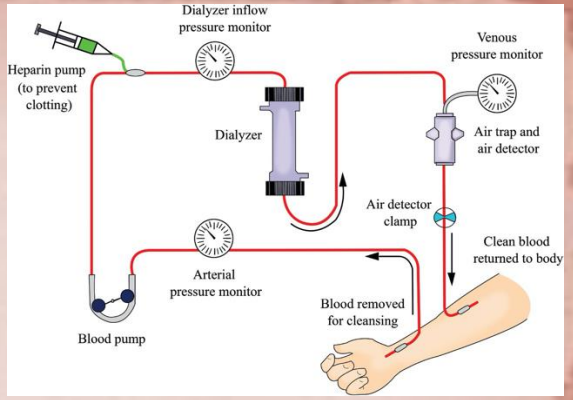
- **Infractionated or LMWH**

"Dry" weight (kg)	Tinzaparin units	Volume (ml)*
0 - 5	250	1
5 - 10	500	2
10 - 20	1000	4
20 - 30	1500	6
30 - 40	2000	8
40 - 50	2500	10

* Dilute 2500 units of Tinzaparin to 10 ml with 0.9% sodium chloride (=250 units/ml)

"Dry" weight (kg)	Tinzaparin units	Volume (ml)*
50 - 60	3000	6
>60	3500	7
	4000	8
	4500	9
	5000	10

* Dilute 5000 units of Tinzaparin to 10 ml with 0.9% sodium chloride (=500 units/ml)



Standard heparinisation

"Dry" weight (kg)	Load (units/kg)	Load dose	Infusion (units/kg/hr)
5 - 15	10 - 16	50 - 250	15 - 25
15 - 25	16 - 20	250 - 500	15 - 25
25 - 35	18 - 20	500 -750	15 - 25
35 - 55	18 - 20	750 - 1000	15 - 25
>55	20	1000	15 - 25

Minimal heparinisation

"Dry" weight (kg)	Load (units/kg)	Load dose	Infusion (units/kg/hr)
5 - 15	5 - 10	25 - 150	5 - 10
15 - 25	5 - 10	75 - 250	5 - 10
25 - 35	5 - 10	125 - 350	5 - 10
35 - 55	5 - 10	175 - 550	5 - 10
>55	5 - 10	275 - 550	5 - 10

Electrolyte settings

- Potassium and calcium determined by the concentrate
- Potassium options 1.0, 2.0 or 3.0 mmol/l
- Calcium options 1.0, 1.25 or 1.5 mmol/l (1.25 standard)
- Magnesium physiological – no options
- Phosphate absent
- Sodium determined by machine, 130 – 160 mmol/l
- Bicarbonate determined by machine 20 -45 mmol/l, default 45 mmol/l

The prescription

Date: ……

Name: …… Hosp No: …… Age: ….. Ht: ….. Dry Wt: ….. BSA: …..

Dialyser: …… Lines: Paediatric [ ] Adult [ ] Dialysate temp: 37.5 or …..

Prime: 0.9% saline [ ] Packed cells [ ] 5% Albumin [ ] 20% Albumin [ ] Bleed out [ ]

Blood flow: ……ml/min Duration of dialysis: ……hr Total UF: ……..ml Isolated UF for 1 hr: Yes / No UF in isolated: ……ml

Potassium: 1 mmol/l [ ] 2 mmol/l [ ] 3 mmol/l [ ] Calcium: 1 mmol/l [ ] 1.25 mmol/l [ ] 1.5 mmol/l [ ]

Sodium: ….. mmol/l or variable [ ] Bicarbonate: 45 mmol/l or ….. Glucose: 0 mmol/l [ ] 1 mmol/l [ ] 2 mmol/l [ ]

Infusion(s) in dialysis: Packed cells [ ] 5% Albumin [ ] 20% Albumin [ ] Volume: ……. ml time ….. hr

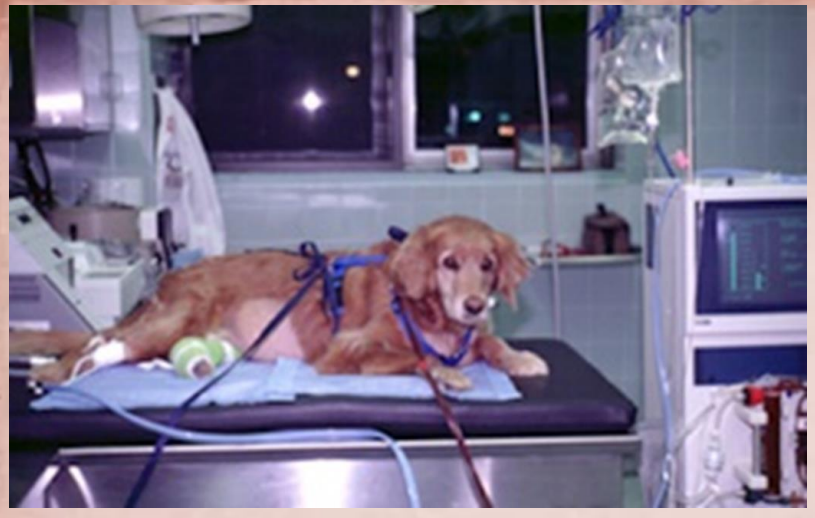
If BP drops below …. mmHg, administer …… ml of 0.9% saline

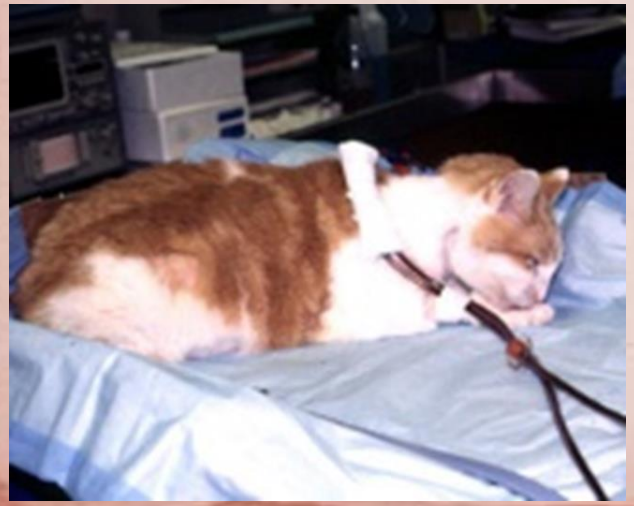
If BP above …. mmHg, administer Nifedipine [ ] Hydrallazine [ ] Captopril [ ], …. mg

Variable Sodium – profiling details if selected:

……

……






24 DEC
I don't care what day it is.
Four hours is four hours.

Childhood Arthritis; Juvenile Idiopathic Arthritis (JIA)

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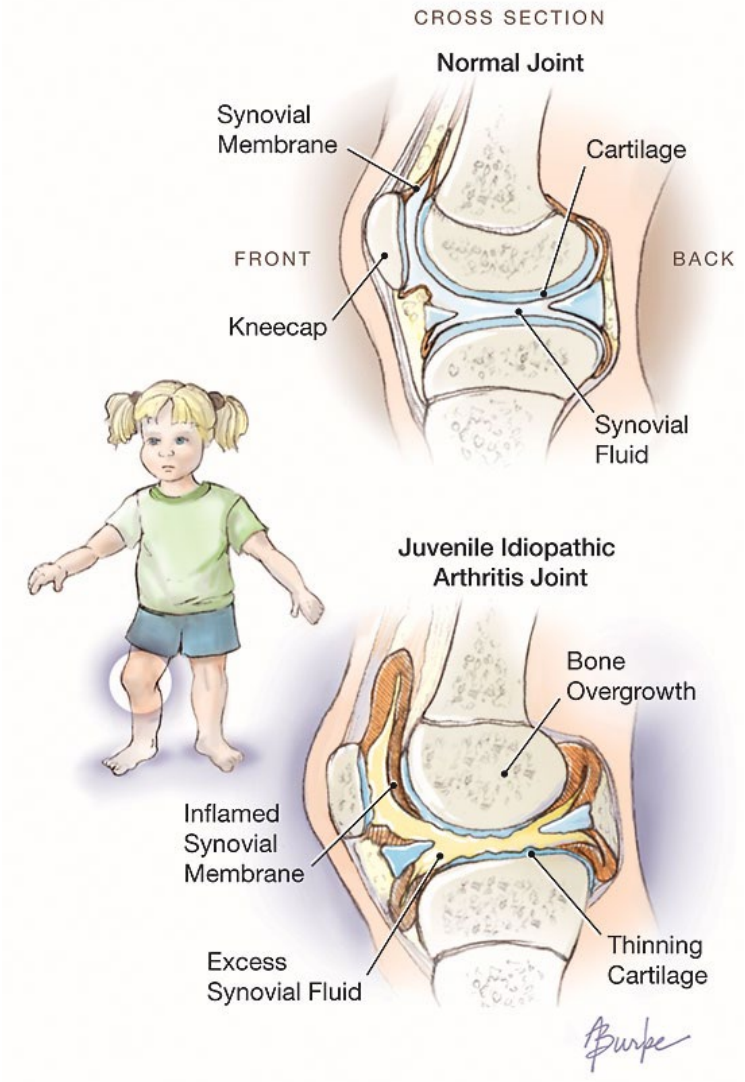
Disclosures

- No disclosure relevant to this presentation.

Juvenile idiopathic arthritis - JIA



aboutkidshealth.ca

JIA

- Arthritis: inflammation of a joint, characterized by an effusion, or by the presence of at least 2 of: swelling, erythema, painful range of motion/tenderness.
- Chronic Arthritis: arthritis lasting in a single joint for at least 6 weeks.
- Juvenile Idiopathic Arthritis: chronic arthritis with onset before age 16.

- Oligoarticular: involvement of no more than 4 joints within the first 6 months (accumulated).
  - Can be classified as “persistent” if never more than 4, and “extended” if eventually includes more than 4 total joints.
- Polyarticular: involvement of at least 5 joints within the first 6 months

Differential Diagnosis

Infectious

Septic Arthritis
Osteomyelitis
Transient Synovitis

Inflammatory

Reactive Arthritis
Post-Strep Reactive Arthritis
Viral Arthropathy
Juvenile Arthritis:
- Juvenile Idiopathic
- IBD-associated
- CF-associated

Systemic Lupus Erythematosus
Vasculitis
Sarcoidosis

Mechanical

Traumautic
- Fracture
- Hemarthrosis

Developmental
- Slipped Capital Femoral Epiphysis
- Legg-Calve-Perthes (AVN)
- Osgood-Schlatter Disease
- Sindig-Larsen-Johansson Disease

Bone/Muscle

Malignancy
- Bone (osteosarcoma, Ewings)
- Muscle (rhabdomyosarcoma)
- Synovium (PVNS)

Cerebral Palsy
Muscular Dystrophy

Classifying JIA

- Arthritis in ≥1 joint for ≥6 weeks (exception: sJIA) onset before the patient's 16th birthday

Table – Classifications of chronic arthritis in children

ACR (1977) JRA	EULAR (1978) JCA	ILAR (2001) JIA
Systemic	Systemic	Systemic
Polyarticular	Polyarticular	Polyarticular RF–negative
Pauciarticular	Pauciarticular	Polyarticular RF–positive
	Juvenile psoriatic	Oligoarticular
	Juvenile ankylosing spondylitis	Persistent
	Arthritis associated with inflammatory bowel disease	Extended
		Psoriatic
		Enthesitis-related
		Undifferentiated

ACR, American College of Rheumatology; JRA, juvenile rheumatoid arthritis; EULAR, European League Against Rheumatism; JCA, juvenile chronic arthritis; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

Epidemiology

- Incidence: 7-21 / 100 000 || Prevalence ~ 200 / 100 000
- 1/1000 children with JIA in Canada
- ~ 10% systemic, 10% psoriatic, 10-15% ERA, 20% polyarticular, 40% oligoarticular

Classifying JIA in 2023

ILAR JIA Subtype	Age, Sex, and % Total Patients with JIA	Typical Joint Involvement
Oligoarticular • Persistent • Extended	F>M Early childhood 40%–50%	≤4 joints Large joints: knees, ankles, wrist Persistent disease: never >4 joints affected Extended disease: involves >4 joints after first 6 mo of disease
Polyarticular (RF-negative)	F>M 2 peaks: 2–4 y and 6–12 y 20%–25%	≥5 joints Symmetric
Polyarticular (RF-positive)	F>M Late childhood/early adolescence 5%	Symmetric small and large joints Erosive joint disease
Systemic	M = F Throughout childhood 5%–10%	Poly or oligoarticular
Enthesitis-related arthritis	M>F Late childhood/ adolescence 5%–10%	Weight-bearing joint especially hip and intertarsal joints History of inflammatory back pain or sacroiliac joint tenderness
Psoriatic arthritis	F>M 2 peaks: 2–4 y and 9–11 y 5%–10%	Asymmetric or symmetric small or large joints
Undifferentiated	10%	

Counting joints:

- Oligo: ≤ 4 joints
- Poly: 5 or more joints

Disease course of Oligo JIA:

- Persistent /extended

Associated findings:

- Enthesitis
- Psoriasis
- Fever/rash/hepato-splenomegaly/lymphadenopathy

Biomarkers:

- RF, HLA-B27, ANA

Investigations

- **ANA:** is a risk factor for uveitis in the context of JIA.
  - ANA **does not** change the risk of JIA whatsoever; whether titer is 1:40 or 1:4000, the likelihood of JIA is unaffected.
  - ANA in high titers may suggest the presence of a connective tissue disease such as SLE. In teenage females it is helpful to consider whether SLE should be thought of.

Investigations

- **Rheumatoid Factor:** unlike adults, 95% of children have **RF negative** disease. Should order it in adolescents or those with polyarticular small joint disease.
  - **RF** is only positive if it persists for beyond 3 months. There are many causes of transiently positive RF, most commonly infection.

Investigations

- **HLA-B27:**
  - is seen in 10% of the HEALTHY population;
  - given the incidence of JIA is low, a positive HLA-B27 affects post-test probability but does not give a diagnosis.
  - It is used for classification and risk stratification.
  - HLA-B27 prevalence depending on ethnicity studied

Investigations: Joint aspiration and Injection

- Joint aspirate is **NOT** part of the work-up for juvenile arthritis;
  - if considering alternate conditions (rule out)
  - to administer medication

- The most common (and in common practice, only) reason to consider a joint aspiration is to rule out septic arthritis – i.e. in the context of acute arthritis.
  - Most often seen in adult medicine, because gout is a common differential and on exam can be indistinguishable from septic arthritis.

Categories of synovial fluid based upon clinical and laboratory findings

Measure	Normal	Noninflammatory	Inflammatory	Septic	Hemorrhagic
Volume, mL (knee)	<3.5	Often >3.5	Often >3.5	Often >3.5	Usually >3.5
Clarity	Transparent	Transparent	Translucent-opaque	Opaque	Bloody
Color	Clear	Yellow	Yellow to opalescent	Yellow to green	Red
Viscosity	High	High	Low	Variable	Variable
White blood cell, per mm^3	<200	0 to 2000	2000 to 100,000	15,000 to >100,000*	200 to 2000
Polymorphonuclear leukocytes, percent	<25	<25	≥50	≥75	50 to 75
Culture	Negative	Negative	Negative	Often positive	Negative

* Lower part of range with infections caused by partially treated or low virulence organisms.

Case 1

New patient in clinic

- 4 year old girl
- 1 swollen knee

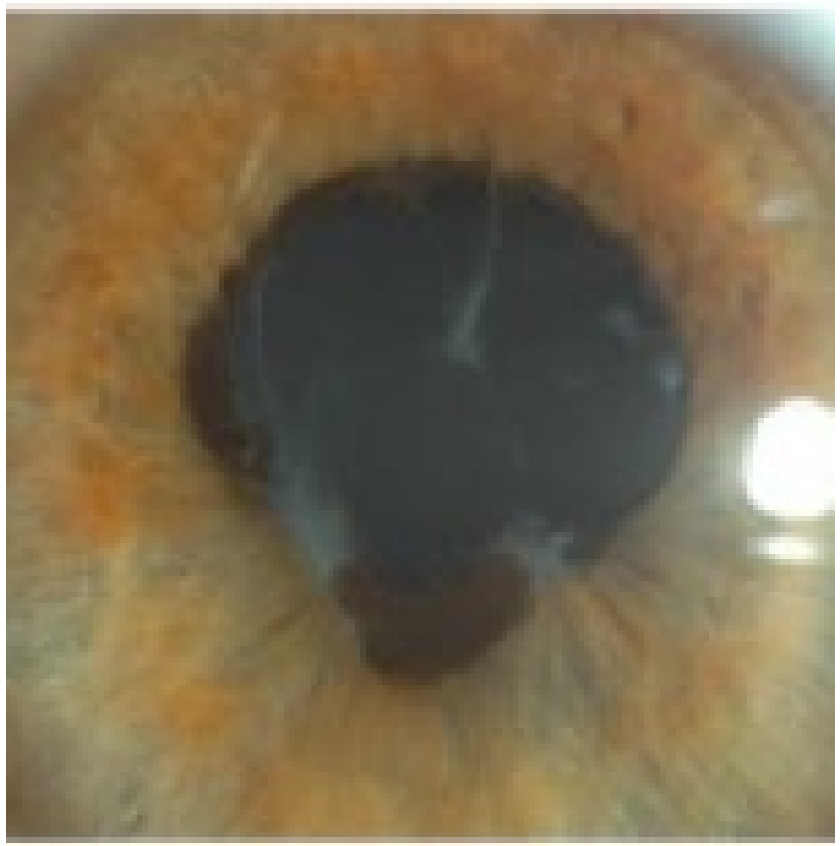
- Dx: Oligo JIA

Case 1

- 4 year old girl
- Dx: Oligo JIA
- ANA pos 1:640
- HLA-B26 neg
- RF neg

ANA

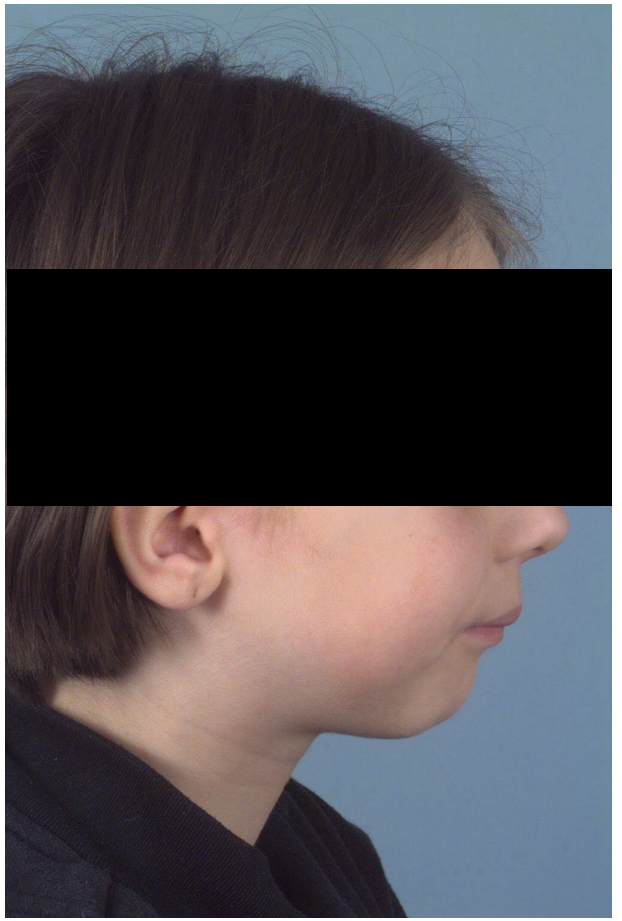
- Think Uveitis
- Anterior uveitis
- Asymptomatic
- Slit lamp examination every 3 months / 4 years



CASE 2

- 14 year-old girl
  - years of finger pain and ankle pain
- Arthritis
  - MCP 3-4-5 L+R and bilateral ankle and subtalar
- Micrognathia

- Poly articular JIA

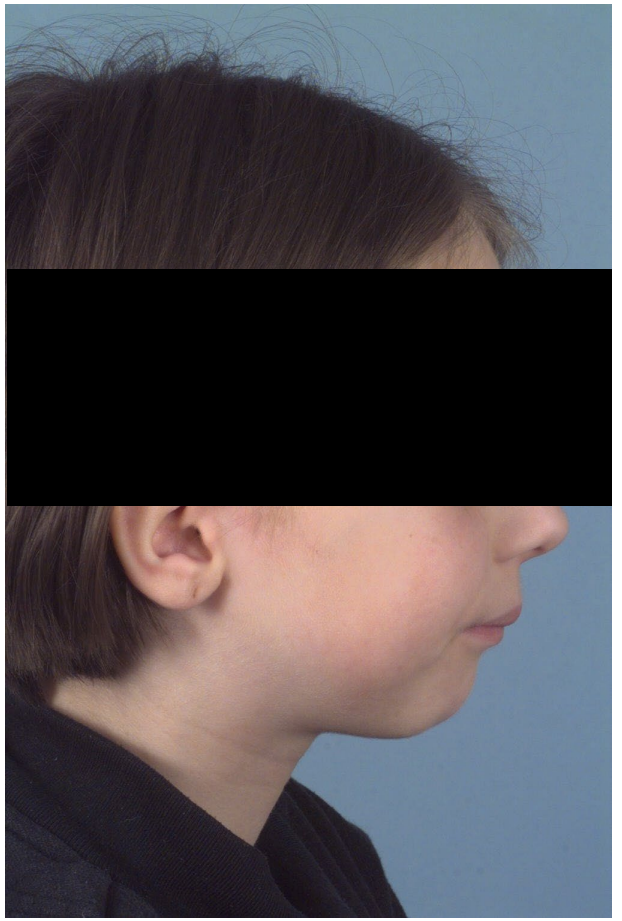


CASE 2

- 14 year-old girl

- ANA negative
- RF positive
- HLA-B27 positive
- Celiac screen positive

- Polyarticular RF positive JIA

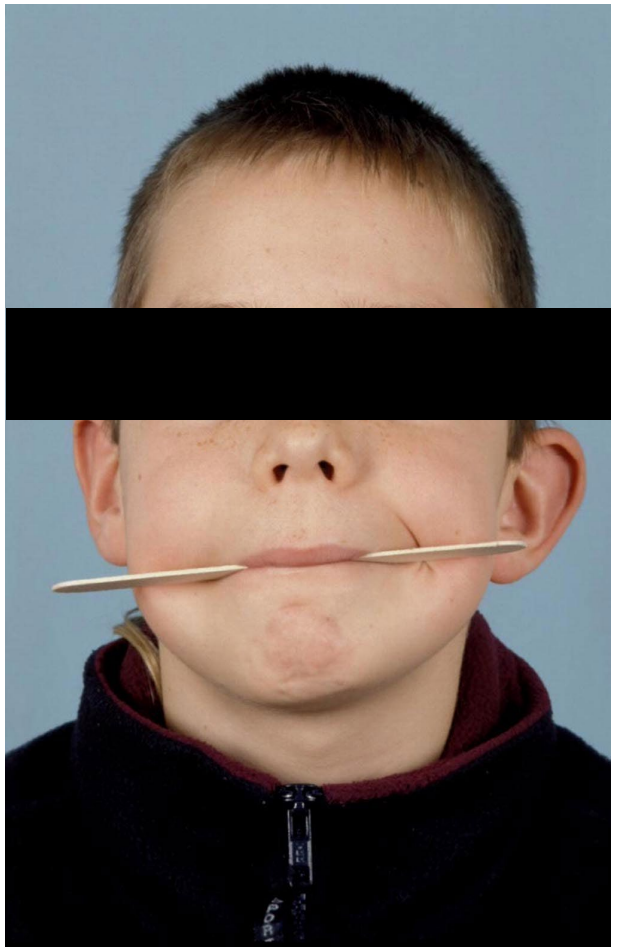


CASE 3

- 9 year old boy, back pain

- HLA-B27 positive
- ANA negative
- RF negative
- MRI – SI joint erosive changes
- Jaw asymmetry – MRI condylar flattening

- Enthesitis related arthritis (ERA)



Treating JIA in 2023

- Evidence based guidelines including the 2011, 2013 and 2021 ACR guidelines for treatment selection:
  - Joint count at diagnosis (oligo/poly)
  - Course (oligo/poly)
  - sJIA: presence or absence of systemic features
  - “Prognostic factors”

Cellucci, 2015 JRheum
Beukelman, 2011 AR
Ringold, 2013 AR

Table 1. Features of poor prognosis and disease activity for a history of arthritis of 4 or fewer joints

FEATURES OF POOR PROGNOSIS (must satisfy 1)
- Arthritis of the hip (23–25) or cervical spine
- Arthritis of the ankle (25–27) or wrist (26,28) AND marked (29) or prolonged (23,25,26,29,30) inflammatory marker elevation
- Radiographic damage (erosions or joint space narrowing by radiograph) (31)

DISEASE ACTIVITY LEVELS
- Low disease activity (must satisfy all)
  - 1 or fewer active joints
  - Erythrocyte sedimentation rate or C-reactive protein level normal
  - Physician global assessment of overall disease activity <3 of 10
  - Patient/parent global assessment of overall well-being <2 of 10
- Moderate disease activity (does not satisfy criteria for low or high activity)
  - 1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity
- High disease activity (must satisfy at least 3)
  - 2 or more active joints
  - Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
  - Physician global assessment of overall disease activity ≥7 of 10
  - Patient/parent global assessment of overall well-being ≥4 of 10

Table 2. Features of poor prognosis and disease activity for a history of arthritis of 5 or more joints

FEATURES OF POOR PROGNOSIS (must satisfy 1)
- Arthritis of the hip (23–25) or cervical spine
- Positive rheumatoid factor (5,23,28,30,32,33) OR anti–cyclic citrullinated peptide (33,34) antibodies
- Radiographic damage (erosions or joint space narrowing by radiograph) (31)

DISEASE ACTIVITY LEVELS
- Low disease activity (must satisfy all)
  - 4 or fewer active joints
  - Erythrocyte sedimentation rate or C-reactive protein level normal
  - Physician global assessment of overall disease activity <4 of 10
  - Patient/parent global assessment of overall well-being <2 of 10
- Moderate disease activity (does not satisfy criteria for low or high activity)
  - 1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity
- High disease activity (must satisfy at least 3)
  - 8 or more active joints
  - Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
  - Physician global assessment of overall disease activity ≥7 of 10
  - Patient/parent global assessment of overall well-being ≥5 of 10

Beukelman, 2011 AR

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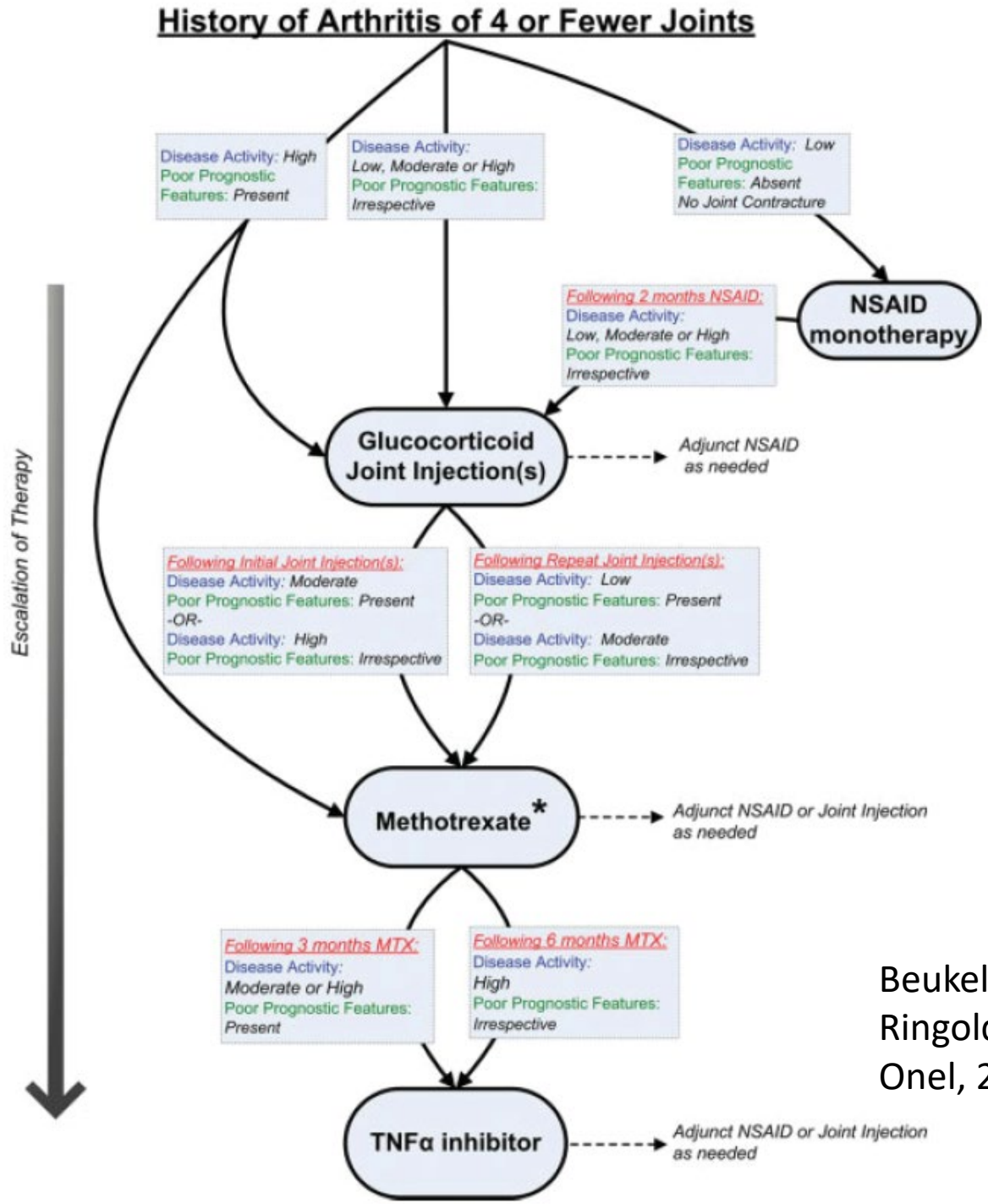
American College of Rheumatology
Empowering Rheumatology Professionals

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis

Karen B. Onel,[1] Daniel B. Horton,[2] Daniel J. Lovell,[3] Susan Shenoi,[4] Carlos A. Cuello,[5] Sheila T. Angeles-Han,[3] Mara L. Becker,[6] Randy Q. Cron,[7] Brian M. Feldman,[8] Polly J. Ferguson,[9] Harry Gewanter,[10] Jaime Guzman,[11] Yukiko Kimura,[12] Tzielan Lee,[13] Katherine Murphy,[14] Peter A. Nigrovic,[15] Michael J. Ombrello,[16] C. Egla Rabinovich,[6] Melissa Tesher,[17] Marinka Twilt,[18] Marisa Klein-Gitelman,[19] Fatima Barbar-Smiley,[20] Ashley M. Cooper,[21] Barbara Edelheit,[22] Miriah Gillispie-Taylor,[23] Kimberly Hays,[24] Melissa L. Mannion,[7] Rosemary Peterson,[25] Elaine Flanagan,[26] Nadine Saad,[27] Nancy Sullivan,[28] Ann Marie Szymanski,[29] Rebecca Trachtman,[30] Marat Turgunbaev,[31] Keila Veiga,[32] Amy S. Turner,[31] and James T. Reston[28]



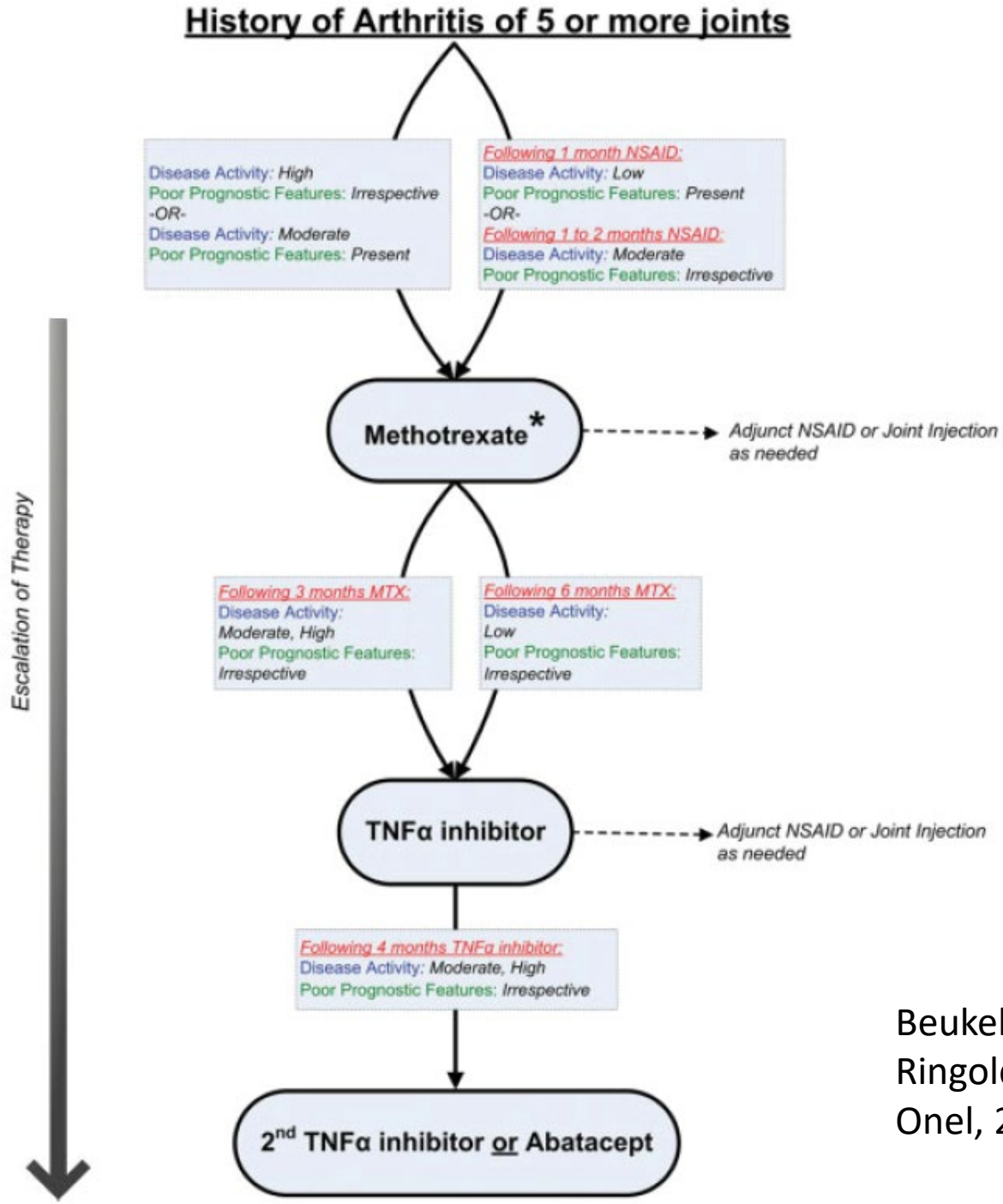
Beukelman, 2011 AR
Ringold, 2013 AR
Onel, 2021 AR

Case 1

- Dx: Oligo JIA

Treatment

- Intra-articular joint injection



Beukelman, 2011 AR
Ringold, 2013 AR
Onel, 2021 AR

CASE 2

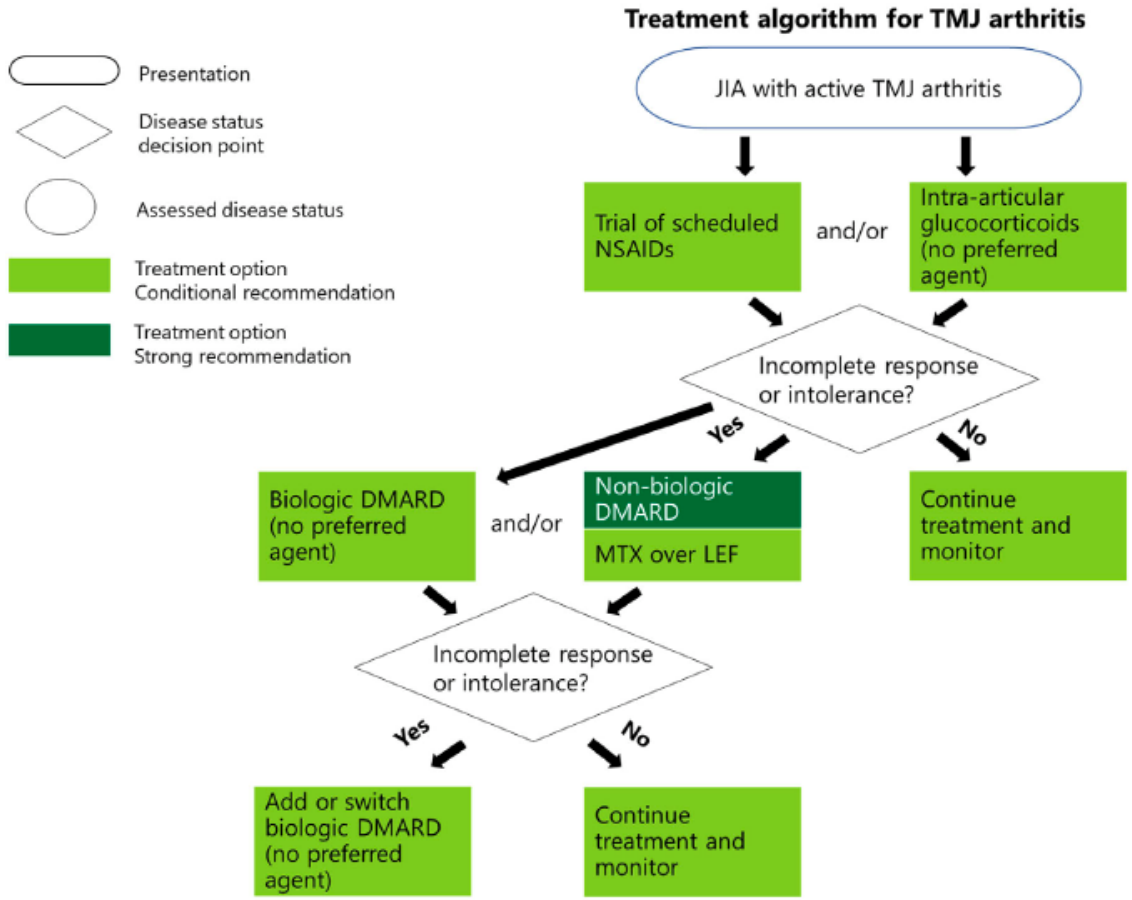
- 14 year-old girl

- JIA- Polyarticular RF positive

- Methotrexate
- Steroids (depending on joints intra-articular or

Systemic steroids) – short oral course

Re-evaluate in 3 months if no or insufficient response – add biologic



DMARD = disease-modifying antirheumatic drug, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, TMJ = temporomandibular joint

Figure 2. Treatment algorithm for temporomandibular joint arthritis.

CASE 3

- 9 year old boy, back pain
- Enthesitis related arthritis
- Axial disease – start biologic as first line agent

TREATMENT - IACS

1. Corticosteroid Injection: direct injection with steroid

- results in rapid improvement or resolution of arthritis, with effects lasting 3-24 months. Is rapid and inexpensive.
- In younger children, will require sedation.
- Will only target the joints you choose (i.e. will miss subclinical joints).
- Complications can include local / cosmetic, infection, bleeding, anesthesia.

TREATMENT - NSAID

- NSAIDs:
  Anti-inflammatory treatment requires high doses in a sustained manner.

- **Naproxen:** 15-20 mg/kg/ ... or at least 2 months
  Ibuprofen 30-40 mg/kg/d d ... or QID for at least 2 months
  Celecoxib 50-100 mg dail ... least 2 months.

- Adverse effects are uncommon and usually preventable. Can see dyspepsia/GI ulcer, renal injury, and pseudoporphyria.

TREATMENT DMARDs

- Systemic Corticosteroids:
  - Effective short term
  - Bridging

- Methotrexate: Disease modifying anti-rheumatic drug (DMARD).
  - First line therapy for all JIA or disease refractory to NSAID/injection.
  - Used in low doses – is well tolerated, safe, and efficacious in 80% of patients. Cannot have **LIVE** vaccinations per current recommendations.

- Other DMARDS: Leflunomide, Sulfasalazine, Thalidomide, +/- Plaquenil.

TREATMENT BIOLOGICS

- Anti-TNF agents first choice
- Enbrel (Etanercept) / Erelzi
  Remicade (Infliximab)
  Humira (Adalimumab)

- Difference in:
  - method of delivery (IV vs. SC),
  - frequency (q1w-q8w)
  - Cannot have live vaccinations.

TREATMENT BIOLOGICS 2

- Rituximab: anti-CD20, used in refractory arthritis and SLE
- Abatacept: anti-CTLA4, used in refractory arthritis
- Anakinra: anti-IL1R antagonist, used in systemic JIA, MAS, fever syndromes.
- Canakinumab: anti-IL1 agent, used in systemic JIA and fever syndromes.
- Tocilizumab: anti-IL6 agent, used in systemic JIA and refractory polyarticular JIA

Other Autoimmune diseases

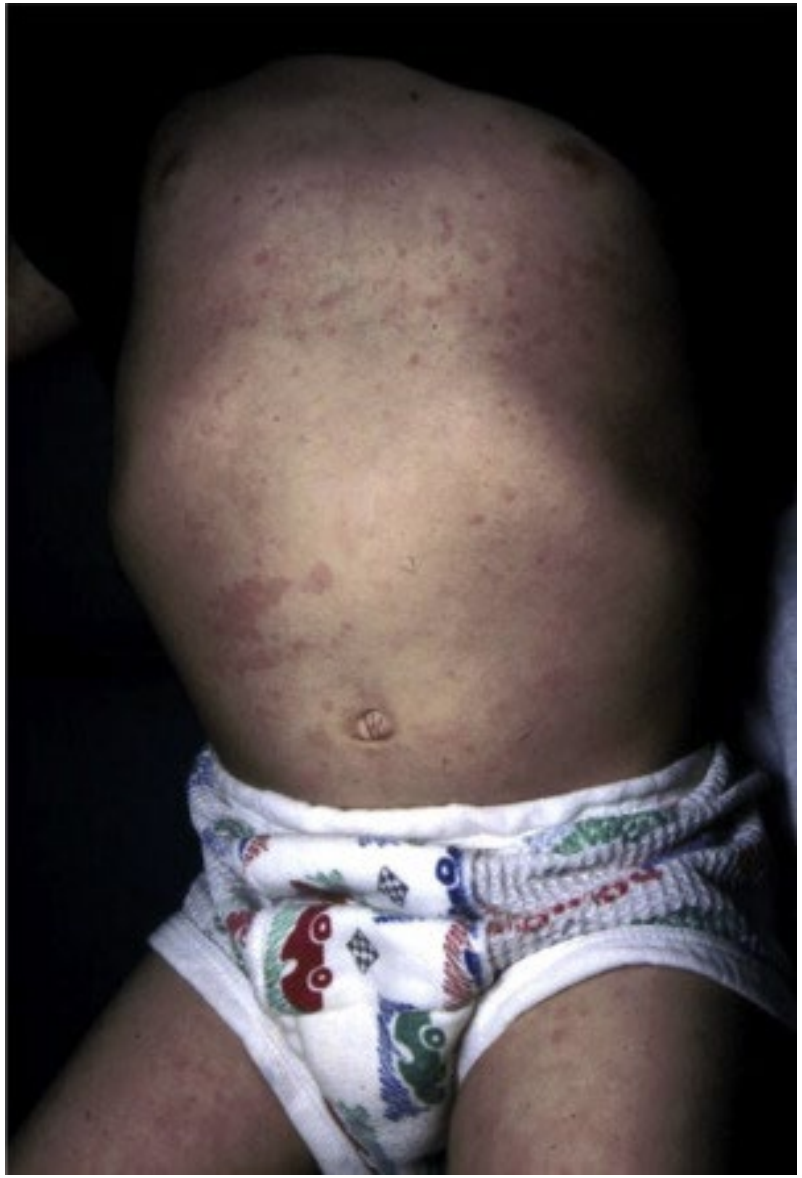
- **IBD-Associated Arthropathy:** one of the most common extraintestinal manifestations of CD > UC. Most common manifestation is arthropathy and arthralgias without true arthritis. 2 major patterns are described:
  - Peripheral and Axial
- **CF-Associated Arthropathy:** seen in up to 8% of patients with CF. Typical presentation is transient arthritis lasting 1-10 days with full resolution and relapses. NSAIDs usually sufficient.
- **Celiac Disease:** It is known that celiac patients can have an inflammatory arthropathy that responds to GFD; however, also higher risk of JIA. If there is likely JIA, should screen for Celiac, and if positive, treat before diagnosing JIA formally.

Systemic JIA (Still's disease)

- Auto-immune vs autoinflammatory

CASE 4

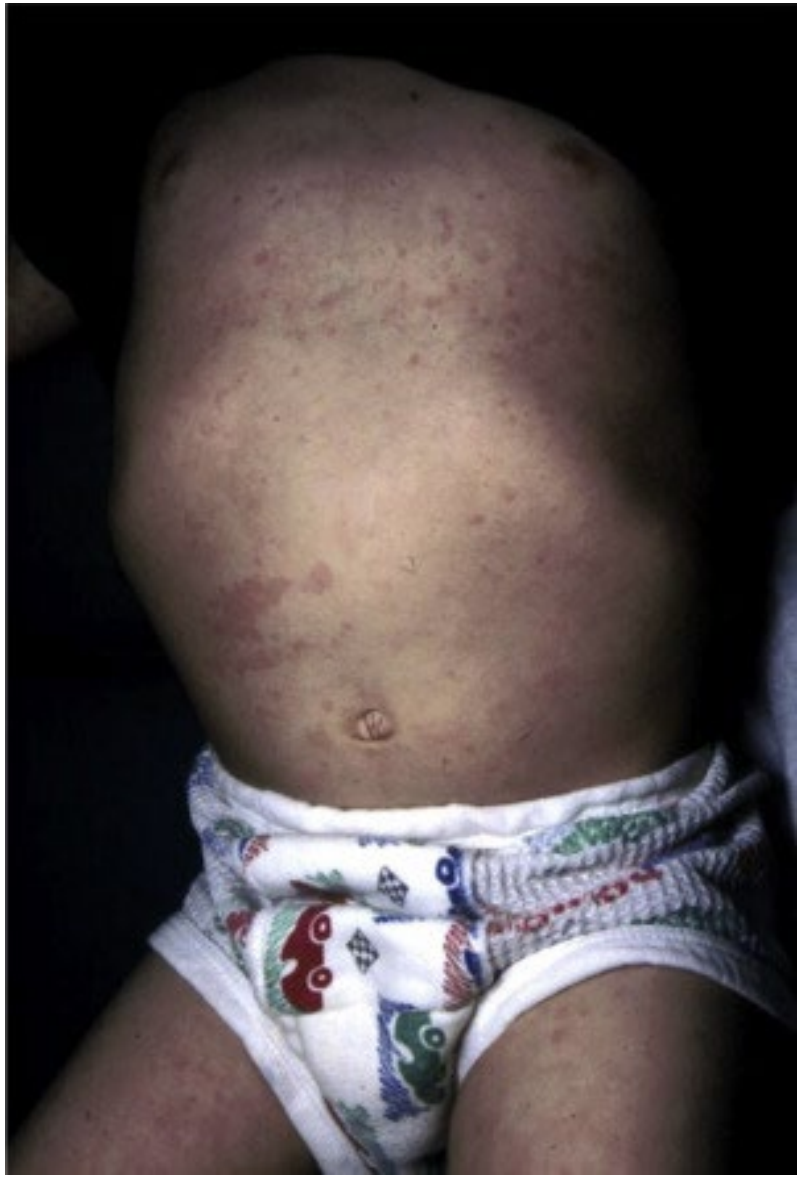
- 3 year old boy
- 2 weeks of unexplained fever
- Evanescent rash
- With fever – lethargic, sick
- Without fever – not so sick
- No arthritis



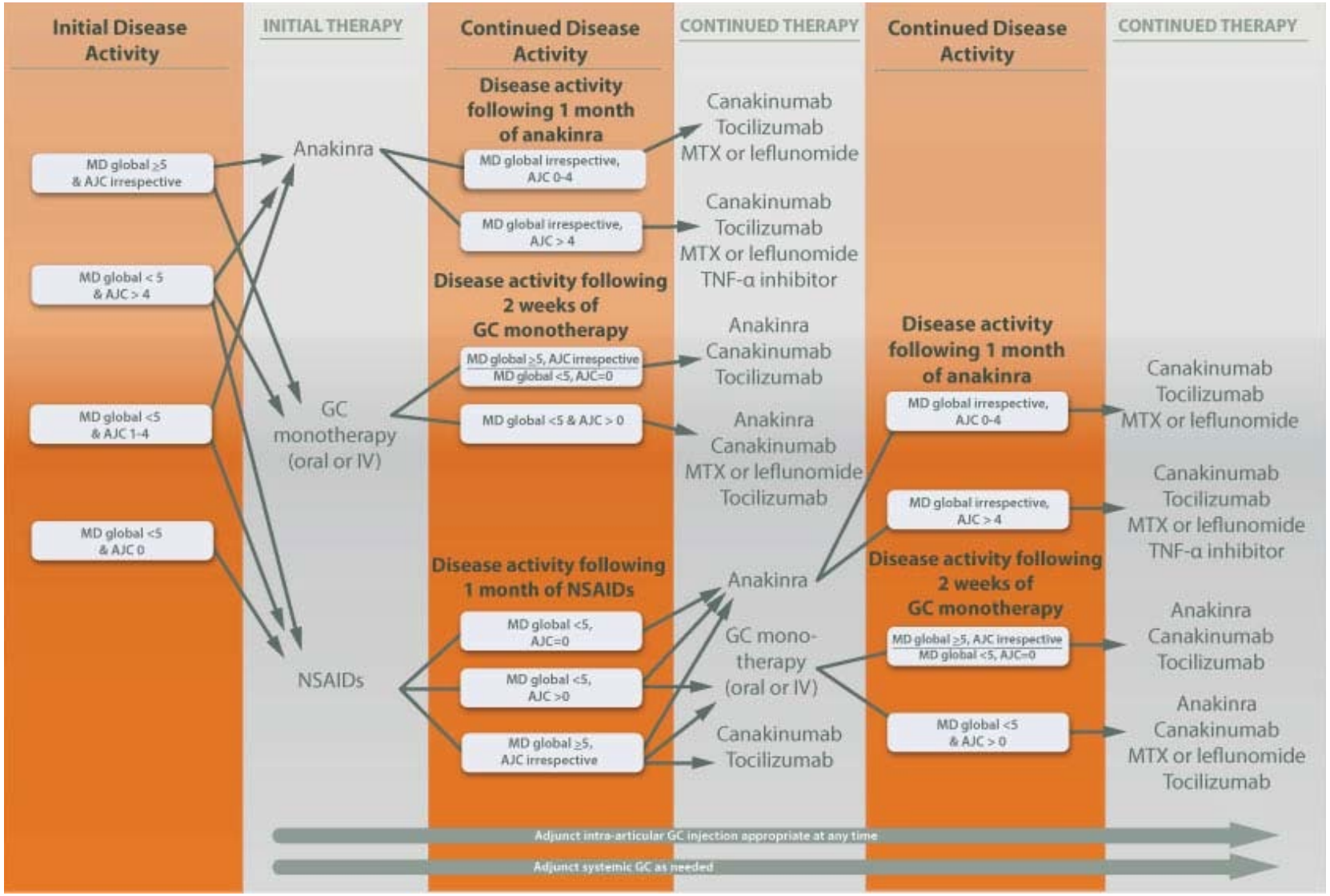
CASE 4

- 3 year old boy

- ANA negative
- HLA-B27 negative
- RF negative
- High CRP

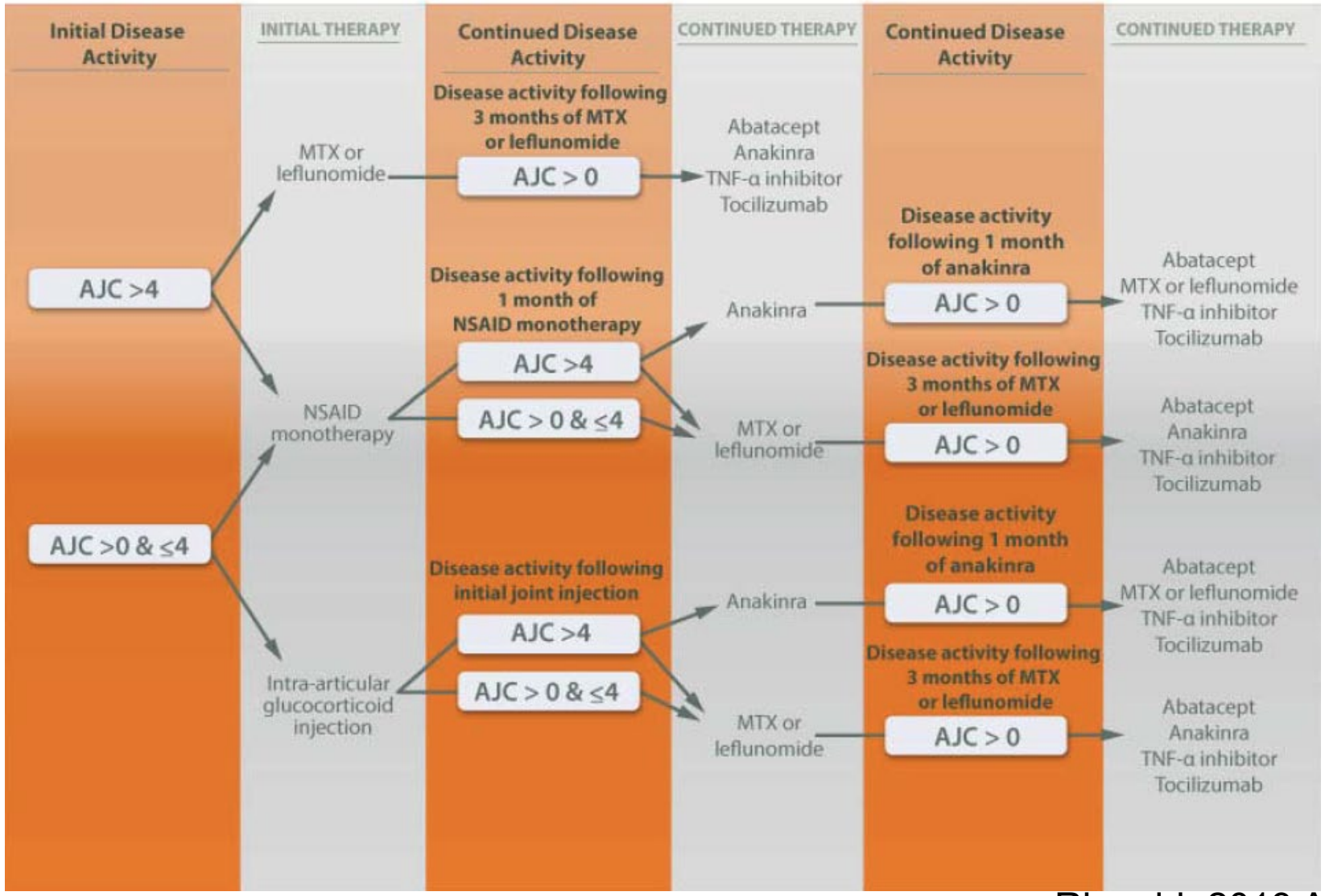


sJIA with systemic features



Ringold, 2013 AR

sJIA without systemic features



Ringold, 2013 AR

JIA outcomes 2007

Table 3 - Frequency of inactivity and clinical remission from JIA, compared with recent literature

	This study	Wallace et al.[20]	Oen et al.[13]	Minden et al.[8]
Mean duration of follow-up	3.6 years	7.7 years*	10 years	16.5 years
Inactivity	52%	89%	56%	47%
Clinical remission	33.3%	26%	39%	40%
Persistent oligoarticular	34.9%	68%	47%†	73%
Extended oligoarticular	33.3%	31%	-	12%
RF+ polyarticular	0	5%	6%	0
RF- polyarticular	18.2%	30%	23%	30%
Systemic arthritis	52.8%	37%	37%	47%
Psoriatic arthritis	0	-	-	33%
Enthesitis-related arthritis	0	-	-	18%

* Patients who attained disease inactivity.
† Persistent oligoarticular and extended oligoarticular included.
RF = rheumatoid factor.

Fernandes, 2007


RUSSIA
N Canada
Arctic Ocean
Ellesmere Island
GREENLAND
ICELAND
Reykjavik
Baffin Bay
Nuuk (Godthåb)
UNITED STATES
Victoria Island
Baffin Island
YUKON TERRITORY
Gulf of Alaska
NORTHWEST TERRITORIES
NUNAVUT
Labrador Sea
Pacific Ocean
Hudson Bay
NEWFOUNDLAND AND LABRADOR
CANADA
ALBERTA
MANITOBA
BRITISH COLUMBIA
SASKATCHEWAN
Vancouver
Winnipeg
ONTARIO
QUEBEC
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Montreal
NOVA SCOTIA
Toronto
Ottawa
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PRINCE EDWARD ISLAND
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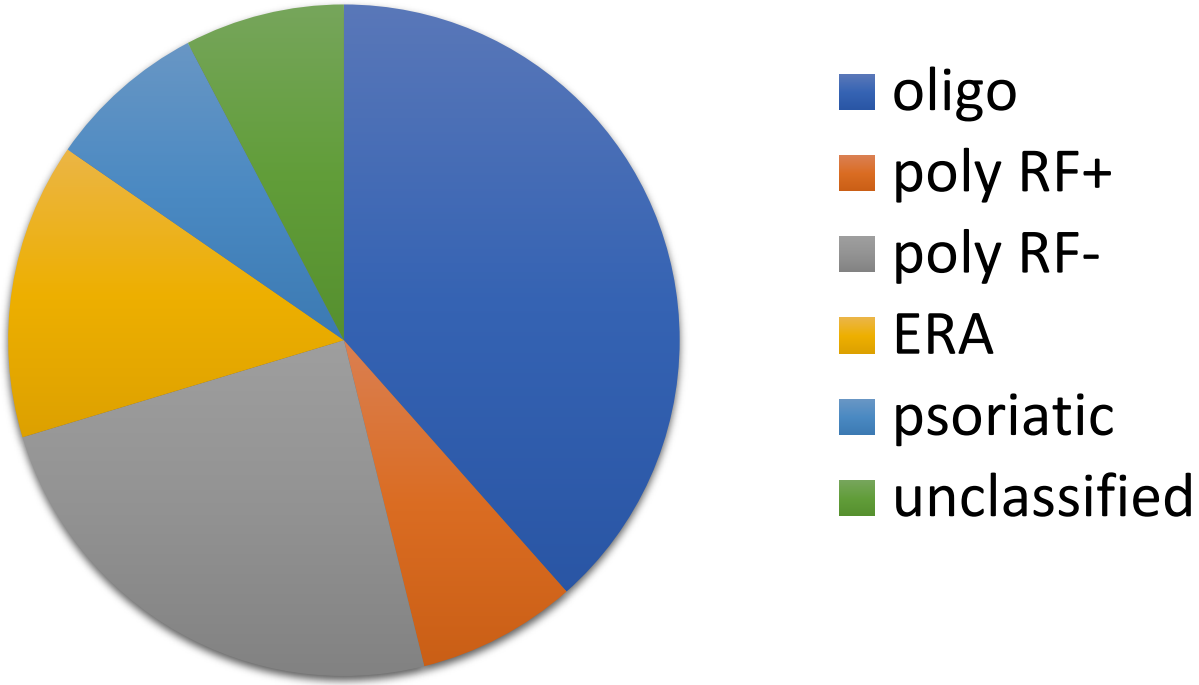
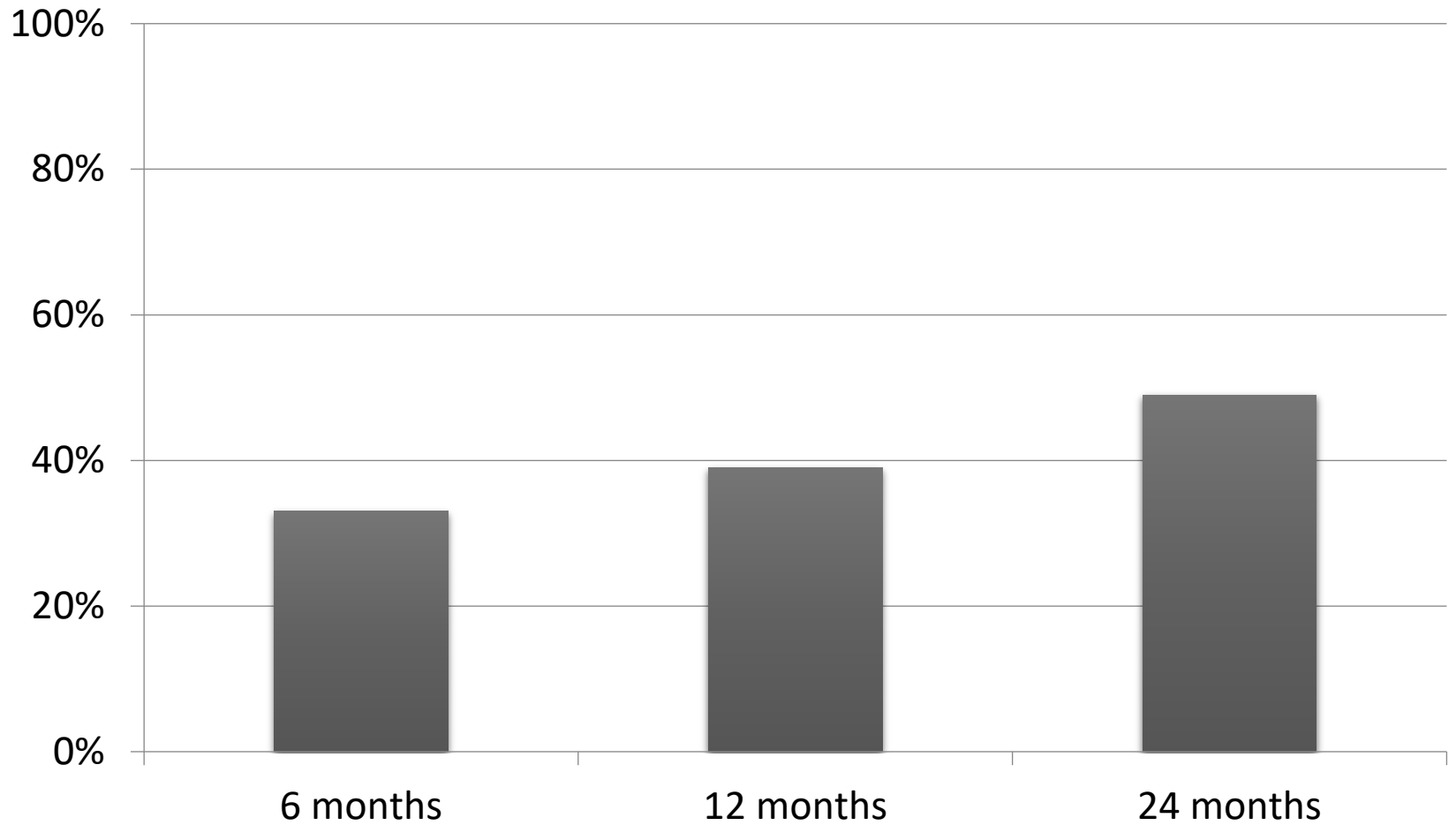
REACCH OUT: Results

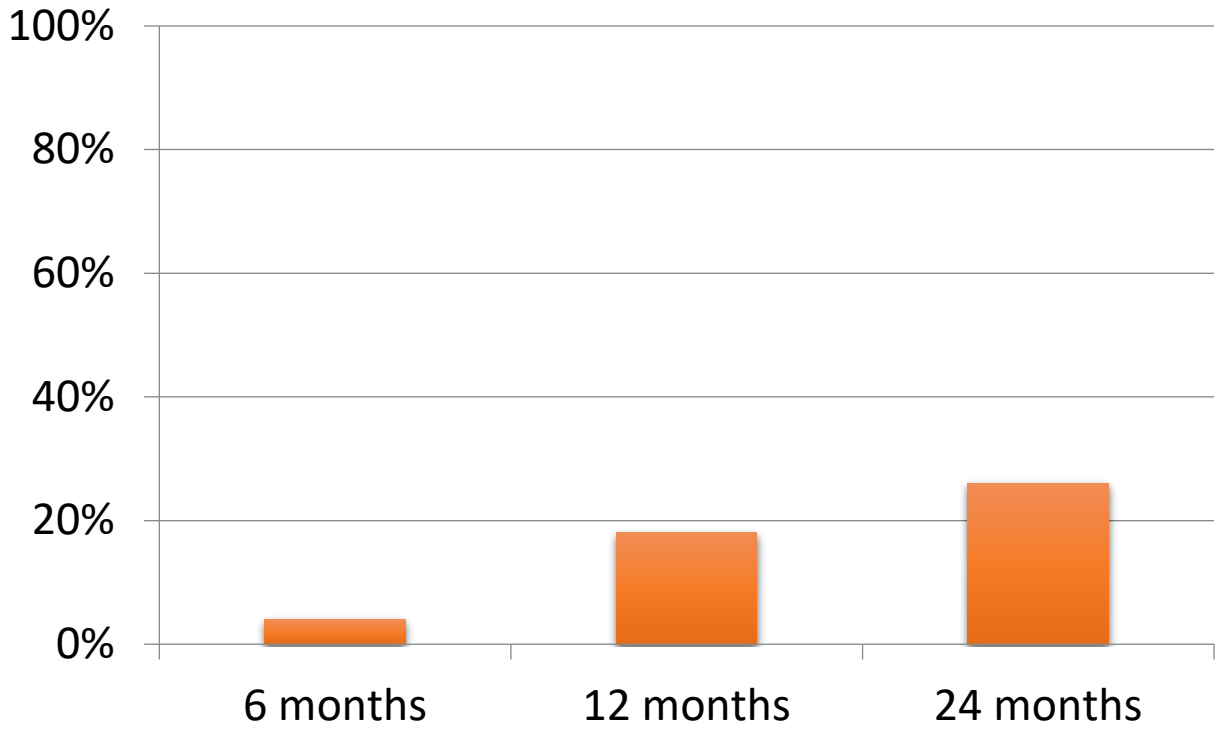
- 1574 children with JIA enrolled
- Median age at disease onset 7.5 yr
- Subtypes:



REACCH OUT: Inactive disease rates



REACCH OUT: Remission on meds



- Clinical remission off medication:
  - 7% at 24 months

Take home messages

- Treatment decisions are based on joint count at diagnosis or over time for all groups other than sJIA with systemic symptoms
- Rates of inactive disease are low. Only 50% of children in Canada reach a state of inactive disease at 24 months.
- Flare rates are the lowest for sJIA and the highest for ERA and poly JIA

THANK YOU

HOW TO WRITE A SUCCESSFUL GRANT APPLICATION

Kimberly Reidy, MD
Associate Professor and Chief, Division of Pediatric Nephrology

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ALBERT EINSTEIN COLLEGE OF MEDICINE

Outline

- Identify the research question
- Identify grant funding opportunities
- Overview of grant funding scoring criteria
- Components of the grant
- Timeline considerations

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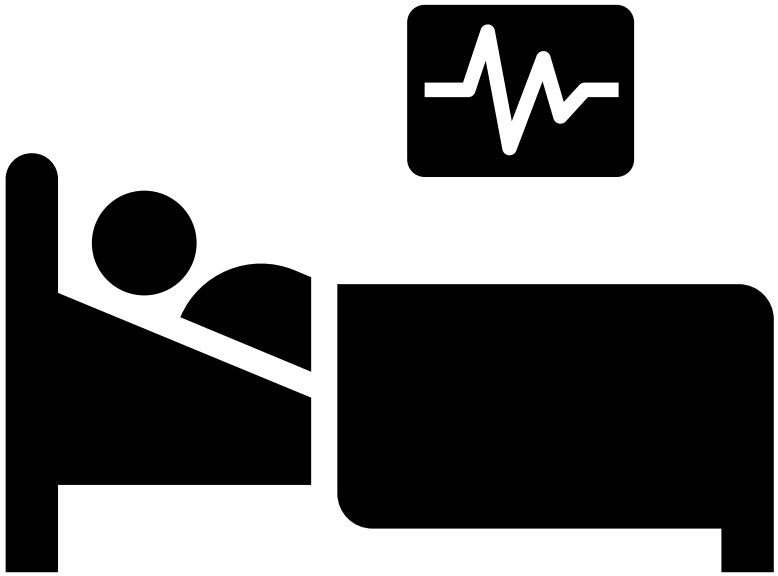
A clinical question



The best grants start with an important clinical problem.

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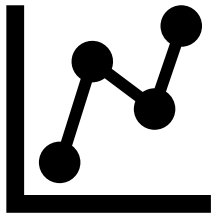
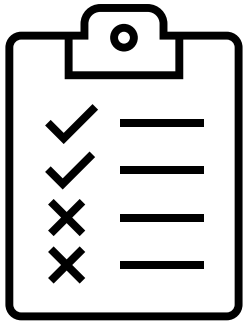
Develop a hypothesis-driven research question

- Clinical question
- Based on past knowledge
  - Review the literature
  - preliminary studies (Eg. observational study, single center)





- Testable
- **Best hypotheses will lead to additional research questions regardless of results**

Identifying a potential funding source

- Does the problem fit within the organizations mission and priorities?

- Read the RFA (request for applications)
  - Eligibility criteria
  - Budget considerations
  - Required/allowed components of grant

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Grant review criteria

Significance	Investigator(s)	Innovation
Approach	Environment	**Overall impact**

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Significance

- Does the project address an important problem or a critical barrier to progress in the field?
- Is there a strong scientific premise for the project?

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Significance

- If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
- How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

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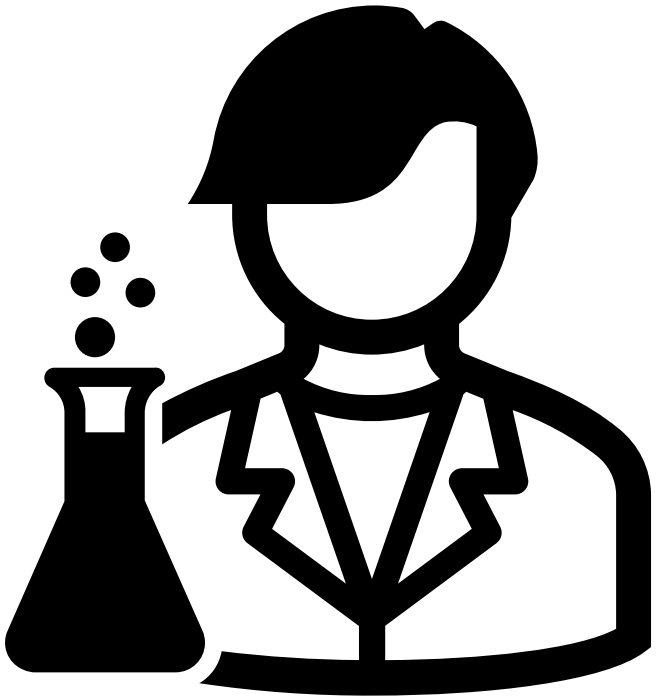
Investigator(s)

- Are the PD/PIs, collaborators, and other researchers well suited to the project?
- Do they have appropriate experience and training?
- Have they demonstrated an ongoing record of accomplishments that have advanced their field(s)?



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Investigator(s)

- If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise?
- Is leadership approach and organizational structure appropriate for the project?

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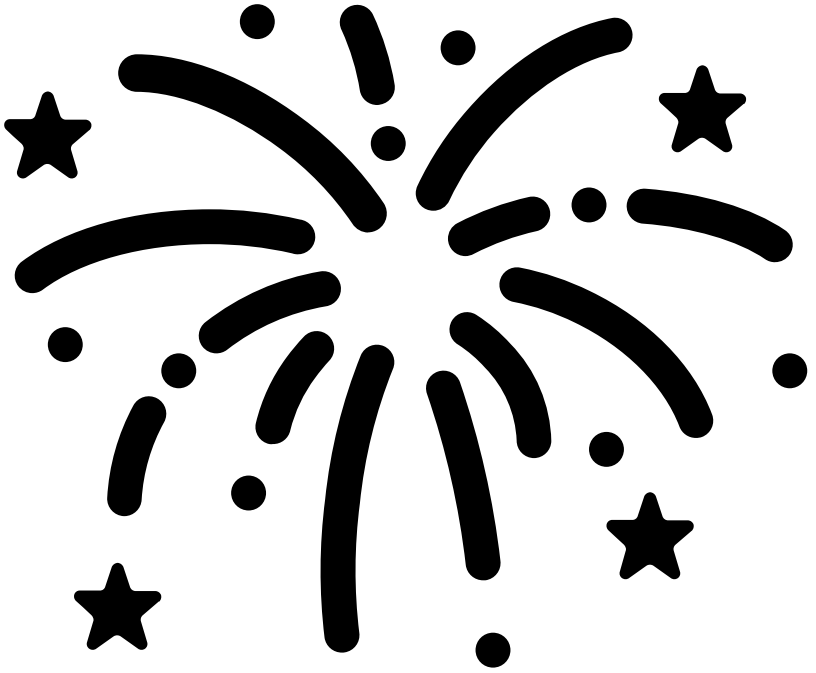
Innovation

- Does the application challenge and seek to **shift current research or clinical practice paradigms** by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?



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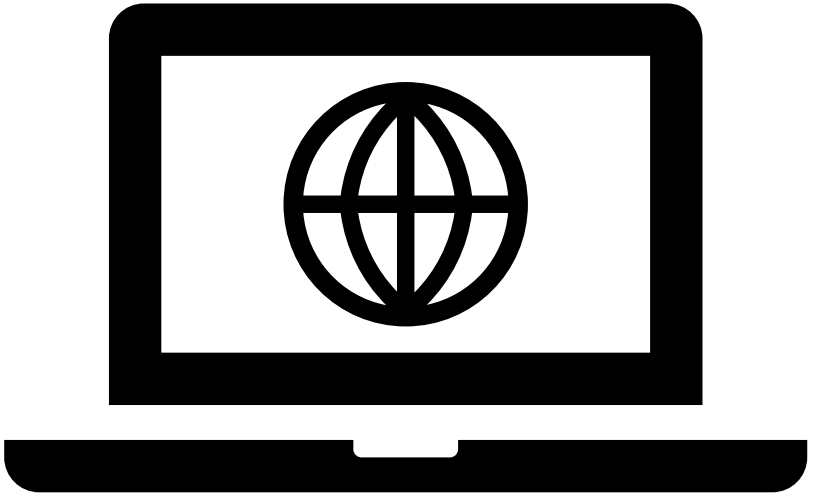
Innovation

- Are the concepts, approaches or **methodologies, instrumentation, or interventions novel**?
- Is **improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions** proposed?



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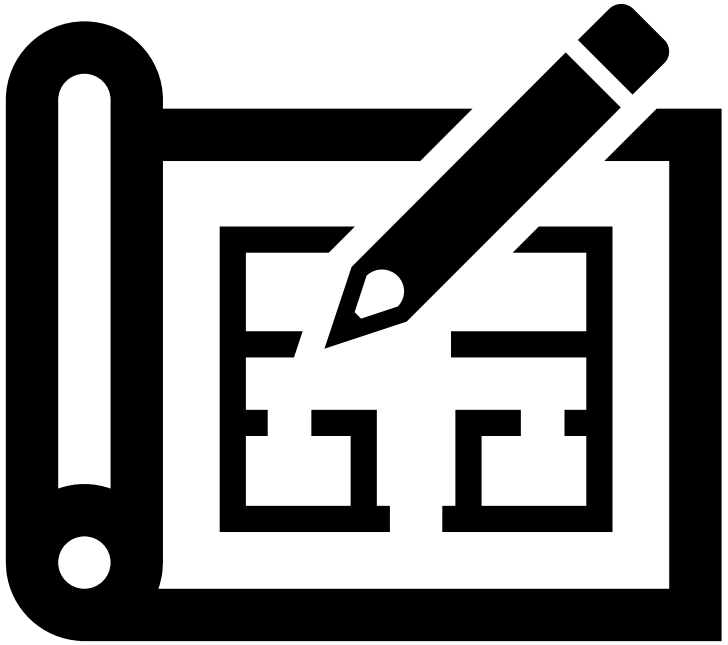
Approach

- Are the overall strategy, methodology, and analyses **well-reasoned and appropriate** to accomplish the specific aims of the project?

- Have the investigators presented strategies to ensure a **robust and unbiased approach**?

Approach

- Are **potential problems, alternative strategies, and benchmarks** for success presented?
- Have the investigators demonstrated **feasibility** ?
- How will particularly risky aspects be managed?



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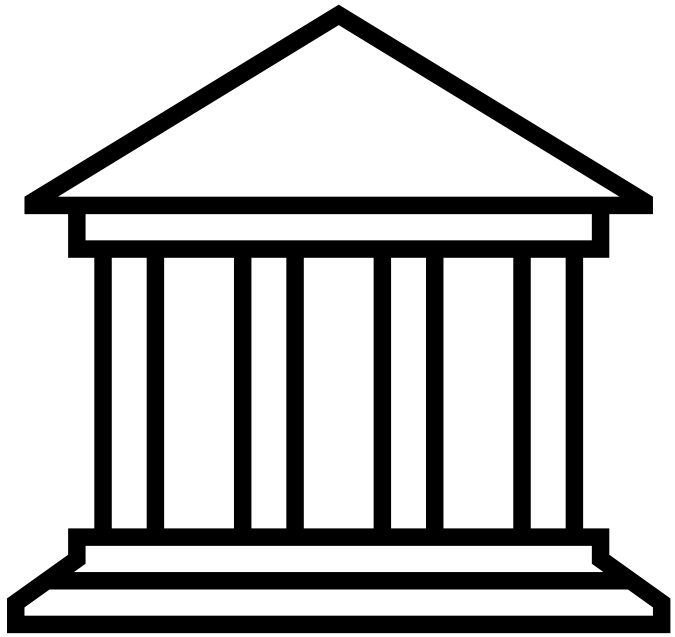
Additional Approach considerations

- Protection of human subjects from research risks
- inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

- ? address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

Environment

- Will the scientific environment in which the work will be done contribute to the probability of success?
- Are the **institutional support, equipment and other physical resources** available to the investigators adequate for the project proposed?



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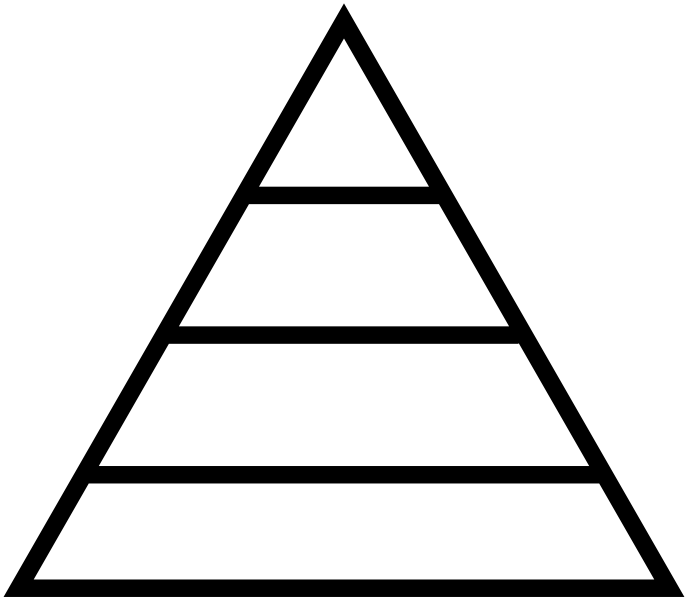
Environment

- Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?



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Additional review criteria

- Protections for Human Subjects
- Inclusion of Women, Minorities, and Children
- Vertebrate Animals
- Biohazards
- Resubmission
- Renewal
- Revision

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Overall Impact:

The likelihood for a project to exert a sustained, powerful influence on research field(s) involved

Evaluating Overall Impact:
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewer's judgment) and other score influences (e.g. human subjects)

Overall Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

e.g. Successful completion of the aims will make a **contribution of high importance** to the field. May have some or no weaknesses.

5 is a good medium-impact application, and the entire scale (1-9) should always be considered.

e.g. Successful completion of the aims may make a **contribution of high importance** to the field, but weaknesses bring down the overall impact to medium.

e.g. Successful completion of the aims may make a **contribution of moderate importance** to the field, with some or no weaknesses.

e.g. Successful completion of the aims may make a **contribution of moderate/high importance** to the field, but weaknesses bring down the overall impact to low.

e.g. Successful completion of the aims may make a **contribution of low or no importance** to the field, with some or no weaknesses.

Specific Aims page

- Succinct summary of what you will do in the grant
- may be the only part read by some members of the committee

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Specific Aims page: Paragraph 1

- *First Sentence/Hook*
- *What is Known*
- *Gap in Knowledge*
- introduce the solution that fills the gap in knowledge.
- What do you want to do?
- Why are you doing it?
- How do you want to do it?
- *Hypothesis and Proposal Objectives:*

Specific Aims page Paragraph 2

- What do you want to do?
- Why are you doing it?
- How do you want to do it?
- *Long-Term Goal*
- *Hypothesis and Proposal Objectives*
- *Rationale*
- *Qualifications*

Specific Aims page (cont)

- Describe briefly each of the aims you will use to test your hypothesis
- Aims should be related, **but not dependent,** upon each other.
- If you do this, the **failure of one aim (or an unexpected result from one aim) does not negatively influence any other aim or prevent the completion of the other aims.**

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Specific Aims page (cont)

- Typically 2-4 Aims

- Within 2-4 sentences each, you should describe the experimental approach and how each aim will help answer your larger hypothesis.

Specific Aims page (cont)

- Give your aim an active title that clearly states the objective in relationship to the hypothesis.
- Include a brief summary of the experimental approach and anticipated outcomes for each aim.

Specific Aims page (cont)

- Can consider a sub-hypothesis for each aim (the small portion of the overall hypothesis)
- To make it easier for the reviewers to clearly read and understand each aim, it is often helpful to use headings and/or bullets to delineate each specific aim.

Research Strategy

- Significance
- Innovation
- Strategy

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Other components

- Cover letter
- Budget and Period Support
- Facilities & Other Resources
- Biosketches
- Bibliography & References Cited
- Care and Use of Vertebrate Animals in Research
- Inclusion of Women, Minorities and Children in Research
- Protection of Human Subjects from Research Risk

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Other components

- Consortium/Contractual Arrangements
- Multiple PD/PI leadership plan
- Applications from Foreign Organizations
- Select Agent
- Resource Sharing Plans
- Authentication of Key Biological and/or Chemical Resources

Career development grants

- ***Candidate's Background***
  - Describe the candidate's commitment to an academic career Research (POR). Describe all of the candidate's professional responsibilities in the grantee institution and elsewhere and describe their relationship to the proposed activities on the career award.
  - Present evidence of the candidate's ability to interact and collaborate with other scientists.
  - Describe prior training and how it relates to the objectives and long-term career plans of the candidate.

Career development grants

- ***Candidate's Background***
  - Describe the candidate's research efforts to this point in his/her research career, including any publications, prior research interests and experience.
  - Provide evidence of the candidate's potential to develop into an independent investigator.

Career development grants

- ***Career Goals and Objectives***
  - Describe a systematic plan:
  - (1) that shows a logical progression from prior research and training experiences to the research and career development experiences that will occur during the career award period and then to independent investigator status; and
  - (2) that justifies the need for further career development to become an independent investigator.

Career development grants

- ***Career Goals and Objectives***
  - The candidate must demonstrate they have received training or will participate in courses such as: data management, epidemiology, study design (including statistics), hypothesis development, drug development, etc., as well as the legal and ethical issues associated with research on human subjects and clinical trials.

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Career development grants

- ***Candidate's Plan for Career Development/Training Activities During Award Period***
  - The candidate and the mentor(s) are jointly responsible for the preparation of the career development plan. A career development timeline is often helpful.
  - The didactic (if any) and the research aspects of the plan must be designed to develop the necessary knowledge and research skills in scientific areas relevant to the candidate's career goals.

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Career development grants

- ***Candidate's Plan for Career Development/Training Activities During Award Period***
  - Describe the professional responsibilities/activities including other research projects beyond the minimum required 9 person-months (75% full-time professional effort) commitment to the career award.
  - Explain how these responsibilities/activities will help ensure career progression to achieve independence as an investigator

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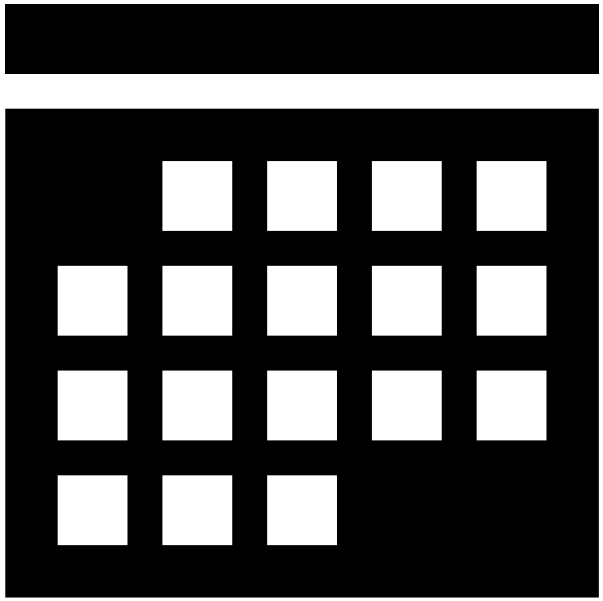
Career development grants

- 1/3 candidate, 1/3 mentor, 1/3 research strategy
- Best applications the career development activities dovetail well with research strategy aims
- Ideally designed so that regardless of result of Aims, will logically lead to next ”R01” level funding
- Mentor/mentor team support is critical!

Timeline

- Count back from the due date of the grant
- Preliminary data
- Budget
- Letters of support from collaborations, agreements from multicenter studies
- Institutional support and agreements
- Time to have others read and critique drafts
- Typically start a minimum of 6 months before grant deadline



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Closing thoughts

- Perseverance is needed – reapply, even more than once
- Respond to critiques
- IMPACT is the key
  - If successful, this grant will …
  - Even if aims NOT successful, this grant will…

Questions?

https://grants.nih.gov/grants/how-to-apply-application-guide

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HOW TO GET A SCIENTIFIC PAPER PUBLISHED

Kimberly Reidy, MD
Associate Professor and Chief, Division of Pediatric Nephrology

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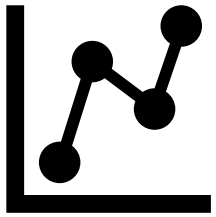
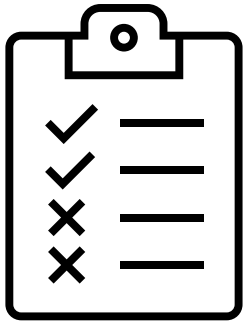
Outline

- Important aspects of research design
- Identify the journal(s)
- Manuscript preparation
- Cover letter
- Revision and resubmission

Designing a project for successful publication

- Clinical question
- Based on past knowledge
  - Review the literature
  - preliminary studies (Eg. observational study, single center)





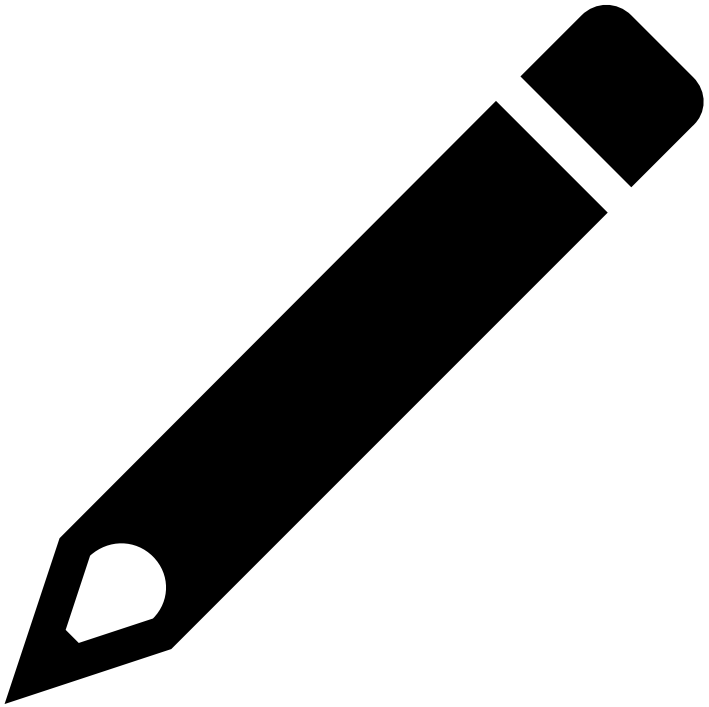
- Testable
- **Best hypotheses will lead to additional research questions regardless of results**

Designing a project for successful publication

- Many studies will be ‘negative’, ie. Testing of the central hypothesis will not lead to statistically significant results
- Ways to design your study to ensure the study is ‘publishable’
  - Perform a power analysis before you start and ensure the population studied is sufficiently powered
  - Prespecify secondary outcomes
  - Consider a ‘descriptive’ aim if the population is novel

Authorship

- Ideally first and last authors should be specified **early on** in the research process
- Should reflect significant contribution to the research
- Shared ‘equal contribution’ first authors[$], shared senior authors[#] increasingly common
- Correspondence author



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Identifying journal(s)

- Consider the target audience of the topic and the journal
  - Pediatricians?
  - Adult and Pediatric Nephrologists?
  - Pediatric Nephrologists?

Identifying journal(s)

- Read the mission/vision statement
- What kind of studies does the journal publish?
  - Methods papers
  - Clinical trials
  - Meta-analyses
- Does the journal publish similar articles?
- Where were the articles that formed the basis of the hypothesis published?

Identifying journal(s)

- Beware of predatory journals!
  - No ISSN (International Standard Serial Number)
  - Not indexed by MEDLINE, Scopus, PsycINFO, Web of Science, or other legitimate abstracting or indexing services or databases
  - Elmore SA, Weston EH. Predatory Journals: What They Are and How to Avoid Them. Toxicol Pathol. 2020 Jun;48(4):607-610. doi: 10.1177/0192623320920209. Epub 2020 Apr 22. PMID: 32319351; PMCID: PMC7237319

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Identifying journal(s)

- Consider the impact factor
  - measure of the frequency with which the average article in a journal has been cited in a particular year.
- Identify 2-4 potential journals
  - Start with your ‘reach’ but be prepared to revise and resubmit to alternates
  - Consider timeline for review if publication speed is a consideration

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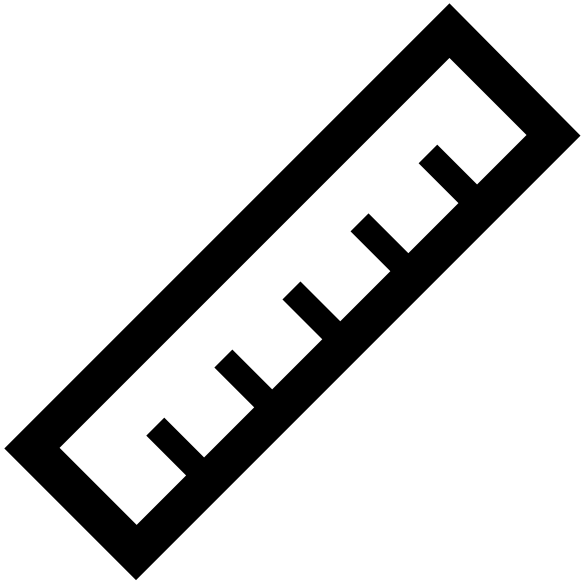
Read the journal author instructions

- Check word limits
- Identify necessary sections
  - Introduction/Background
  - Methods
  - Results
  - Discussion
  - Abstract
  - Key words?
  - Acknowledgements
  - Limits on tables/ figures?
  - Figure legends and location of in submission
  - Publication feeds/ Fees for color?



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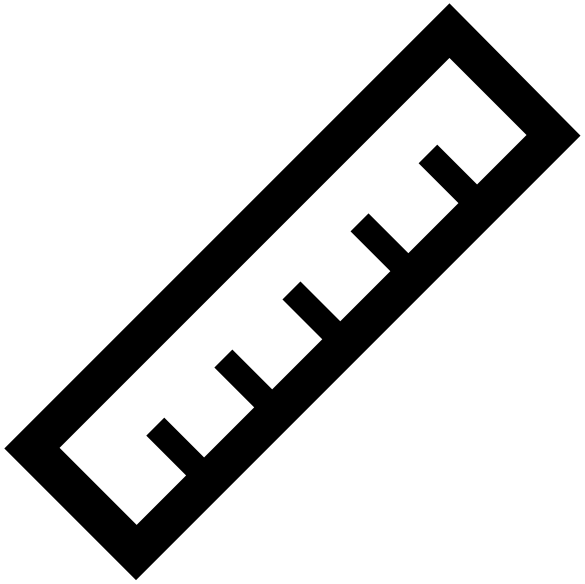
Read the journal author instructions

- Conflict of interest statements
  - Consider logistics of submission (will you need all authors to sign agreement to submit)



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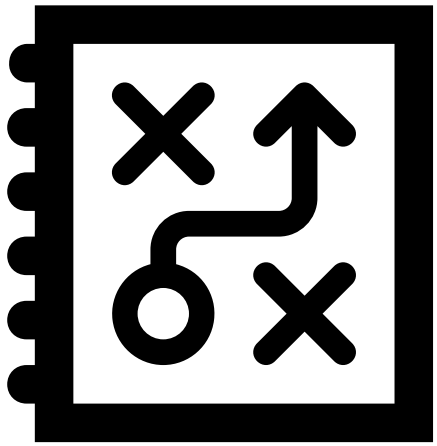
Use a reference manager

- Eg. Endnote, Paperpile, Sciwheel
- Automatically reorders during editing process
- Easy conversion to different journal formats for resubmission



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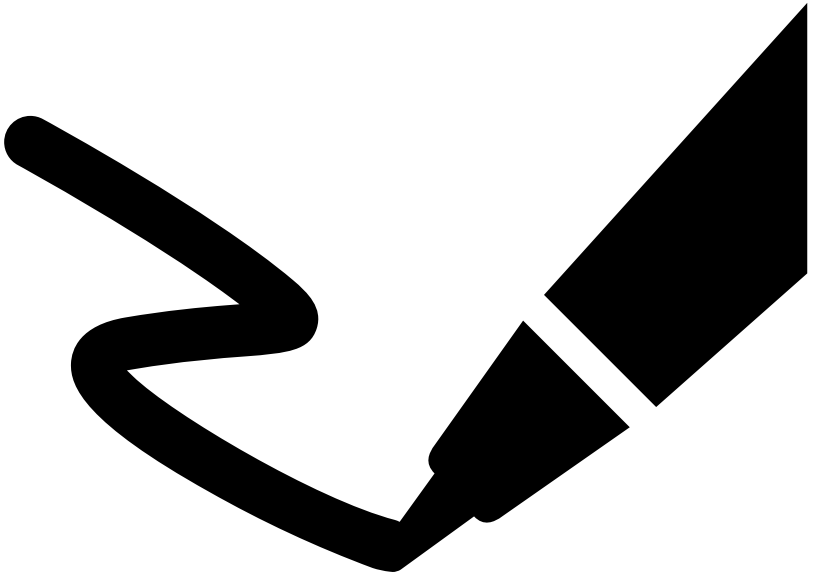
Manuscript preparation

- It's never too early to start!
- Draft your introduction as you start the project
- Write the methods section as you design and implement the project
- If you present the research as an abstract, write the paper on the way to the meeting.
  - Edit for any feedback you get during presentation



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Abstract

- Concisely summarize
- Should stand alone to get main message of study across
- May be structured:
  - Background
  - Methods
  - Results
  - Conclusions

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Background/Introduction

- Why is the clinical problem important
  - Emphasize Significance/ Impact
- Succinct summary of what is known
- Identify the knowledge gaps
- Explain objectives and hypothesis of the study

Methods

- ‘reproducibility’: Should allow other investigators to replicate your study
- Emphasize rigor
  - Prespecified outcomes/endpoints
  - Who was blinded to outcomes
  - Statistical approach/ Power analysis
  - Correction for multiple comparisons
- Include ethics (eg. IRB approval statement)

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Use available checklists depending on the type of study

1. Checklist for Reporting of Race and Ethnicity
2. CHEERS Checklist for Economic Evaluation of Health Interventions
3. CONSORT Checklist for Clinical Trials
4. COREQ Checklist for Reporting Qualitative Studies
5. PRISMA Checklist for Systematic Reviews and meta-analysis
6. SQUIRE Checklist (Standards for Quality Improvement Reporting Excellence
7. STROBE Checklist for Observational Studies
8. TRIPOD Checklist for Prediction Model Development and Validation

https://journals.lww.com/asnjournals/Pages/Information-for-Authors.aspx

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STROBE Checklists

- STROBE Checklist:
  cohort, case-control, and cross-sectional studies (combined)
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- STROBE Checklist (fillable):
  cohort, case-control, and cross-sectional studies (combined)
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  conference abstracts
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Section/Topic	Checklist Item
Background	Specific objectives clearly stated, including any pre-specified hypotheses.
METHODS	
Study Design	Key elements of study design presented early in the paper.
Setting	Setting and location from where study participants drawn clearly described.
	Relevant dates for periods of recruitment, exposure, follow-up, and data collection.
Participants	Eligibility criteria or matching criteria, as appropriate, clearly described.
	Sources and methods of selection of participant (or cases and controls) selection.
	Number of exposed/unexposed OR number of controls per case, as appropriate.
	Methods of follow-up clearly described.
Variables	Exposures, outcomes, predictors, potential confounders, effect modifiers clearly defined.
Data Sources/ Measurement	Sources of data and details of methods of assessment.
	Comparability of assessment methods, if more than one group.
Bias	Clear description of efforts to address potential sources of bias.
Statistical Methods	All statistical methods clearly described, including those used to control for confounding.
	Methods used to examine subgroups and interactions clearly described.
	Extent of missing data, and how it was handled clearly described.
	Extent of loss to follow-up and how it was addressed clearly described.
	Sensitivity Analyses appropriate and clearly described.

Results

- Read other manuscripts in your target journal to understand the journals ‘style’
- Headline key findings?
- Consider starting with Tables and Figures
- Logically organized
  - Description of cohort
  - Primary outcome result
  - Secondary outcome results
  - Sensitivity analyses

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Figures and Tables

- Figures and figure legends
  - detailed and clear
  - Easy to read!
  - as self—explanatory as possible
  - For many readers, this is the only part they may look at!
- Key figures/tables
  - Table 1 (Demographics)
  - Flowchart showing eligible and excluded patients

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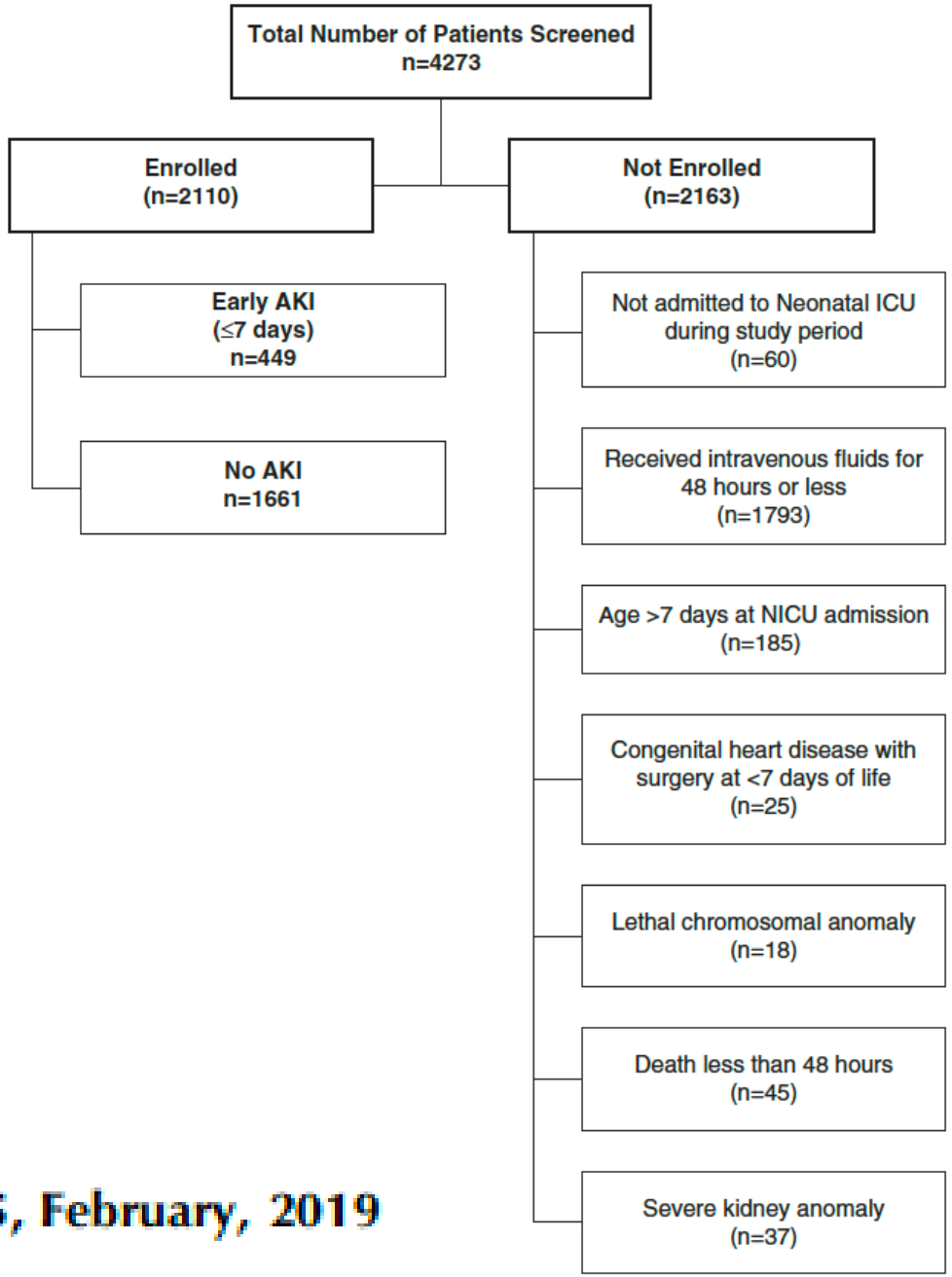
Flow diagram



Clin J Am Soc Nephrol 14: 184–195, February, 2019

Table 1

Table 1. Demographics of the overall cohort of AWAKEN with and without early AKI and stratified into gestational age cohorts (22–28, 29–35, ≥36 wk)

Characteristic	Overall Cohort (*n*=2110)		22–28 wk (*n*=265)		29–35 wk (*n*=936)		≥36 wk (*n*=909)	
	AKI (*n*=449)	No AKI (*n*=1661)	AKI (*n*=75)	No AKI (*n*=190)	AKI (*n*=127)	No AKI (*n*=809)	AKI (*n*=247)	No AKI (*n*=662)
Gestational age, wk	34.6±5.2	34.0±4.2	25.0±1.5	26.0±1.6	32.7±2.0	32.5±1.8	38.4±1.5	38.1±1.5
Birth weight, g	2479±1085	2249±962	797±198	900±258	2047±693	1871±562	3213±618	3101±703
Sex (male)	269 (60)	932 (56)	44 (59)	105 (55)	71 (56)	449 (56)	154 (62)	378 (57)
Race (White)	265 (59)	916 (55)	38 (51)	87 (46)	72 (57)	457 (57)	155 (63)	372 (56)
Ethnicity (Hispanic)	43 (10)	243 (15)	13 (17)	14 (7)	9 (7)	129 (16)	21 (9)	100 (15)
Apgar-1	6 (3, 8)	7 (4, 8)	4 (1, 6)	4 (2, 6)	7 (4, 8)	7 (5, 8)	8 (4, 8)	8 (5, 9)
Apgar-5	8 (6, 9)	8 (7, 9)	6 (4, 8)	7 (6, 8)	8 (7, 9)	8 (8, 9)	9 (6, 9)	9 (7, 9)
Antimicrobials[a]	195 (43)	1258 (76)	44 (59)	179 (94)	58 (46)	611 (76)	93 (38)	468 (71)
Methylxanthines[a]	60 (13)	467 (28)	36 (48)	173 (91)	20 (16)	270 (33)	4 (2)	24 (4)
Diuretics[a]	15 (3)	70 (4)	2 (3)	16 (8)	4 (3)	10 (1)	9 (4)	44 (7)
Vasopressors[a]	38 (9)	140 (8)	17 (23)	40 (21)	6 (5)	35 (4)	15 (6)	65 (10)
NSAIDs[a]	13 (3)	77 (5)	13 (17)	68 (36)	0 (0)	8 (1)	0 (0)	1 (0)
AKI by creatinine	224 (50)	0	70 (93)	0	75 (59)	0	79 (32)	0
AKI by urine output	282 (62)	0	10 (73)	0	68 (53)	0	204 (83)	0
Mortality	37 (8)	40 (2)	17 (23)	20 (11)	10 (8)	8 (1)	10 (4)	12 (2)
Length of stay, d	33±42	30±31	80±47	81±40	33±48.0	29±22	19±21	17±20

Data are shown as mean±SD or *n* (%) and Apgar are median and IQR. Antimicrobial medications: acyclovir, amphotericin B, aminoglycosides, piperacillin-tazobactam, and vancomycin; methylxanthine medications: caffeine and theophylline; diuretic medications: bumetanide, chlorothiazide, furosemide, and spironolactone; vasopressor medications: dobutamine, epinephrine, milrinone, norepinephrine, and dopamine; and NSAID medications: indomethacin and ibuprofen. NSAIDs, nonsteroidal anti-inflammatory drugs. AWAKEN, Assessment of Worldwide AKI Epidemiology in Neonates.

[a]All medications were given before the episode of AKI.

Checklists for results:

RESULTS	
Participants	Number of individuals at each stage – e.g., number eligible, examined for eligibility, confirmed eligible, included in study, completing follow-up and analyzed.
	Reasons for non-participation at each stage clearly described.
Descriptive Data	Characteristics of study participants presented .
	Information on exposures and potential confounders available.
	Number of participants with missing data for each variable of interest provided.
	Follow-up time summarized (average and total, as appropriate).
Outcomes	Number of outcome events or summary measures over time available.
	For case-control study, numbers in each exposure category, or summary measures of exposure provided.
	For case-control study, numbers of outcomes events or summary measures.
Main Results	Unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (95% confidence interval) provided.
	Category boundaries, when continuous variables were categorized, available.
	Estimates of relative risk translated into absolute risk for a meaningful period.
Other Analyses	Sub-group analyses, interactions, sensitivity analyses adequately presented.

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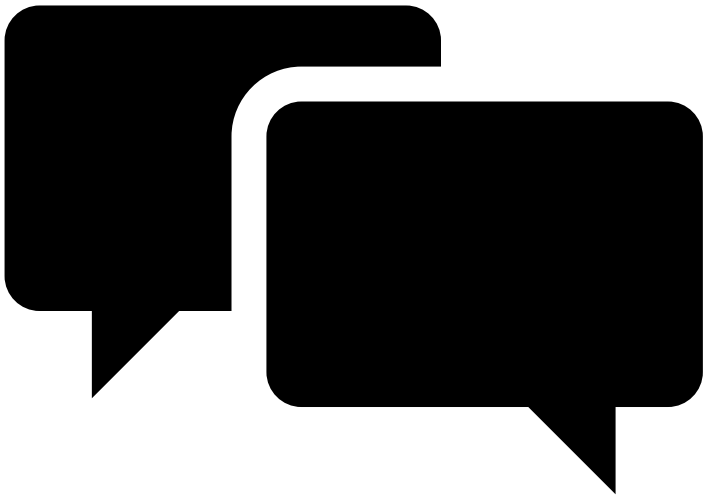
Discussion



- Not a re-statement of all the results
- Concisely summarize in opening what the study showed
- Integrate study findings with published data
- Highlight the impact and most important findings
- How were study findings similar or different to other studies? Can you propose why?

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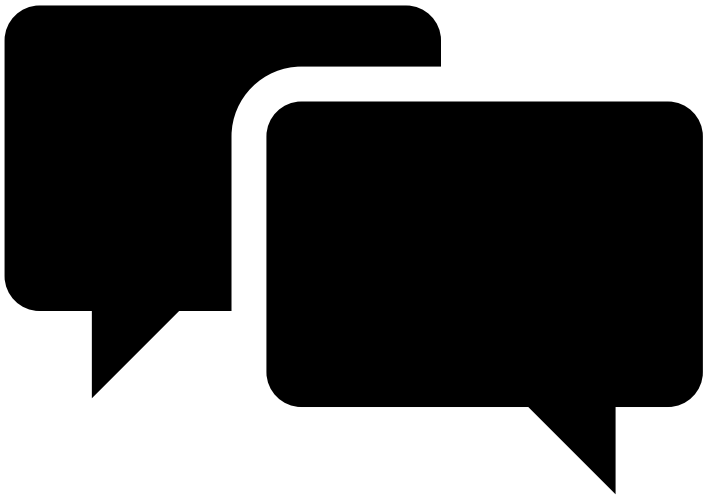
Discussion



- Does the study identify new areas for additional research?
- Surprising findings? Conclusions that went against hypothesis? Can you generate an alternative hypothesis
- Summarize strengths and limitations
- Conclusion summary

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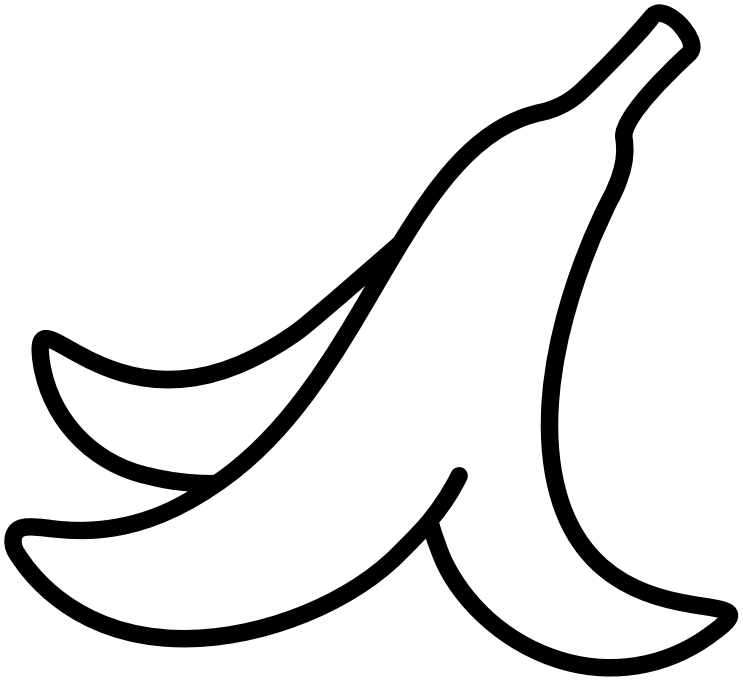
Pitfalls to avoid

- Avoid plagiarism (even self plagiarism!)
- Have an outside reader not familiar with the study review to make sure understandable from a ‘non-expert’
- Highlight the **new knowledge gained and impact**
  - ‘incremental’ knowledge or reproducing other study findings will be harder to find a manuscript ‘home’



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Revision and review prior to submission

- Allow time for co-authors/others to review and comment
  - Give a deadline (eg. 2-4 weeks) when you request review and comments
  - Send a reminder a few days before the deadline
  - Consider sending required paperwork for submission (eg. COI disclosures) and confirm spelling of names and institutions

Cover letter

- May be used to ‘triage’ manuscripts – highlight the impact of your study!
- Identify the best editor/associate editor for your research topic
  - Check the journal website
  - Pubmed search the editor/associate editors
- Editors that publish in a similar content area may be more excited/interested to publish your work
- Reviewer recommendations
  - Identify reviewers with expertise in the study area
  - Can request NOT to be reviewed by direct competitors

Cover letter

- Addressee's information and date of submission.
- Opening salutation.
- Purpose statement and administrative information.
- **Summary of main research findings and implications.**
- **Statements or information required by the journal.**
- Closing salutation and your contact information.

Revision and resubmission

- Very few manuscripts are accepted without revision!
- If rejected
  - read the reviews, consider addressing low hanging fruit
  - revise for one of your alternative journals

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Revision and resubmission

- If major revision:
  - Read the reviews
  - Consider what tasks are ‘do-able’ or addressable in some fashion
  - Check the deadline for resubmission!
  - No guarantee that they will publish but most often will be accepted if address reviewer critiques
  - Most authors do NOT do all the recommended additional analyses/studies by reviewers
    - Sweet spot is ‘enough’ that you address any serious limitation/issue

Revision and resubmission

- If minor revision:
  - Unusual for a first manuscript submission, but not uncommon following a submission with a major revision
  - Typically involves a revision of language or minimal additional analysis
  - May be needed for an editor's critique/ journal style requirements

Manuscript acceptance

- Thank your co-authors!
- Disseminate the study!
- Consider highlighting in social media and/or your local institution, professional organization, etc.

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Questions?

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Making Peritoneal Dialysis Fluid

Wherever possible it is best to use commercially available PD fluid. Making PD fluid increases the risks to the patient as the composition of the fluid is not exact and there is a much greater chance of inadvertent contamination whilst preparing the fluid that can lead to the development of peritonitis.

In general there are three fluids used.

1.5% glucose solution is slightly hypertonic. In some patients this will lead to the generation of some fluid loss. In many the patient will end up with an even balance and occasionally patient will become positive through fluid absorption.

2.5% glucose solution is the fluid used if there is a need to generate ultrafiltration

4% glucose solution is significantly hypertonic and is only needed if large amounts of ultrafiltration are rapidly needed (e.g. patient with heart failure or pulmonary oedema), or if for some reason 2.5% glucose solution is not removing fluids.

	Solution		
Constitution	**1.5% glucose**	**2.5% glucose**	**4% glucose**
0.9% saline	1000 ml	1000 ml	1000 ml
Remove	350 ml	350 ml	350 ml
Add:			
5% glucose	300 ml	100 ml	0 ml
10% glucose	0 ml	200 ml	200 ml
20% glucose	0 ml	0 ml	100 ml
8.4% sodium bicarbonate	40 ml	40 ml	40 ml
10% calcium gluconate	7.5 ml	7.5 ml	7.5 ml

Note:

This solution gives a sodium concentration of ~140 mmol/l

The bicarbonate is 40 mmol/l

Potassium between 2 and 5 mmol/l can be added to the PD fluid according to the patient's biochemistry. Hyperkalaemic patients should have non added. Once the serum potassium is below 3.5 mmol/l adding 4 mmol/l of potassium chloride to the solutions should prevent hypokalaemia.

The calcium gluconate needs to be added immediately before the bag is used and mixed well. If the calcium is added and the bag hangs around for hours it will precipitate with the bicarbonate.

If Calcium gluconate is not available then 2.6 ml of 10% Calcium chloride can be used. It is possible to perform the PD with no calcium added but this runs the risk of the patient suffering complications of hypocalcaemia - particularly as patients with acute kidney injury frequently have low serum calcium levels.

The normal cycle volume for PD is between 30 and 50 ml/kg body weight

This needs to be dry body weight not oedematous body weight

Start at 30 ml/kg then work up if increase clearance required

If the patient has respiratory problems starting with lower volumes may prevent splinting of the diaphragm and further respiratory compromise

Start with a dwell time of 1 hour then adjust according to response.

Prof Malcolm A. Lewis (drmal1956@gmail.com, +447743446222)

CHALLENGES AND OPPORTUNITIES IN CHILDHOOD NEPHROTIC SYNDROME

Steroid sensitive

Susan M. Samuel, MD FRCPC MSc
Professor, Canada Research Chair

3– Day Paediatric Nephrology Workshop
19 – 21 June 2023
University College Hospital
Ibadan, Nigeria

UNIVERSITY OF CALGARY

CHILDNEPH

OUTLINE

1. Clinical case and features of SSNS
2. Challenges in the management of SSNS
3. Case presentation, management of SRNS
4. Insights into the pathogenesis of nephrotic syndrome

CASE

ILLUSTRATIVE CASE

3 year old girl

- Experienced a mild viral illness several days ago
- Woke up with swelling over the eyes
- Swelling disappears during the day
- Not feeling herself
- Abdomen may be slightly distended
- Mom is concerned

Hazel and her mother, used with permission

What proportion of children presenting like this are prescribed antihistamines before a diagnosis of nephrotic syndrome is made?

What proportion of children presenting like this are prescribed antihistamines before a diagnosis of nephrotic syndrome is made?

>90%

Hollis A. Pediatr Child Health 2019

BACK TO THE CASE

After several visits to the doctor, someone did a urinalysis

- > 3 g/L protein on dipstick
- Confirmed with a urine protein to creatinine ratio of 2154 mg/mmol
- Blood tests revealed serum albumin of 9 g/L
- No other abnormalities in clinical evaluation
- A diagnosis of childhood nephrotic syndrome was made

CLINICAL PRESENTATION

- Nephrotic range proteinuria
- Low serum albumin <30 g/L
- Gravity dependent edema

- Urine
  - Primarily albuminuria
  - Minimal blood or casts
- Blood
  - High cholesterol
  - Normal C3

NEPHROTIC RANGE PROTEINURIA

Measurement method	First morning spot urine	24 hour urine
Urine dipstick or urine protein	3+ (300-1000 mg/dL) or 4+ (≥ 1000 mg/dL)	≥ 1000 mg/m^2 per day > 40 mg/m^2/hour
Urine protein to creatinine ratio	≥ 200 mg/mmol (≥2 mg/mg)	≥ 200 mg/mmol (≥ 2 mg/mg)

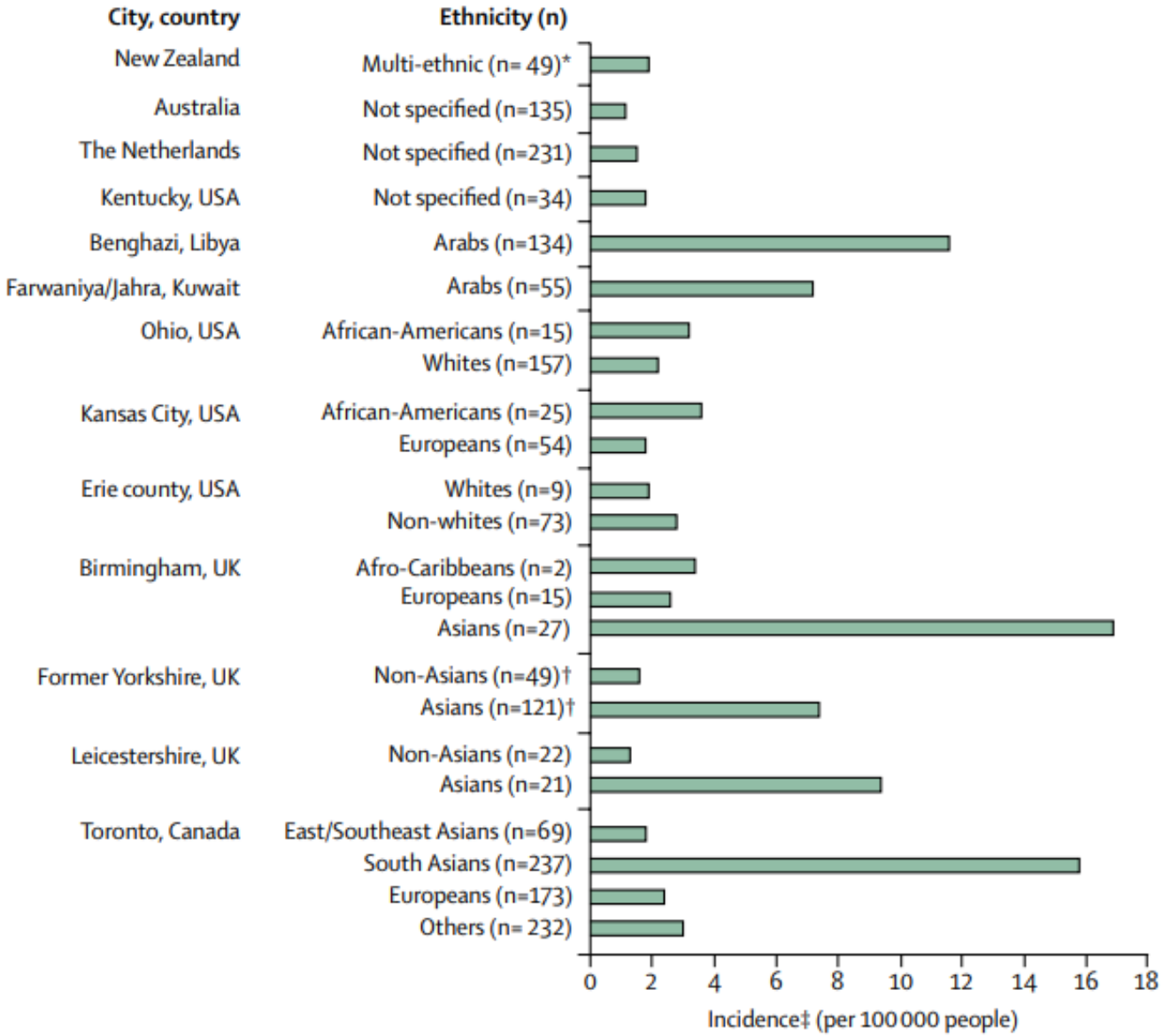
COMPLICATIONS TO NOTE

- Infections
- Thrombus in lungs, kidney, brain (3% of cases, almost all venous)
- Acute kidney injury
- Severe edema, ascites, pleural effusions

Kerlin BA Pediatr Nephrol 2014

INCIDENCE
1-17/100,000 CHILDREN

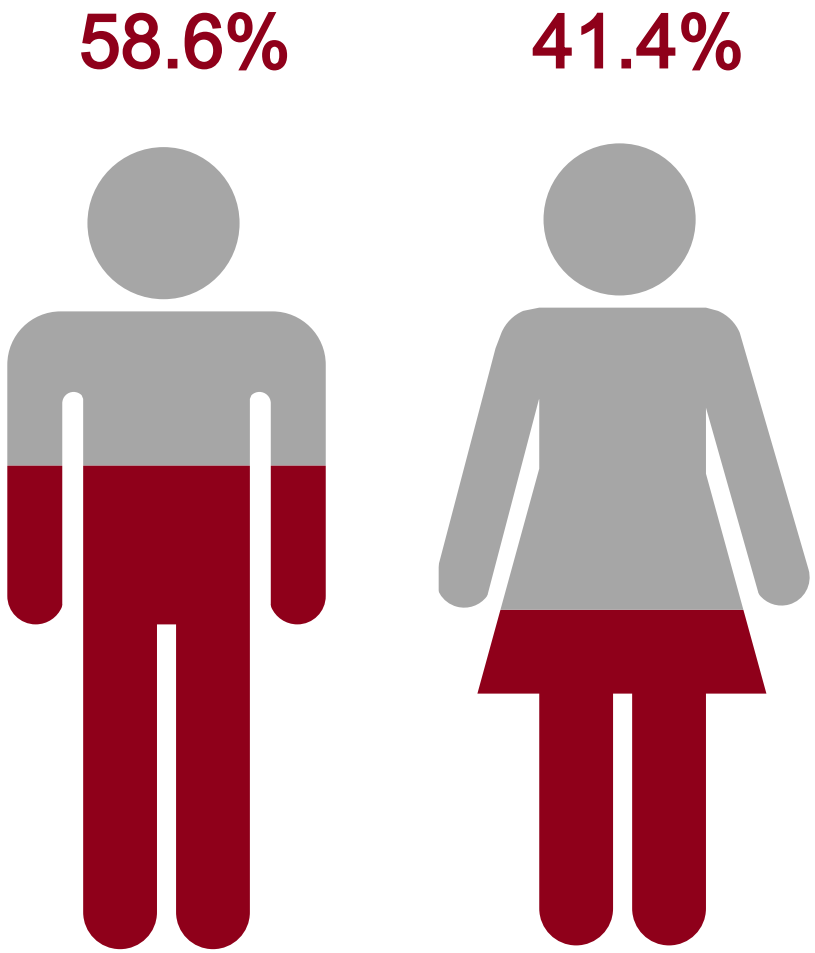
SOUTH ASIANS HIGHER RISK



Noone D. Lancet 2018

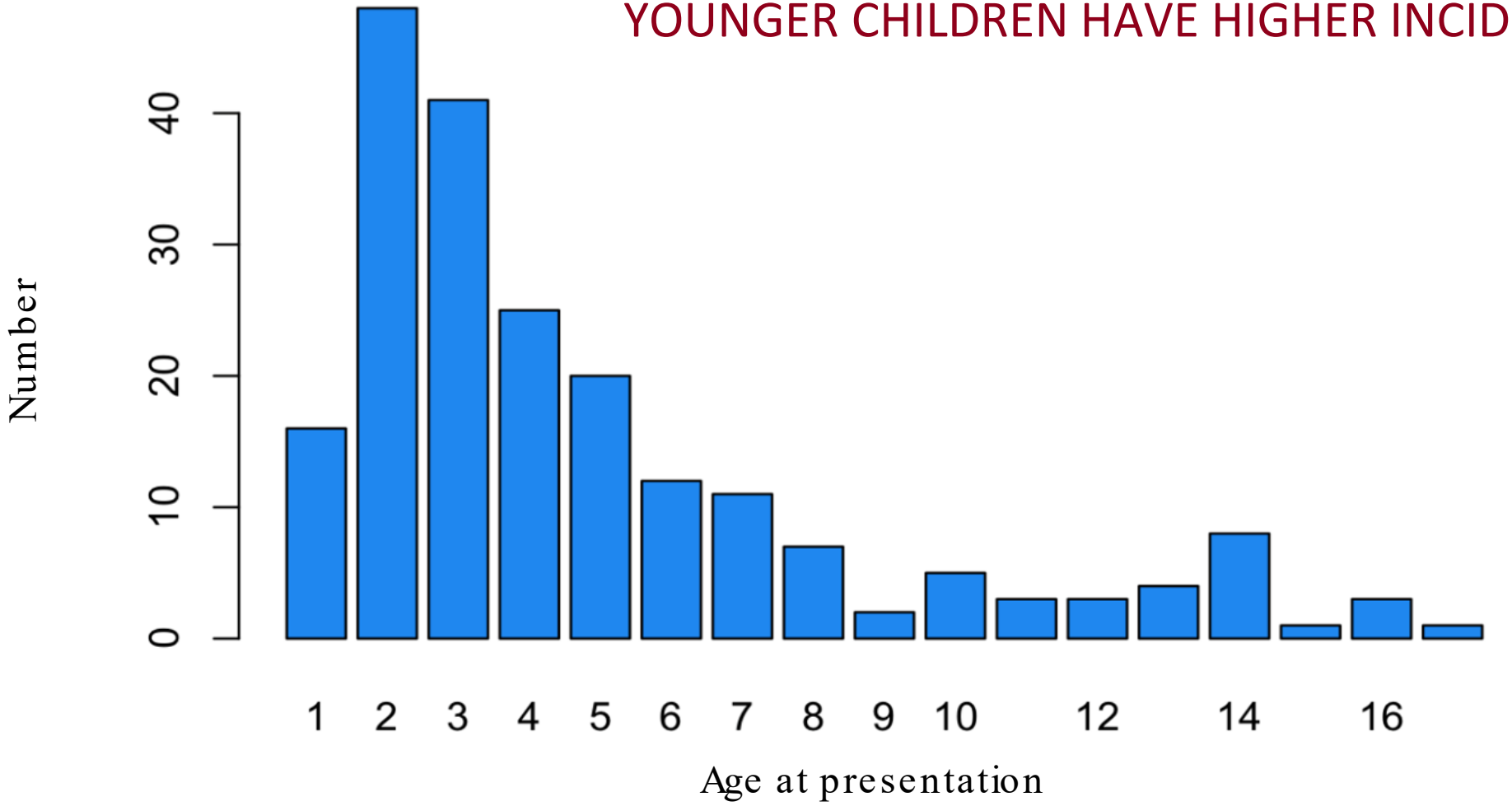
What proportion of all new patients with nephrotic syndrome are biologically male?

MALES AFFECTED DISPROPORTIONATELY



CHILDNEPH Registry Data

YOUNGER CHILDREN HAVE HIGHER INCIDENCE



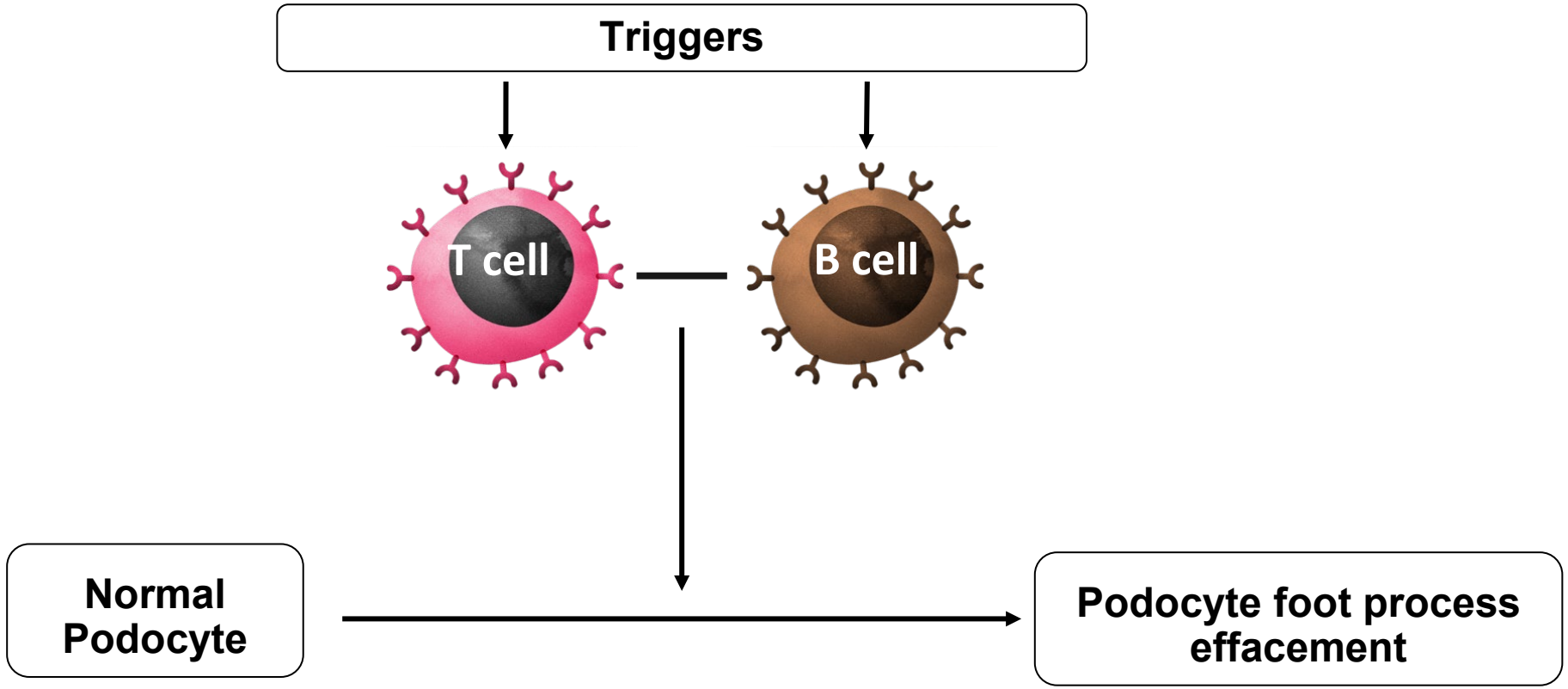
Childneph Registry Data

AGE OF PRESENTATION KEY TO DIAGNOSIS AND MANAGEMENT

<3 Months	3-12 Months	> 1 Year
• Genetic testing • Extrarenal manifestations • Congenital infection	• Genetic testing • Extrarenal manifestations • Kidney biopsy • *Idiopathic immune*	• Idiopathic immune • Genetic causes less likely • Kidney biopsy **not** performed

Boyer O, Nat Rev Nephrol 2021

Immune pathogenesis of nephrotic syndrome



Shalhoub Lancet 1975

AGE OF PRESENTATION KEY TO DIAGNOSIS

<3 Months	3-12 Months	> 1 Year
• Genetic testing • Extrarenal manifestations • Congenital infection	• Genetic testing • Extrarenal manifestations • Kidney biopsy • *Idiopathic immune*	• Idiopathic immune • Genetic causes less likely • Kidney biopsy not performed

Decision to start Prednisone

Boyer O, Nat RevNephrol2021

TREATMENT OF NEPHROSIS WITH PREDNISOLONE

GAVIN C. ARNEIL
M.D. Glasg., M.R.C.P., F.R.F.P.S., D.C.H.
LECTURER IN CHILD HEALTH IN THE UNIVERSITY OF GLASGOW ;
PÆDIATRICIAN, ROYAL HOSPITAL FOR SICK CHILDREN,
GLASGOW

Lancet 1956

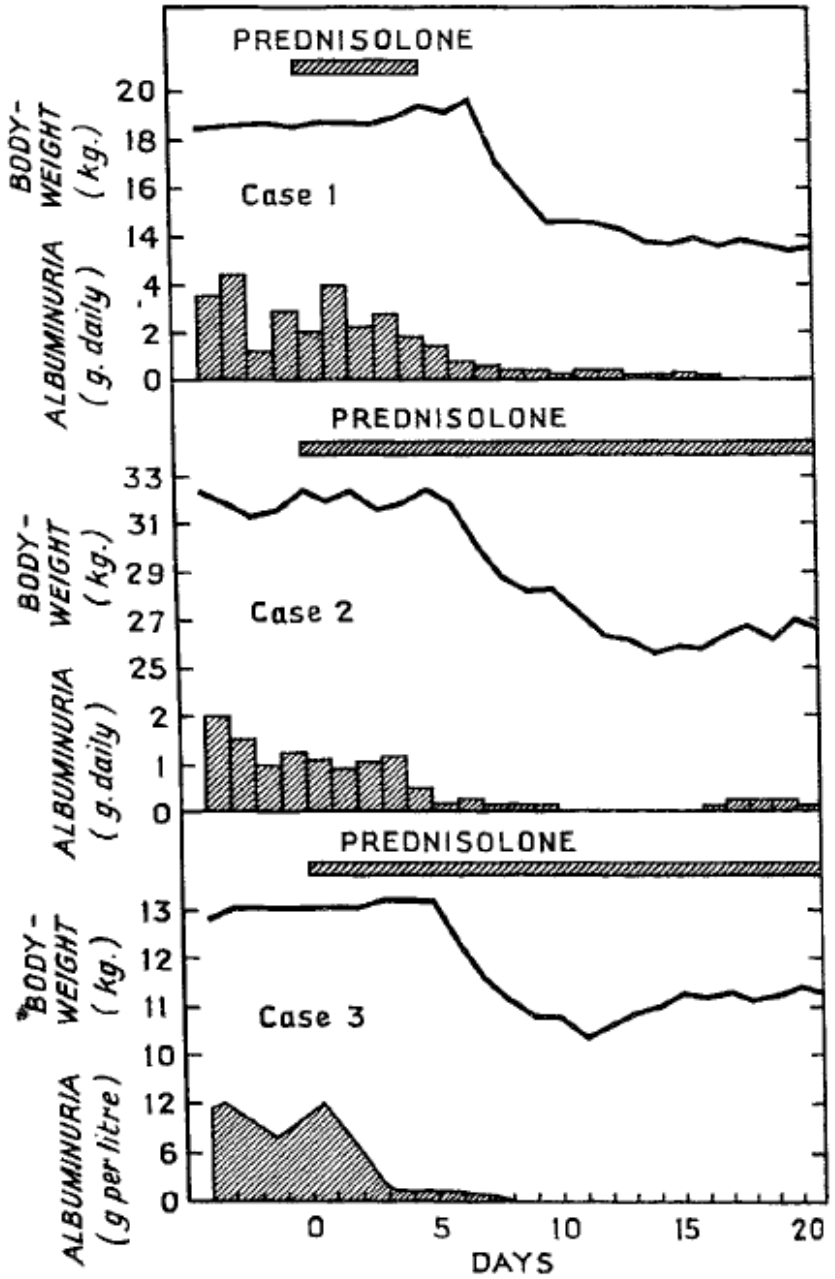


Fig. 1—Relation of prednisolone treatment and albuminuria to loss of œdema and consequent loss of weight.

Kidney International, Vol. 13 (1978), pp. 159–165

Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis

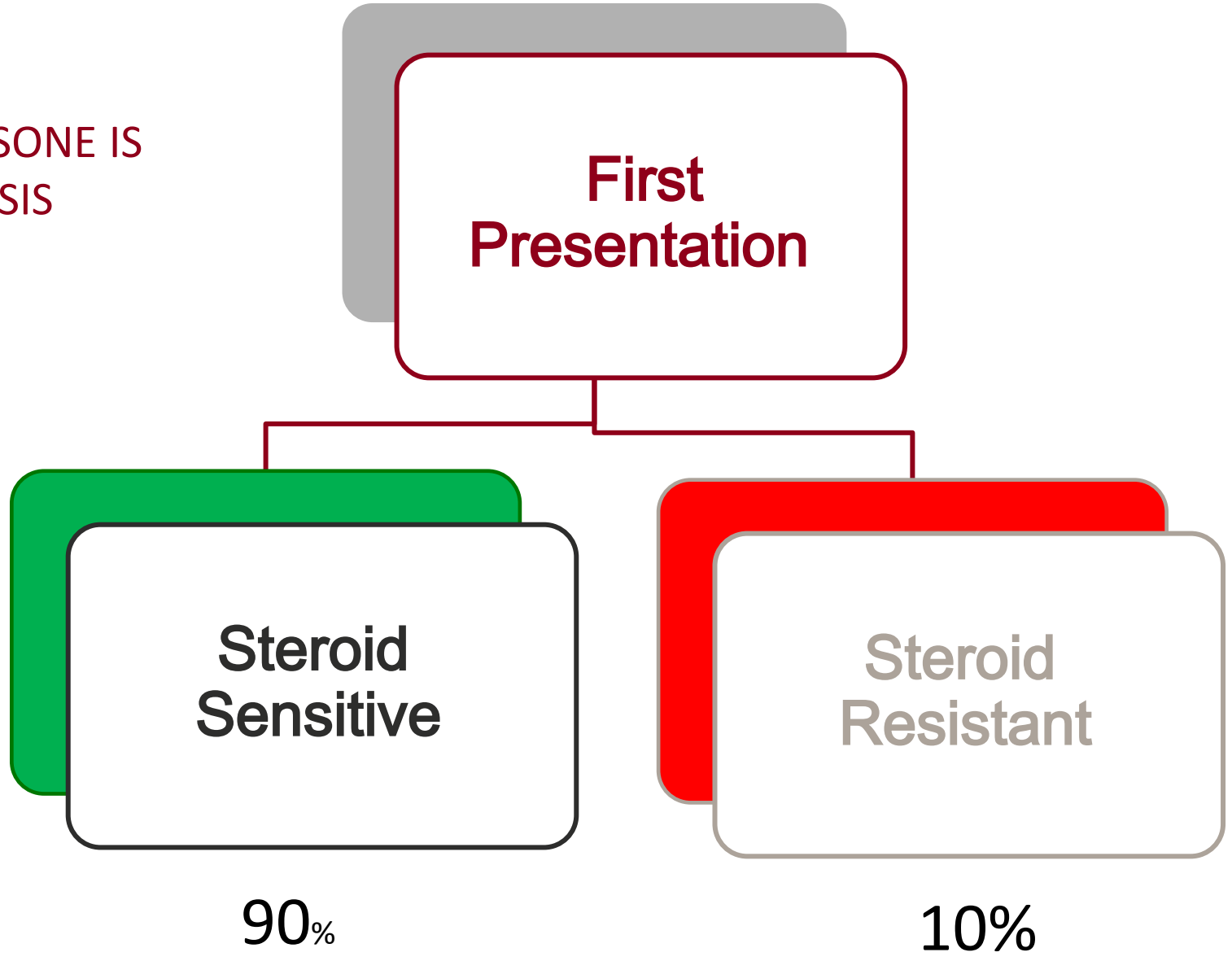
A Report of the International Study of Kidney Disease in Children

- Prospective International Cohort (ISKDC)
  - 1967 - 1974
  - 521 nephrotic syndrome patients
  - >12 weeks of age and < 16 years
  - 76% were Minimal Change Disease
- Steroid protocols subsequently modified
  - Various other groups
  - Longer duration to reduce relapse frequency

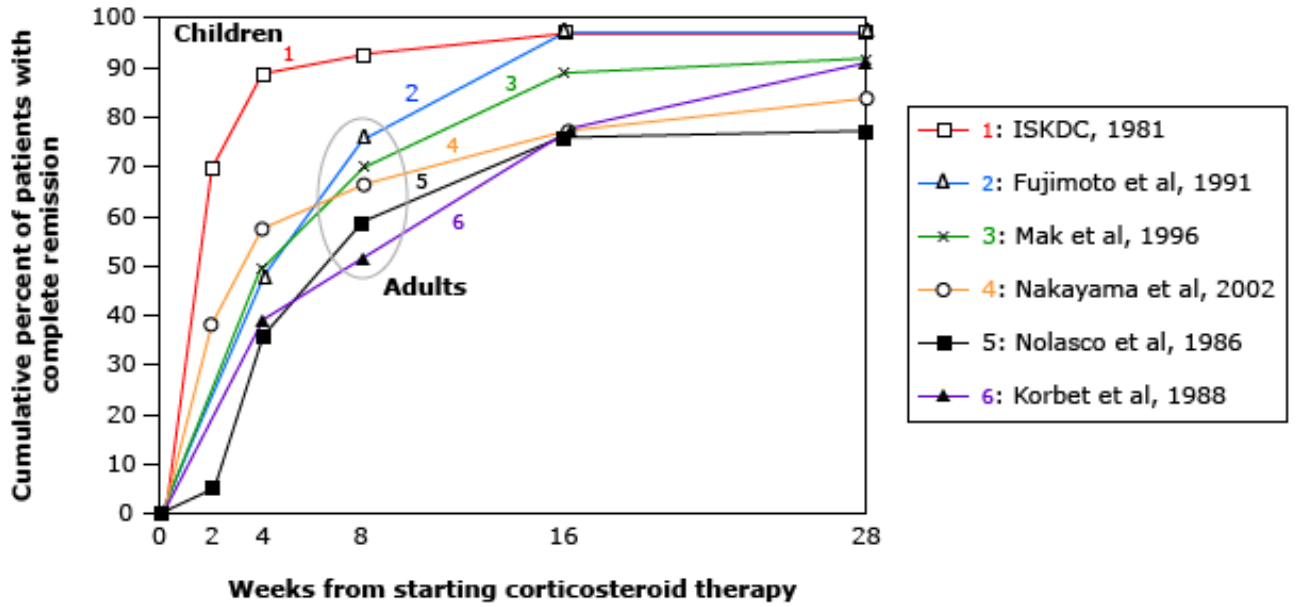
Led by Henry Barnett and Chester Edelman

PATIENT'S RESPONSE TO PREDNISONE IS MOST IMPORTANT FOR PROGNOSIS

Cannot predict response



Cumulative rate of remission in response to steroids in MCD



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

ISKDC: International Study of Kidney Disease in Children.

Nakayama AJKD 2002; UptoDate

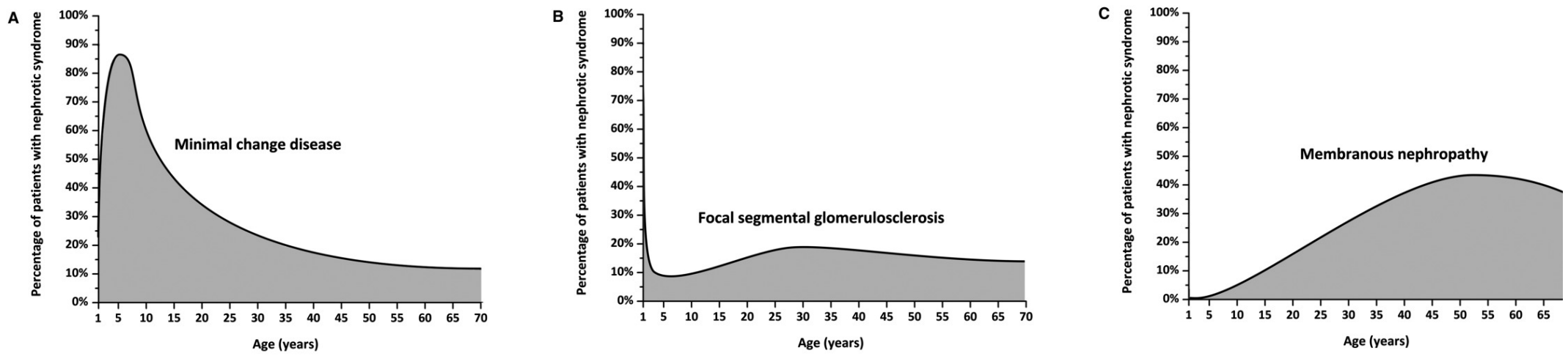
Kidney biopsy

Initial diagnostic work-up

- We recommend that children presenting with NS undergo a diagnostic work-up as outlined in Fig. 2 and Table 2 (grades are given in the table).
- We do not recommend routine kidney biopsy and genetic testing in the initial diagnostic work-up of children with NS who present with typical features and age > 1 year (grade B, moderate recommendation).
- We recommend considering genetic testing and/or kidney biopsy in infantile onset NS (age 3–12 months) (grade B, weak recommendation).

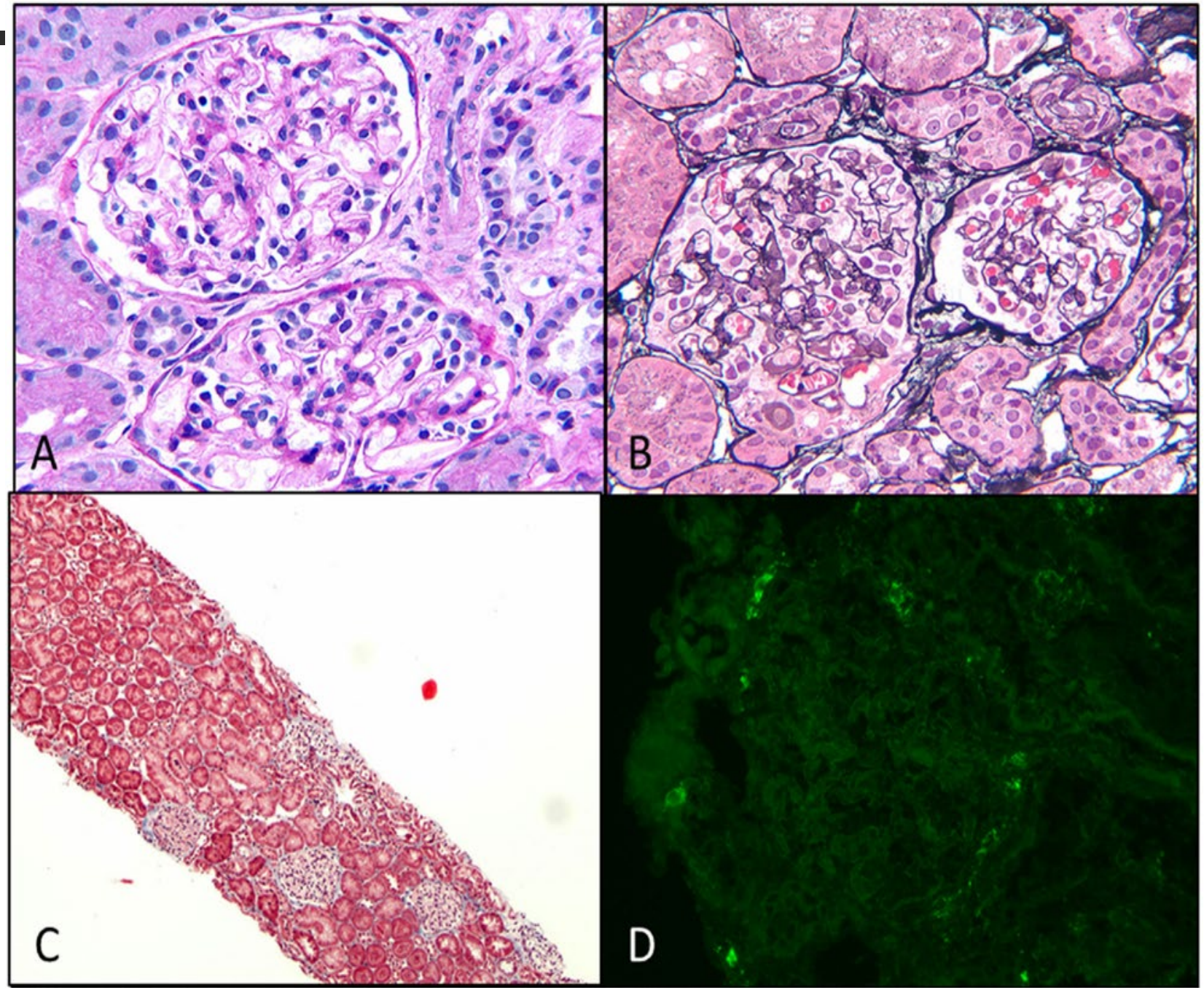
IPNA CPR SSNS 2023, *Pediatr Nephrol*

Changing pathological findings by age



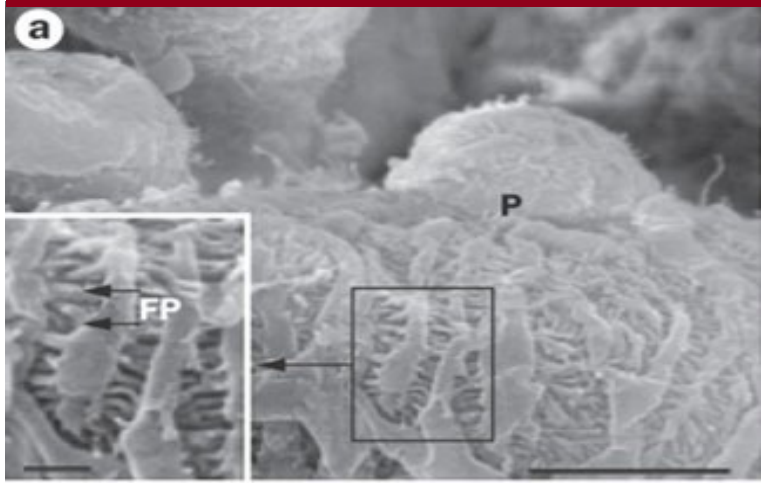
Vivarelli CJASN 2017

MINIMAL CHANGE DISEASE

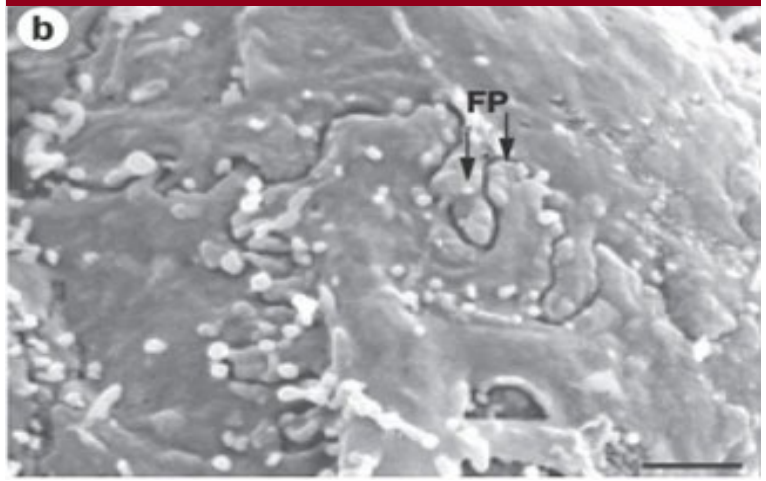


Ranganathan S. Front Pediatr
2016

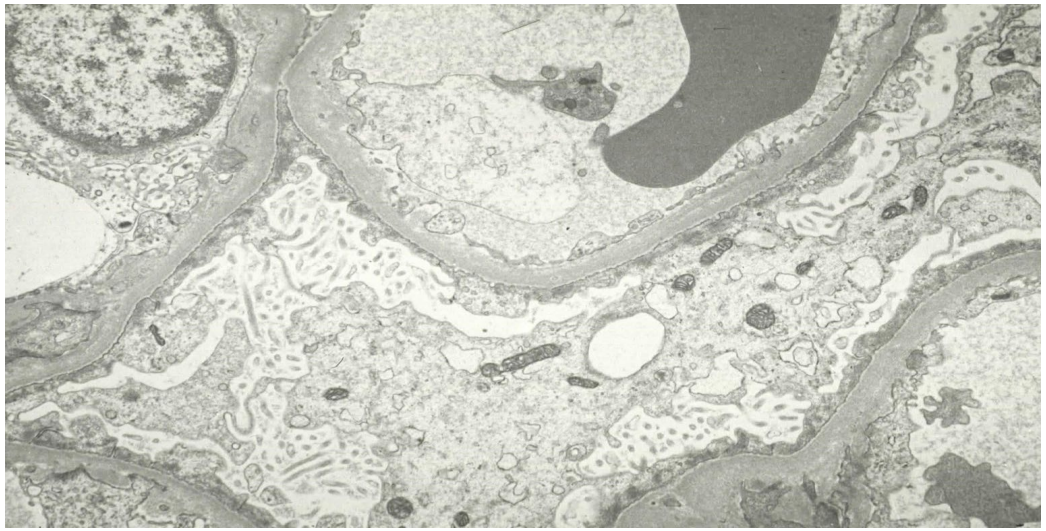
HEALTHY

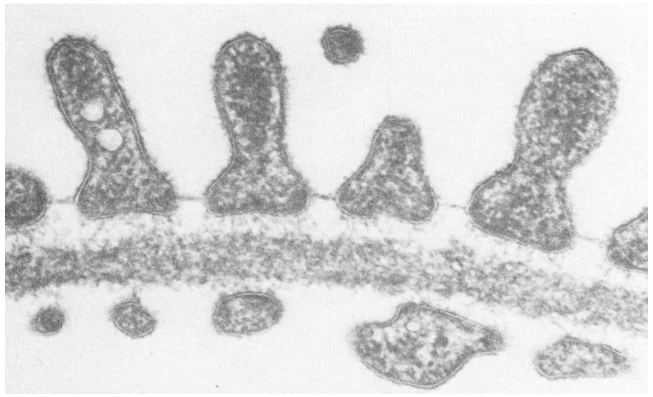


Podocyte effacement



MINIMAL CHANGE DISEASE - PODOCYTE EFFACEMENT



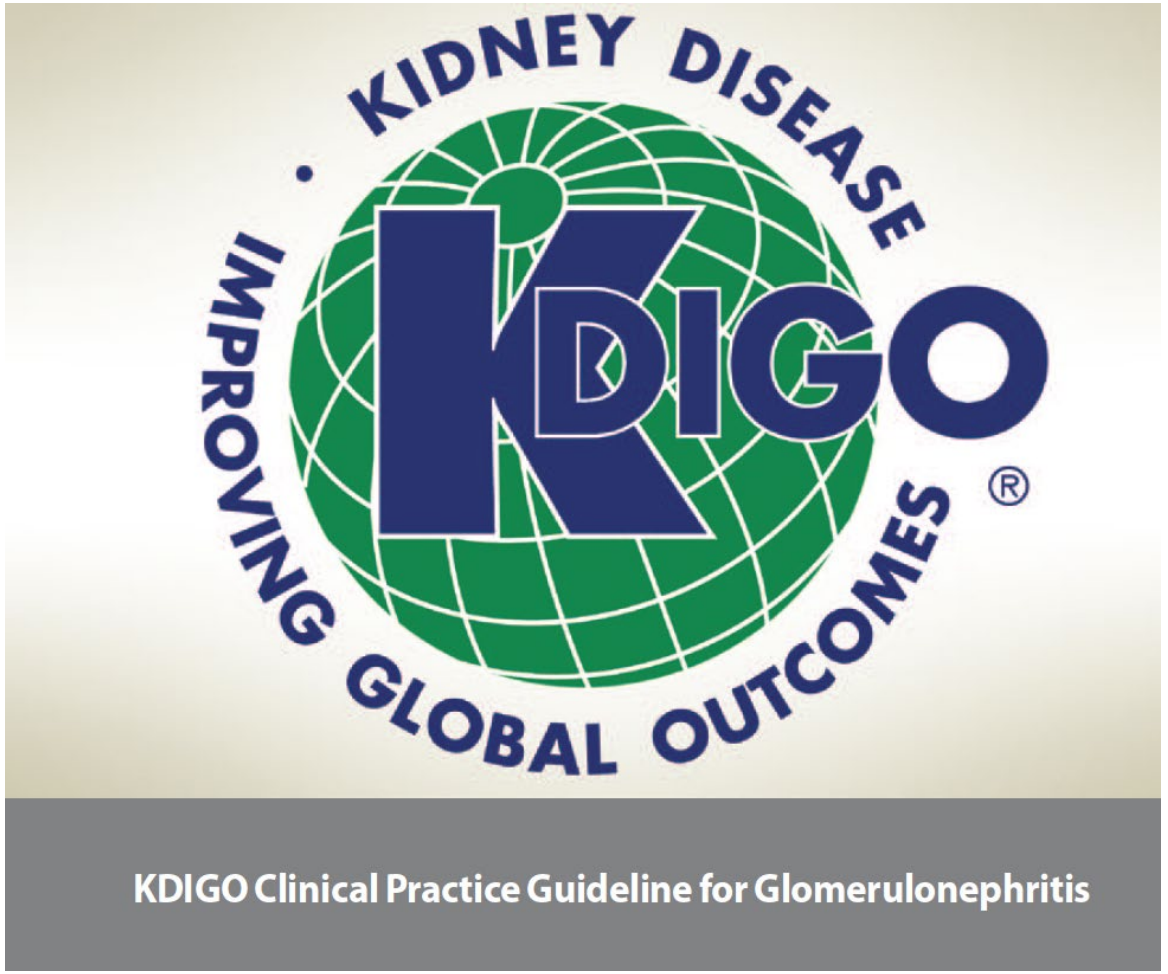


Tryggvason et al. NEJM 2006

INTERNATIONAL TREATMENT GUIDELINES 2021

4.3.1 Initial Treatment of NS in Children

- Recommendation 4.3.1.1: We recommend that oral **glucocorticoids be given for 8 weeks** (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) **or 12 weeks** (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) (1B)

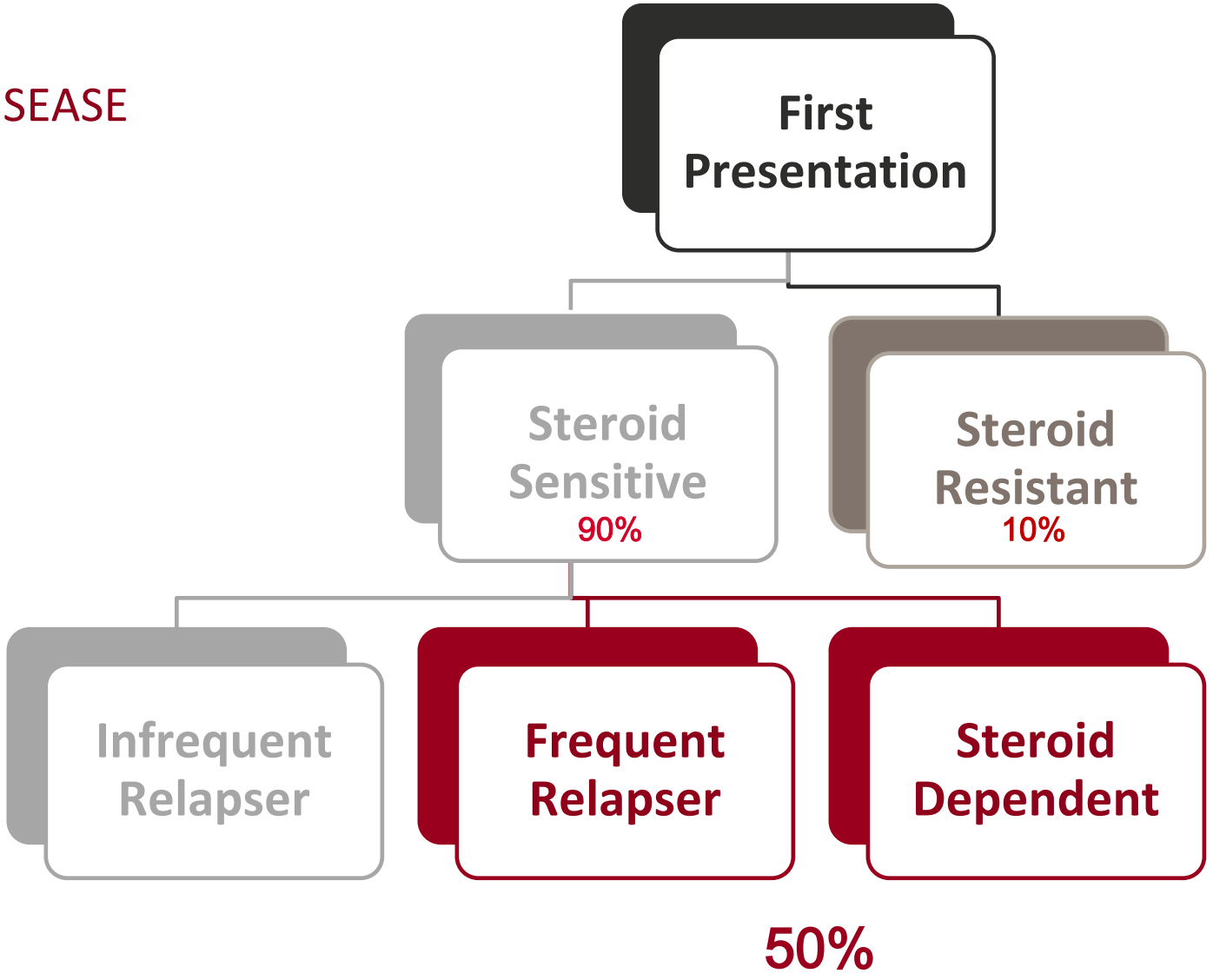


IPNA Clinical Practice Recommendation 2023
Prednisone treatment guidelines

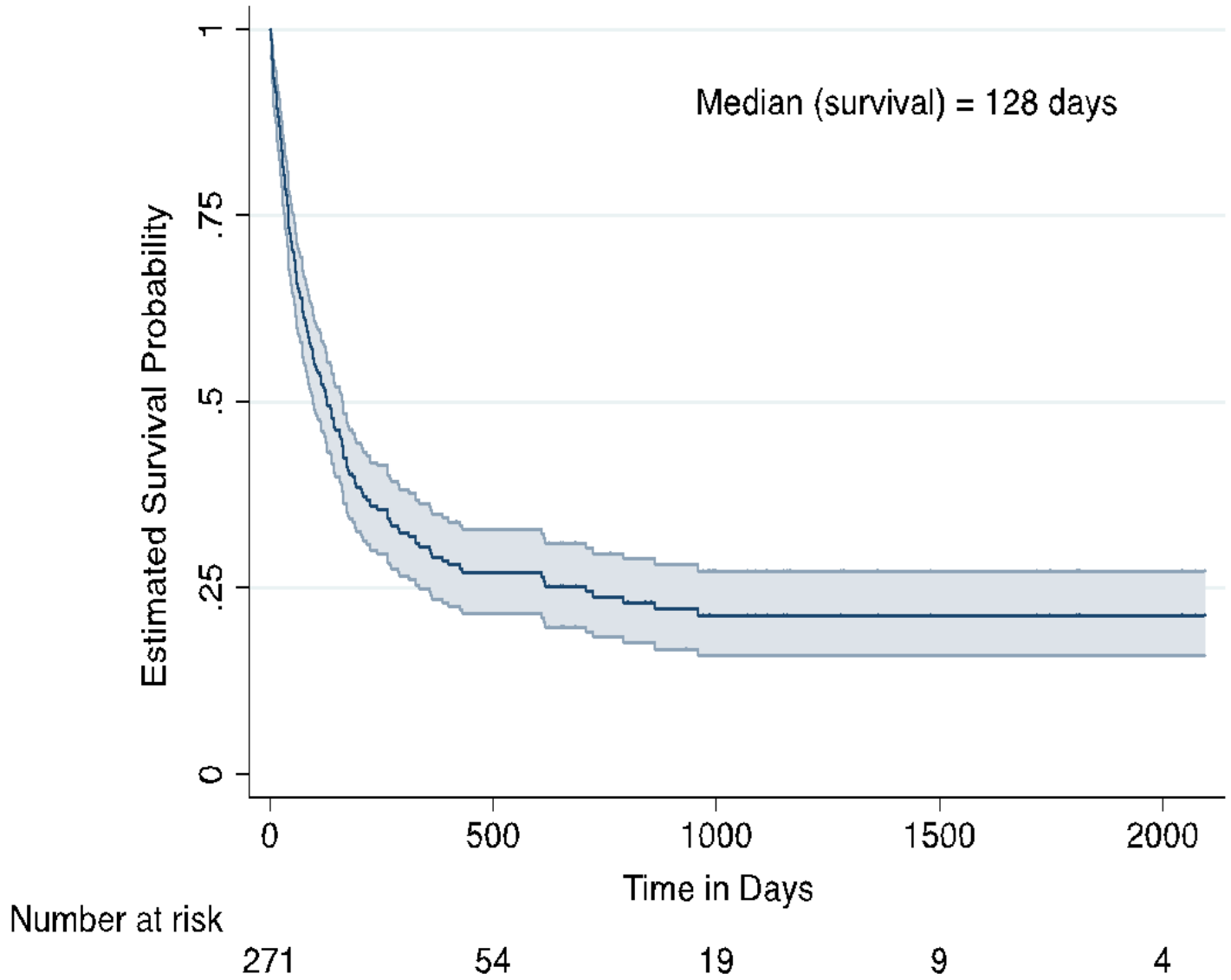
- 4 weeks at 60 mg/m^2 or 2 mg/kg (maximum dose 60 mg/day), followed by alternate day PDN at 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for 4 weeks, or
- 6 weeks at 60 mg/m^2 or 2 mg/kg (maximum dose 60 mg/day), followed by alternate day PDN at 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for 6 weeks (grade A, strong recommendation).

IPNA SSNS CPR *Pediatr Nephrol 2023*

RELAPSING-REMITTING DISEASE



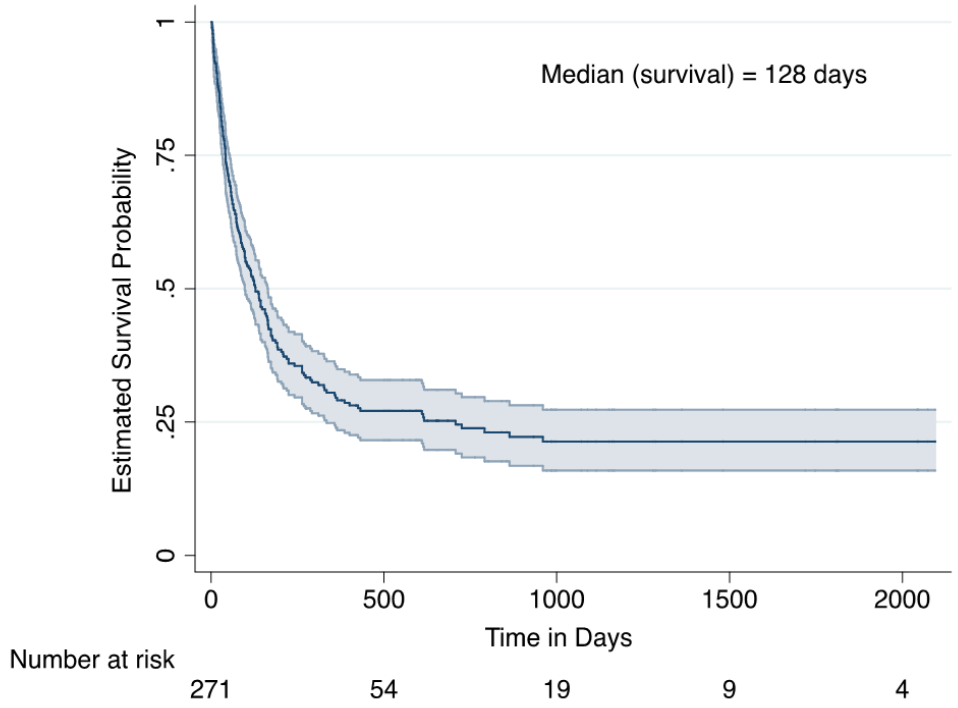
RELAPSE IS COMMON



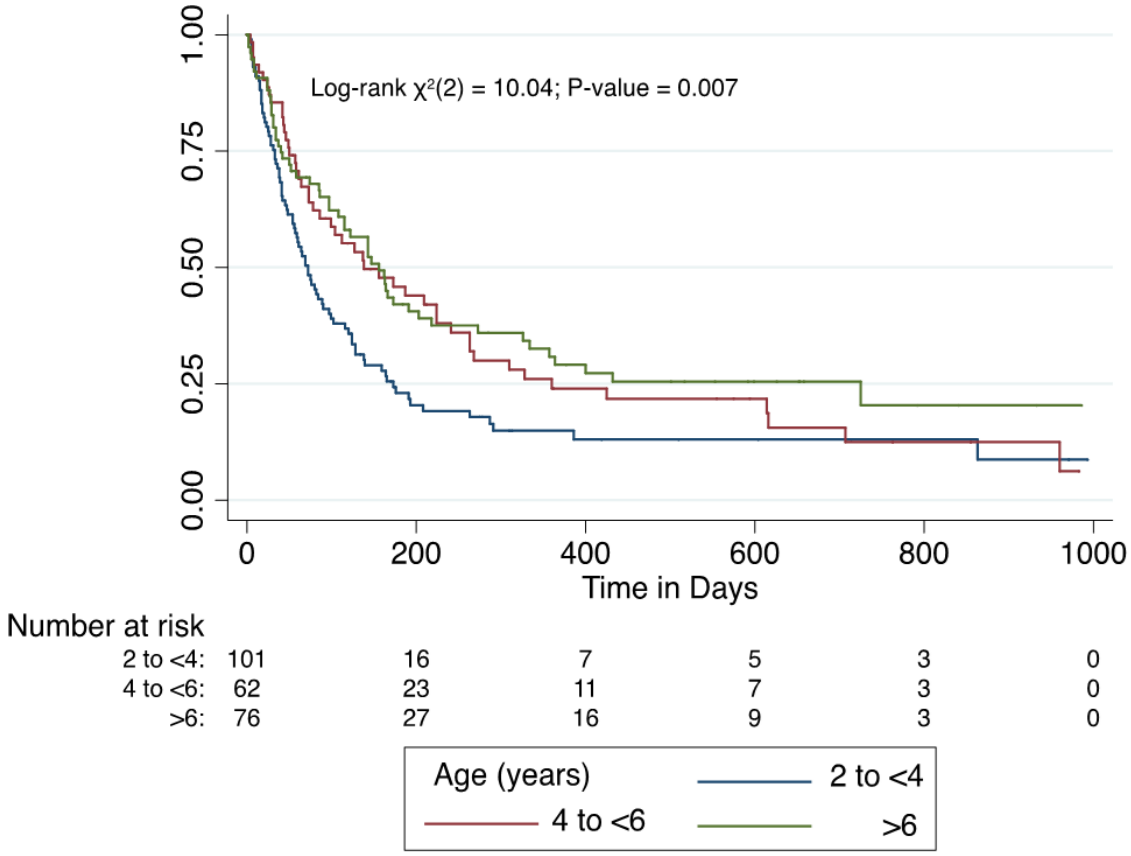
Chanchlani et al. Manuscript in submission

Key findings

Age is an important determinant of relapse frequency



Kaplan-Meier survival curve showing time to first observed relapse in the study treatment



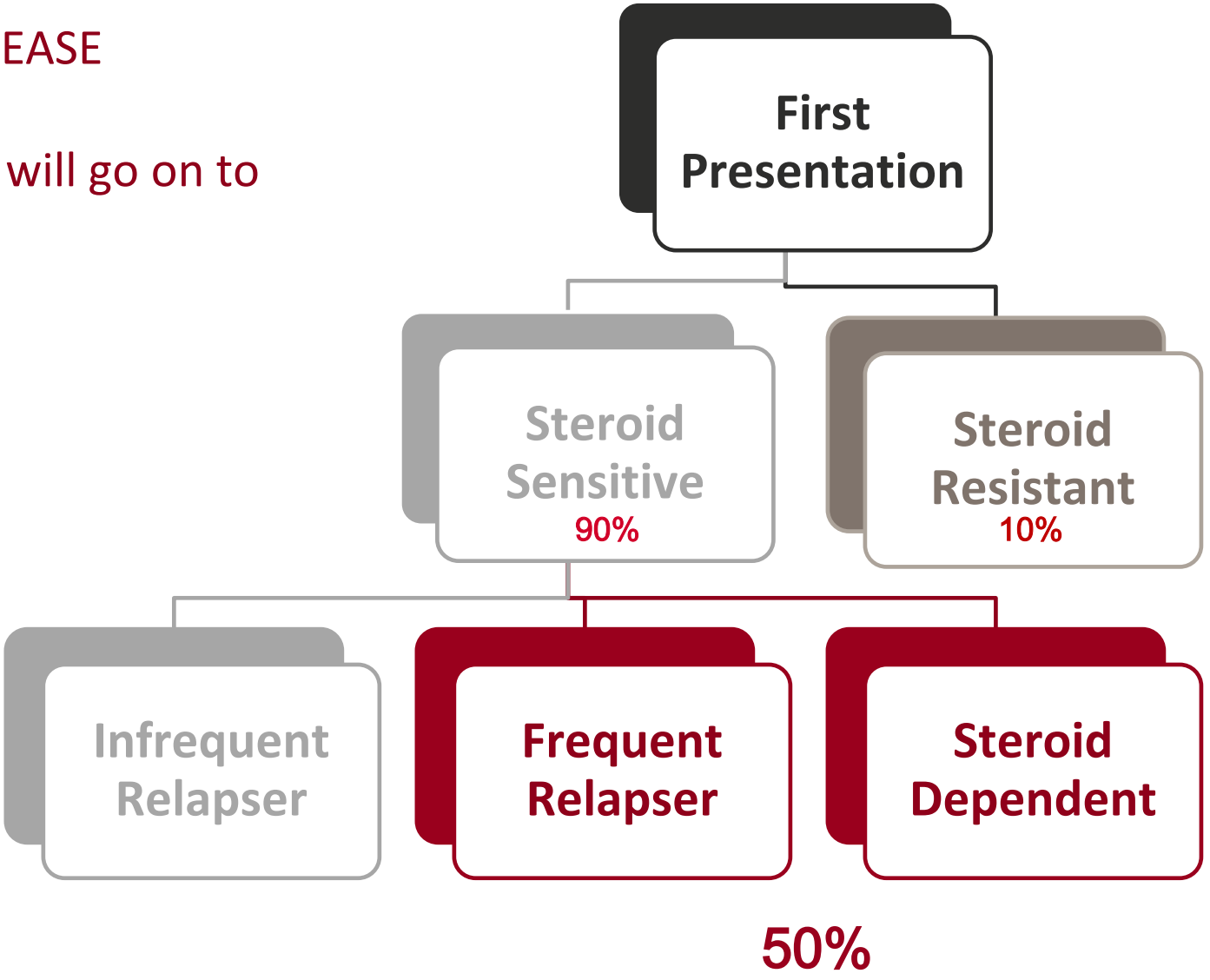
DEFINITIONS OF CLINICAL COURSE OF NEPHROTIC SYNDROME

TERMS	DEFINITION
Infrequently relapsing nephrotic syndrome	<2 relapses in 6 months following remission of the initial episode or fewer than 3 relapses in any subsequent 12 month period
Frequently relapsing nephrotic syndrome	≥ 2 relapses in 6 months following remission of the initial episode or ≥ 3 relapses in any 12 months
Steroid dependent nephrotic syndrome	2 consecutive relapses during recommended prednisone therapy for first presentation or relapse or within 14 days of discontinuation

IPNA CPR SSNS *Pediatr Nephrol* 2023

RELAPSING-REMITTING DISEASE

No markers to predict who will go on to have frequent relapses



RELAPSING-REMITTING DISEASE

Treatment with prednisone for each relapse

60 mg/m^2 until 3 days of remission of proteinuria

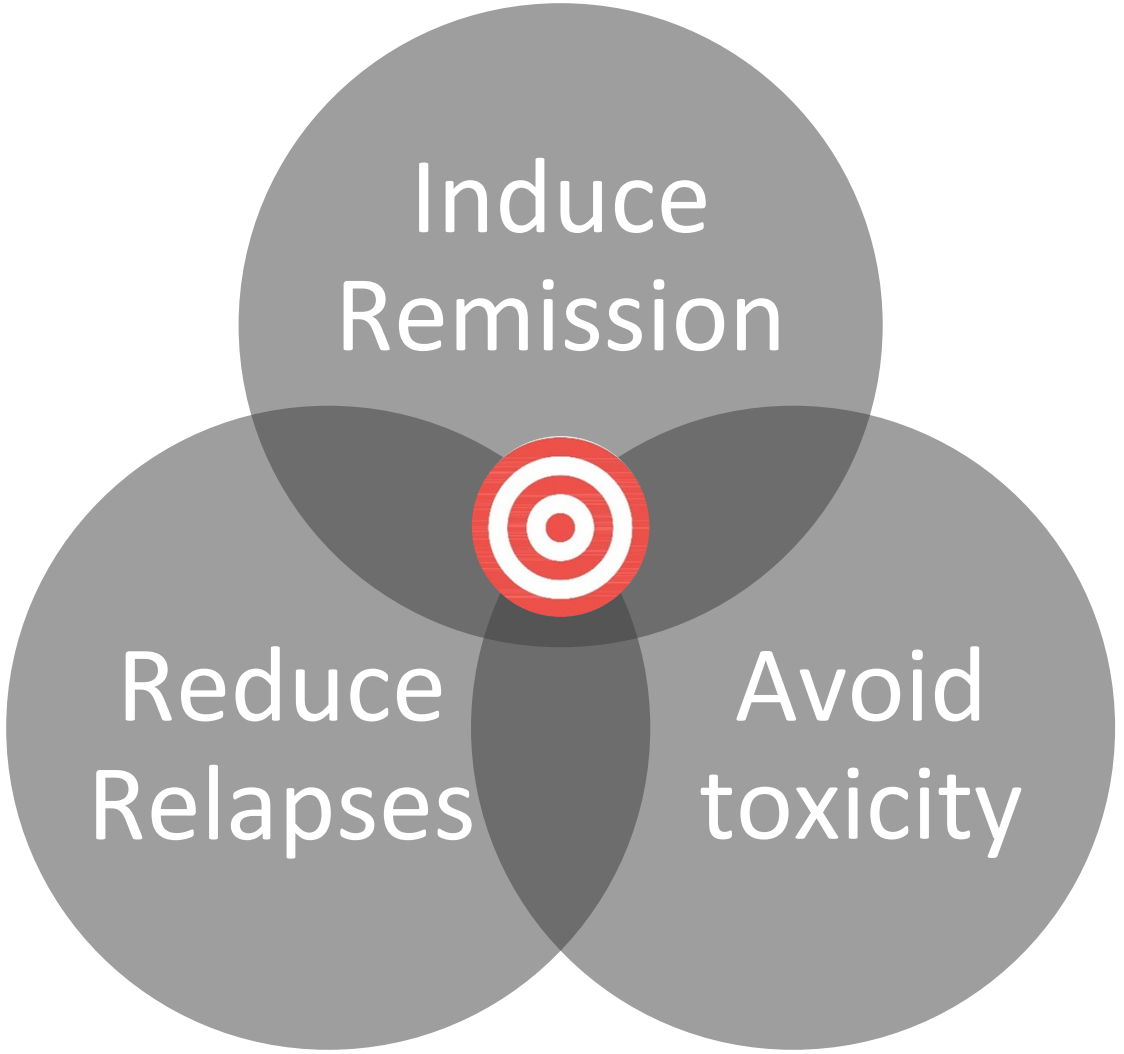
40 mg/m^2 every other day for at least 4 weeks, variable taper

STEROID TOXICITY

Complications	Reported prevalence
Overweight/obesity	8-23%
Growth failure	8-16%
Osteoporosis	13-63%
Fractures	20%
Cataracts	6-20%

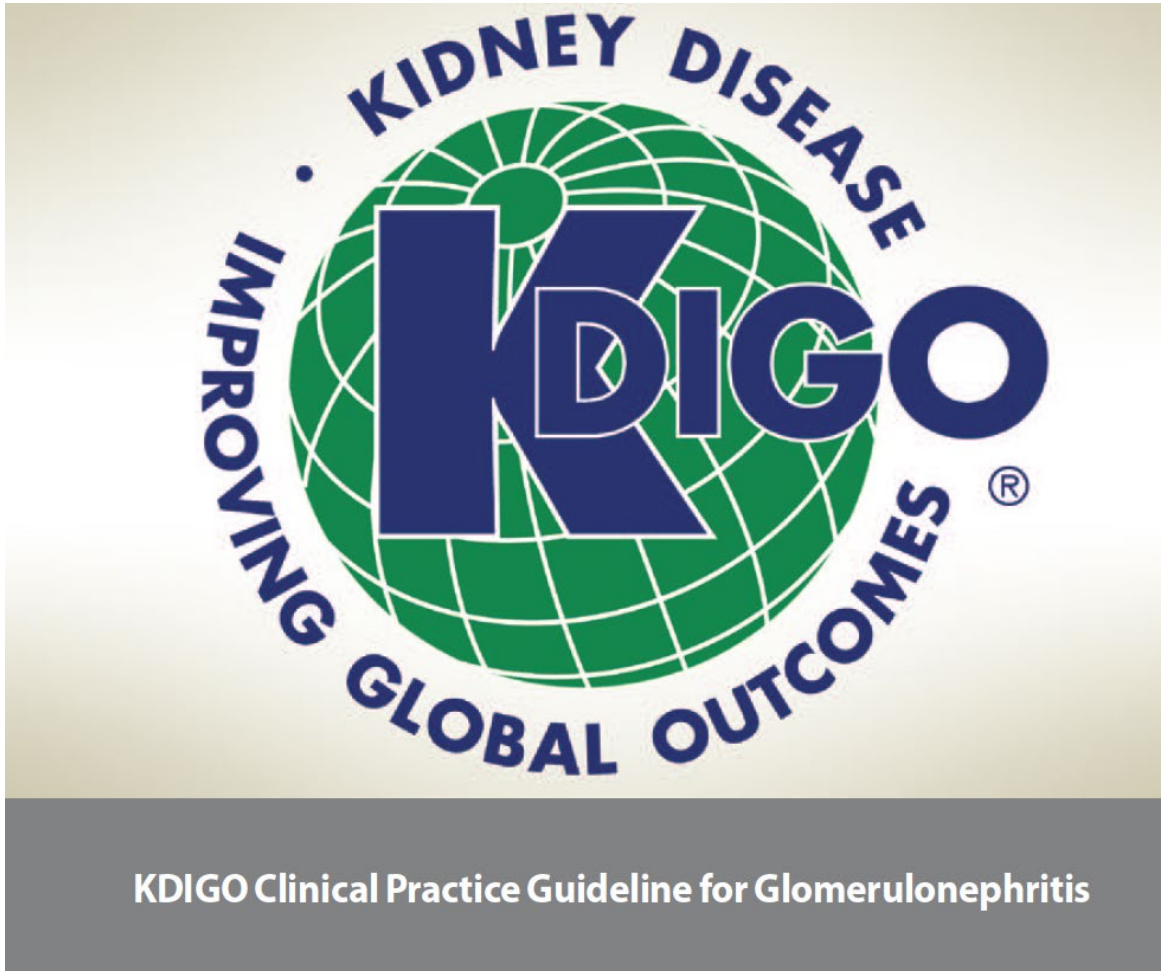
Hjorten Front Pediatr 2016

OVERALL TREATMENT GOALS



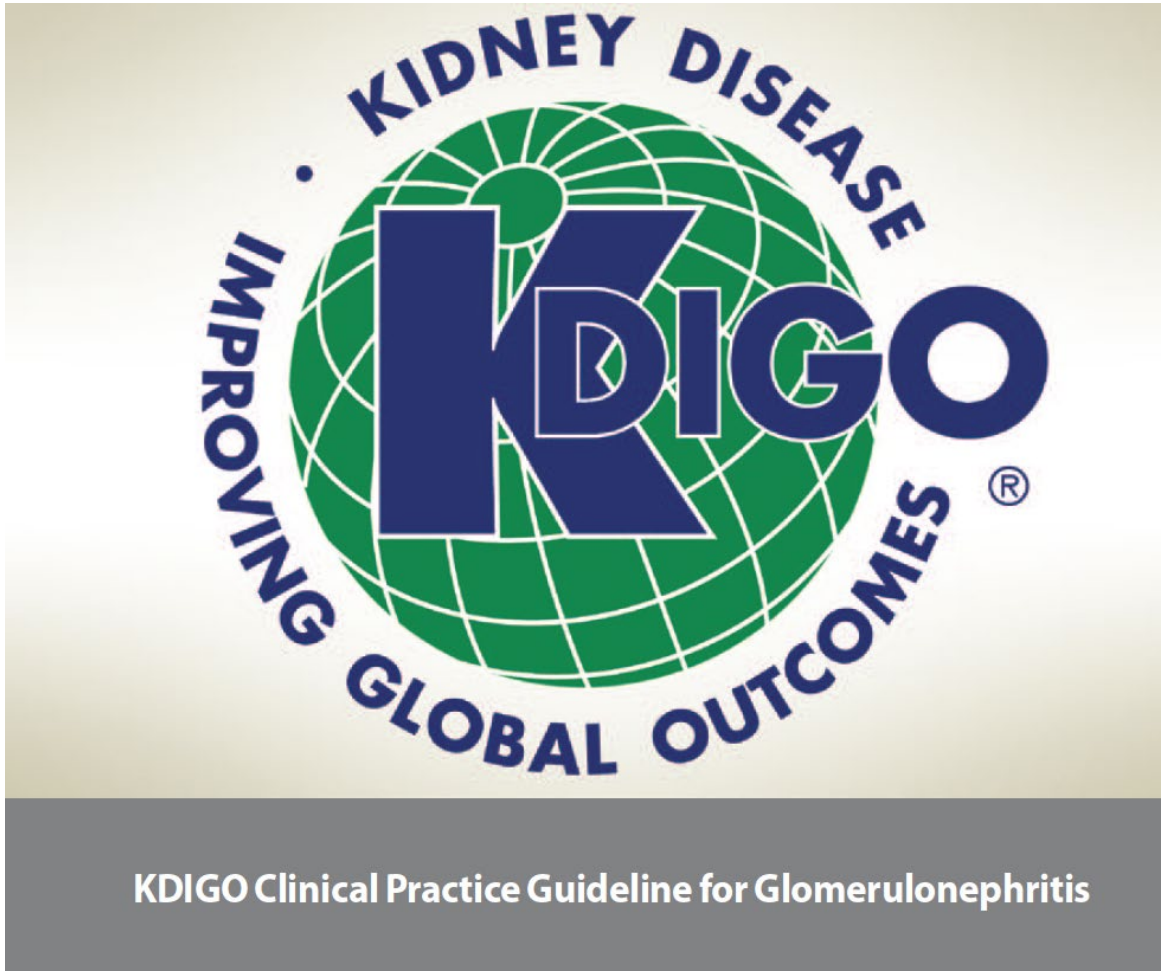
INTERNATIONAL TREATMENT GUIDELINES 2021

- Recommendation 4.3.2.2: 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).



INTERNATIONAL TREATMENT GUIDELINES 2021

- Practice Point 4.3.2.6: **Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and calcineurin inhibitor** is a decision that requires **careful consideration** of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences.



STEROID SPARING DRUGS

Prior decades	Present	Rarely Used
• Cyclophosphamide • Cyclosporine	• Tacrolimus • Mycophenolate mofetil • Rituximab	• Chlorambucil • Levamisole

What do the patients say?

“Doctors seemed stumped”
“Shots in the dark”
“Trial and error”

….Quotes from mother of a patient

Comparisons and descriptors of studies	Primary outcome	Pooled estimates (95% CI)	Grading of Evidence	Interpretation
MMF vs CSA ***2 RCTs*** (2013, 2008) 82 participants Events: 17 in MMF, 10 in CSA	Relapse yes/no by 12 months	RR 1.9 (0.66-5.46)	Low certainty	MMF may make little or no difference to number of relapsing patients within 12 months compared to CSA.
MMF vs CSA ***3 RCTs*** (2016, 2013, 2008) 142 participants	Relapse rate/year	MD 0.83 (0.33-1.33)	Low certainty	MMF may make little or no difference to relapse rate per year compared to CSA.
Alkylating agents (e.g. CYP) vs CSA ***2 RCTs*** (1988, 1992) 95 participants Events: 19 in alkylating agents, 43 in CSA	Relapse by end of therapy (6-9 months	RR 0.91 (0.55-1.48)	Low certainty	CSA when compared with CYP may make little or no difference to the risk of relapse by 6-9 months.

MMF: mycophenolate, CSA: cyclosporine, CYP: cyclophosphamide

Adapted from Larkins et al. 2020 Cochrane Review

Comparisons and descriptors of studies	Primary outcome	Pooled estimates (95% CI)	Grading of Evidence	Interpretation
Low risk of bias Levamisole vs Steroids or Placebo or both, or no treatment ***3 RCTs*** (1991, 2015, 1993) 208 participants Events: 71 in Lev, 89 in control	Relapse during treatment	RR 0.84 (0.57-1.25)	Low certainty	Levamisole when compared with steroids, or placebo or both, or no treatment may reduce the number of children with relapse during treatment.
High risk of bias Levamisole vs Steroids or Placebo or both, or no treatment ***5 RCTs*** (2006, 1996, 2006, 2001, 1994) 266 participants	Relapse during treatment	RR 0.36 (0.25, 0.53)	Low certainty	Levamisole when compared with steroids, or placebo or both, or no treatment may reduce the number of children with relapse during treatment.

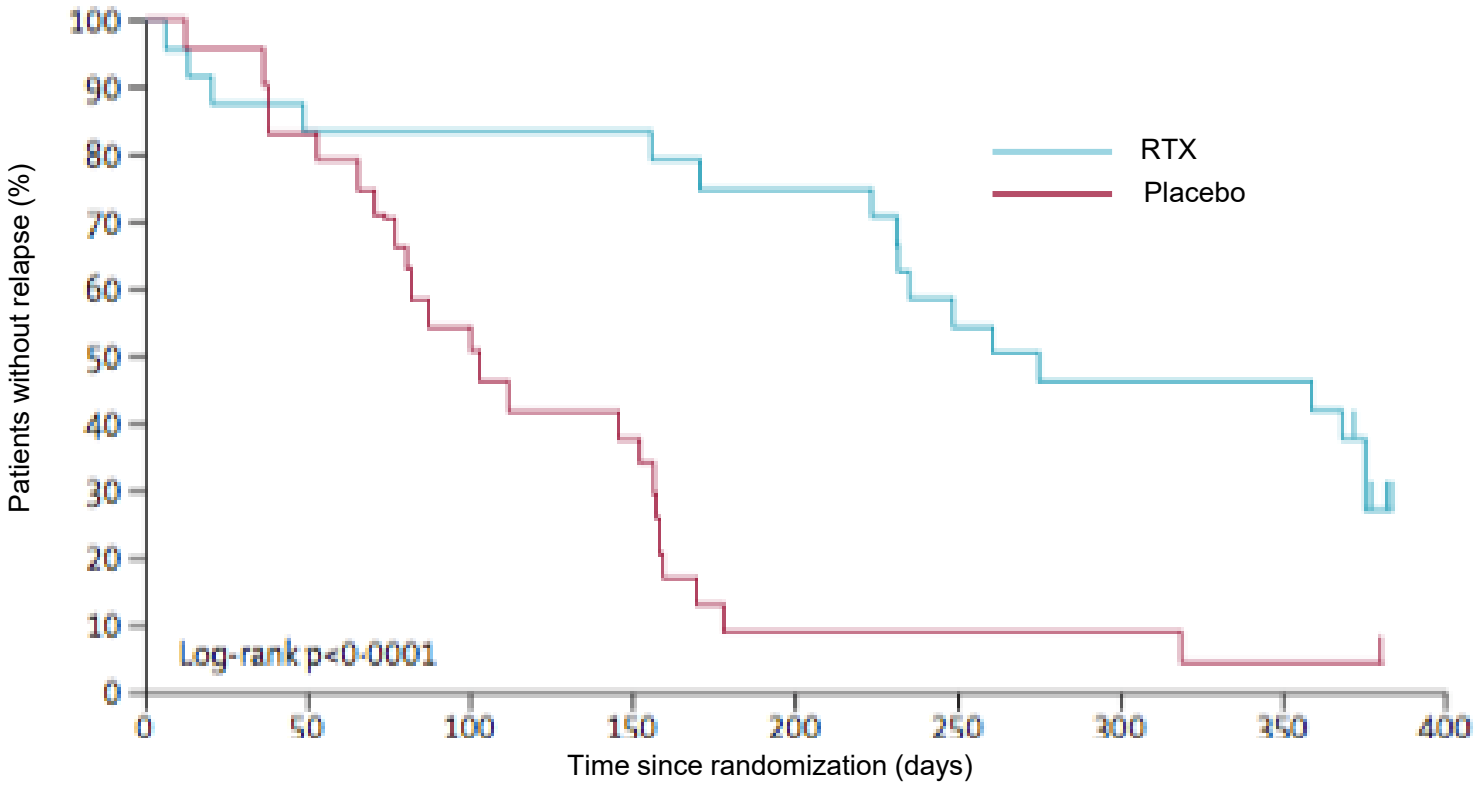
Adapted from Larkins et al. 2020 Cochrane Review

Comparisons and descriptors of studies	Primary outcome	Pooled estimates (95% CI)	Grading of Evidence	Interpretation
Levamisole vs cyclophosphamide ***2 RCTs*** (2001, 2005) 97 participants	Relapse at end of therapy	RR 2.14 (0.22-20.95)	Low certainty	Levamisole when compared with cyclophosphamide may make little or no difference in children with relapse at end of therapy

Adapted from Larkins et al. 2020 Cochrane Review

Rituximab (RTX) known to maintain remission
Implicates B cells in pathogenesis

- **RTX**chimeric monoclonal antibody against CD20 on B cells



Iijima et al. Lancet 2014

Comparisons and descriptors of studies	Primary outcome	Pooled estimates (95% CI)	Grading of Evidence	Interpretation
RTX vs Placebo or Control ***3 RCTs*** (2015, 2011, 2011) 132 participants	Relapse at 3 months	RR 0.32 (0.14-0.70)	Moderate certainty	RTX used alone or with prednisone and CNI, versus placebo, prednisone, or CNI and prednisone probably reduces number of children experiencing relapse at 3 months
RTX vs Placebo or Control ***5 RCTs*** (2018, 2015, 2018, 2011, 2018) 269 participants	Relapse at 6 months	RR 0.23 (0.12-0.43)	Moderate certainty	
Alkylating agents (e.g. CYP) vs CSA ***3 RCTs*** (2015, 2018, 2011) 198 participants	Relapse by 12 months	RR 0.63 (0.42-0.93)	Moderate certainty	

Adapted from Larkins et al. 2020 Cochrane Review

Rituximab

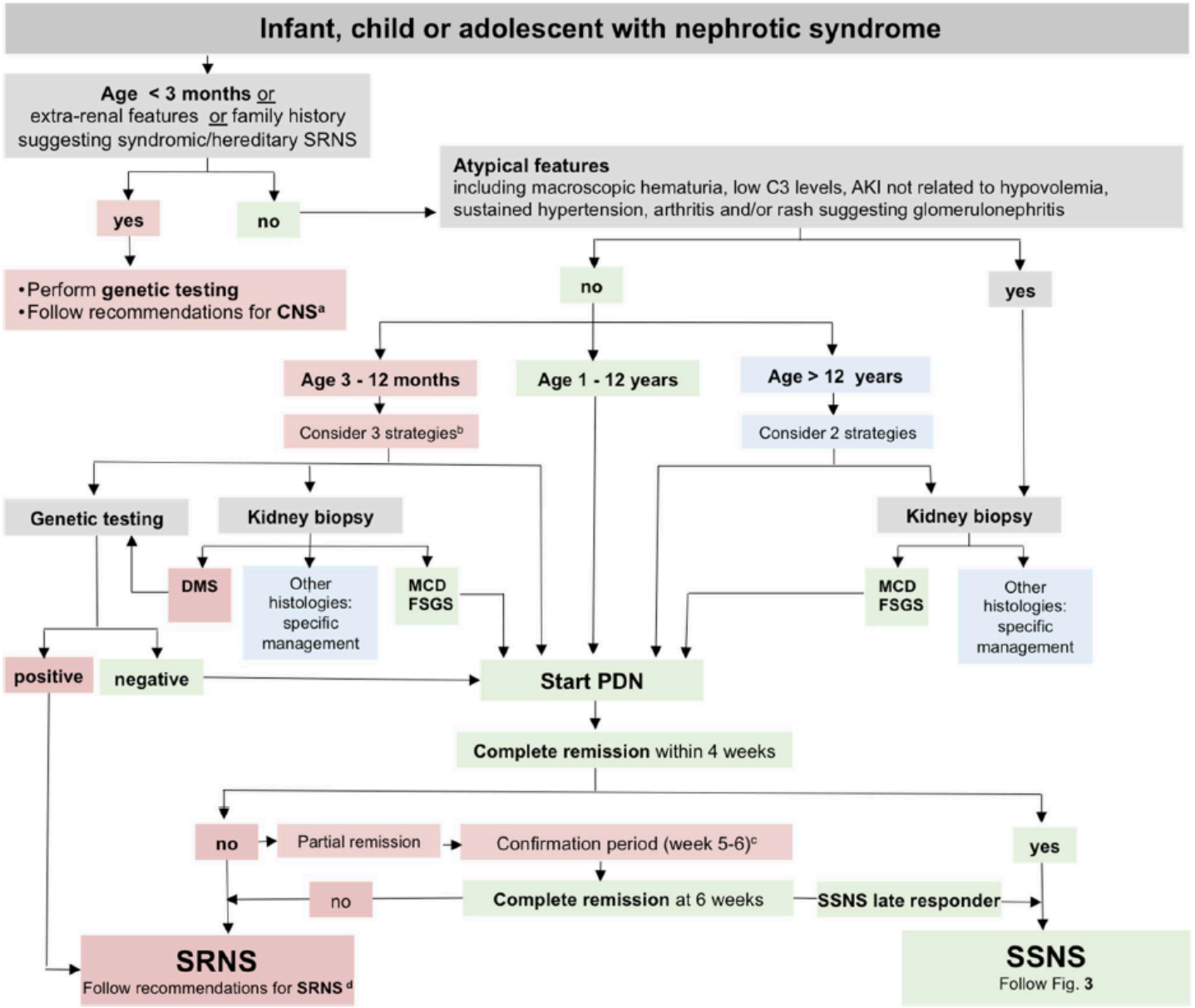
- Hypogammaglobulinemia
- Infection
- Pulmonary
- Cost

Prednisone not helpful to prevent relapses during URTI

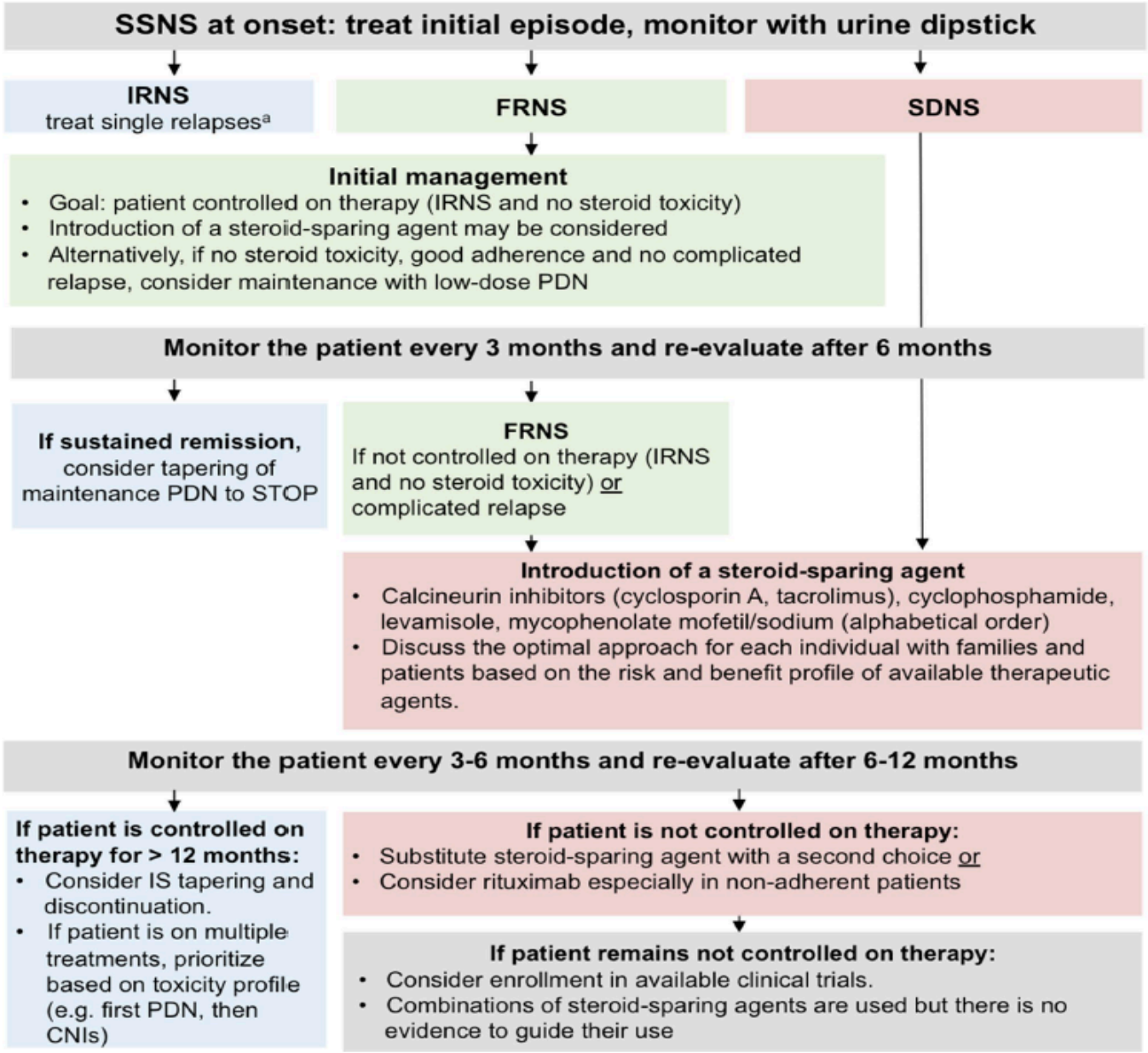
- PREDNOS-2 Trial Christian et al *JAMA Pediatr* 2022
- Double Blind RCT, placebo controlled
- 365 children in the UK with SSNS, randomized to prednisolone (182) or placebo (183)
- Followed for 12 months
- Outcome is an upper respiratory tract infection (defined criteria)

Proportion with URTI	Prednisolone (n =134)	Placebo (n=137)
No	75 (57.3%)	73 (55.7%)
Yes	56 (42.7%)	58 (44.3%)

RR = 0.96 (0.73-1.37)
p>0.05



IPNA Clinical Practice Guideline
Pediatr Nephrol 2023



Management of steroid sensitive nephrotic syndrome
At a glance

Questions

https://www.cbc.ca/news/canada/calgary/alberta-children-s-hospital-covid-surgery-1.6180991

CHALLENGES AND OPPORTUNITIES IN CHILDHOOD NEPHROTIC SYNDROME

Steroid resistant

Susan M. Samuel, MD FRCPC MSc

Professor, Canada Research Chair

3– Day Paediatric Nephrology Workshop
19 – 21 June 2023
University College Hospital
Ibadan, Nigeria

UNIVERSITY OF CALGARY

CHILDNEPH

Case Presentation

Patient Alberta – 3 year old girl

- History of presenting illness
  - Unwell for 2 weeks with fatigue
  - 10 days of facial oedema
  - Some loose stools
  - No rash
- **Past History**
  - Pneumonia

Examination

- Oedema – puffy eyes
- 16.5 kg (90th centile)
- 98.5 cm (90th centile)
- 110/63 mm Hg (95th centile 109/68 mmHg)

What would you do next?

- A diagnostic test was done.

Investigations

- Urinalysis
  - SG 1.020
  - Protein >3 g/L
  - Blood Moderate
  - RBCs 6 – 10 cells/hpf
  - WBCs 3 – 5 cells/hpf
  - Casts None

Investigations - 2

Haemoglobin	89	g/L
MCV	62	fL
WBC	10.6	$x10^9/L$
Creatinine	10	umol/L
Urea	4.1	mmol/L
Sodium	133	mmol/L
Albumin	9	g/L
Urine PCR	2104	mg/mmol

Other Investigations

Cholesterol	10.44	mmol/L	
C_3	1.22	g/L Ref Range	0.6 – 1.6
C_4	0.32	g/L	0.1 – 0.4
IgA	0.57	g/L	0.35 – 2.4
ANCA	neg		
Anti-MPO	<2.0	KEU/L	<5
Anti-PR3	<2.0	KEU/L	<5
ANA	neg		

What would you do next?

Initial Management

- Low Na diet

IV Methylprednisolone 150 mg	(225 mg/m^2/dose)	one dose
Prednisone 17 mg bid	(2 mg/kg/day)	(50 mg/m^2/day)
Iron elemental 25 mg bid	(3 mg/kg/day)	
Albumin 65 ml (25%) x 4	(1 g/kg/dose)	

plus fuorsemide 1 mg/kg half way through infusion

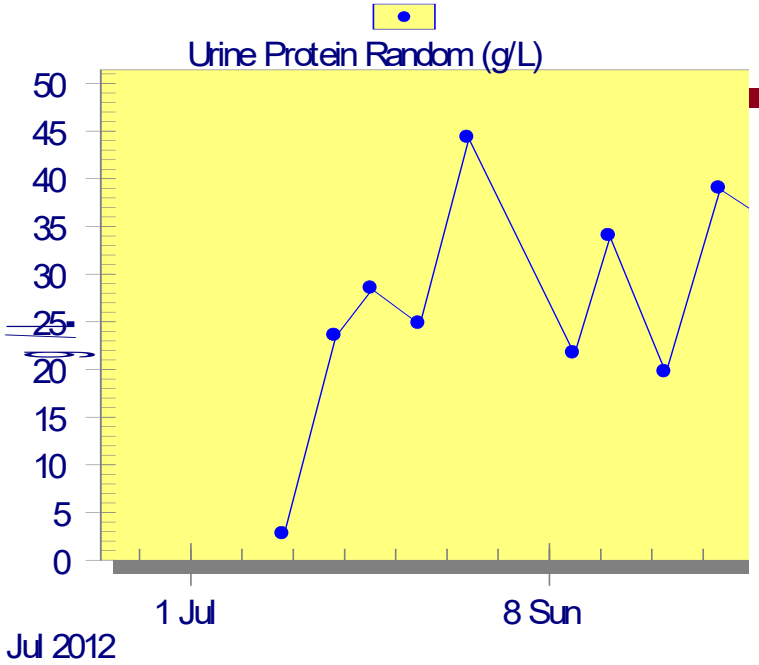
Careful History and Physical Exam

- History
  - Family history, consanguinity, birth history
  - Risk factors (secondary causes sickle cell, HIV, Hep B, malaria, parvovirus B19, CMV, syphilis, TB)
  - Other glomerular diseases (SLE, membranous, C3 GN)
  - Infections, adrenal insufficiency

- Physical exam
  - Skeletal, neuro, eye, ear, congenital anomalies, ambiguous genitalia
  - Pubertal exam

Other laboratory tests to consider

- Liver tests, lipid profile, clotting
- TSH
- Viral tests (Hep Bs Ag, anti-HCV-IgG, syphilis, HIV)
- Chest Xray
- Renal ultrasound


Urine Protein Random (g/L)
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25
20
15
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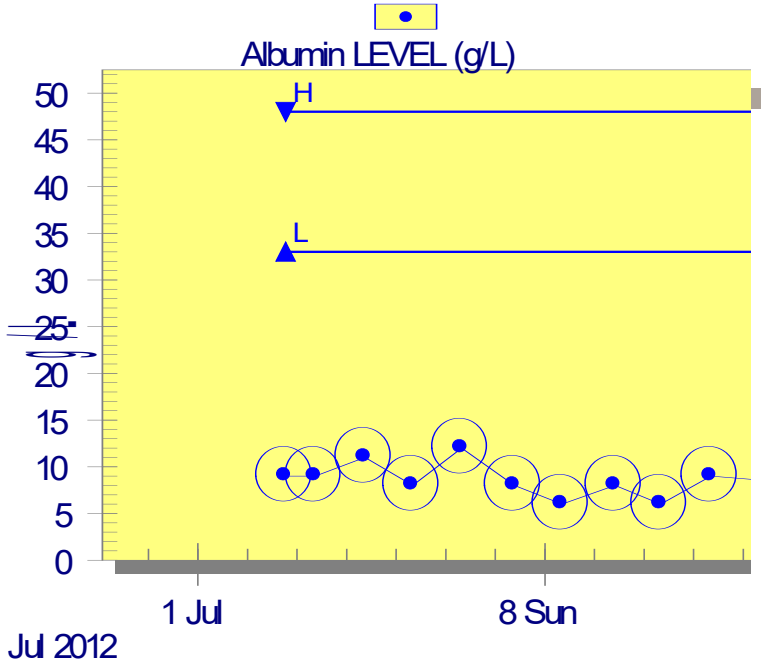
1 Jul
8 Sun
Jul 2012


Albumin LEVEL (g/L)
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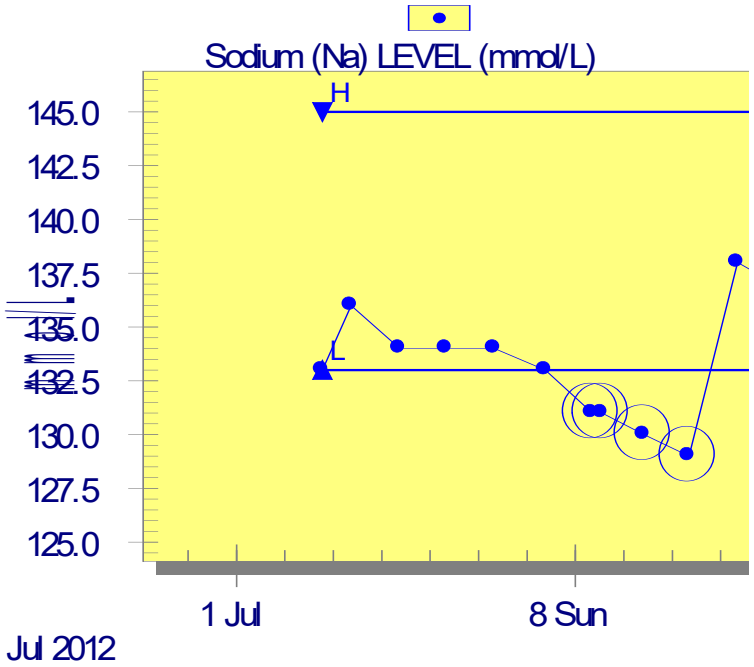
Sodium (Na) LEVEL (mmol/L)
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132.5
130.0
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1 Jul
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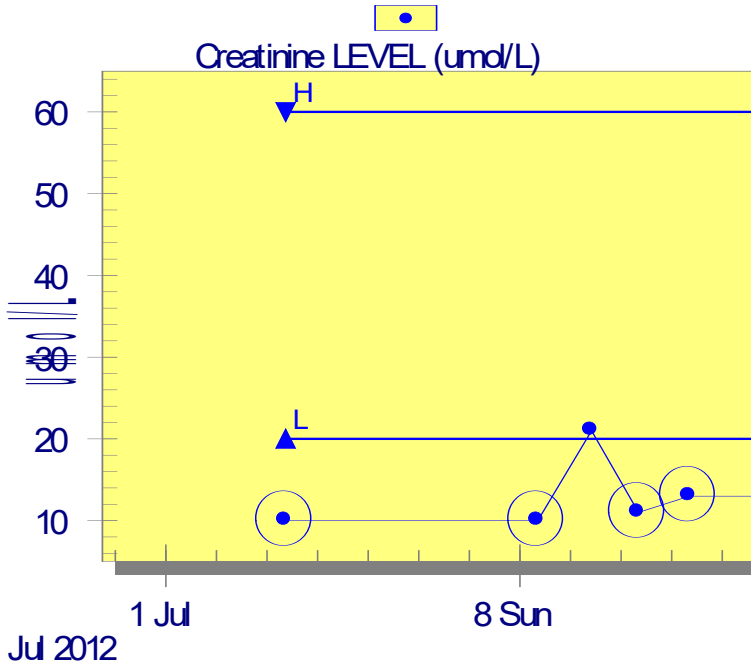
Jul 2012


Creatinine LEVEL (umol/L)
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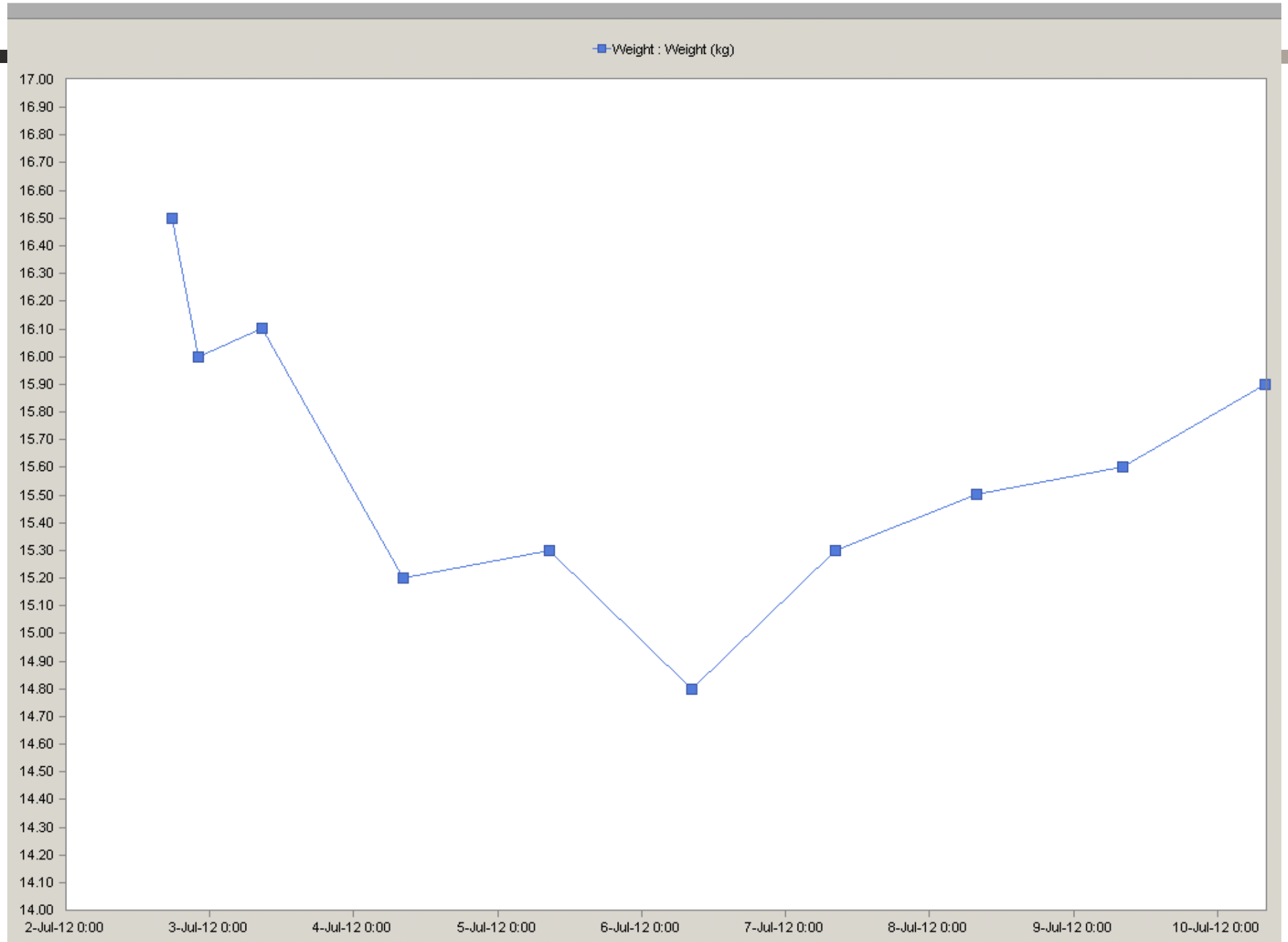
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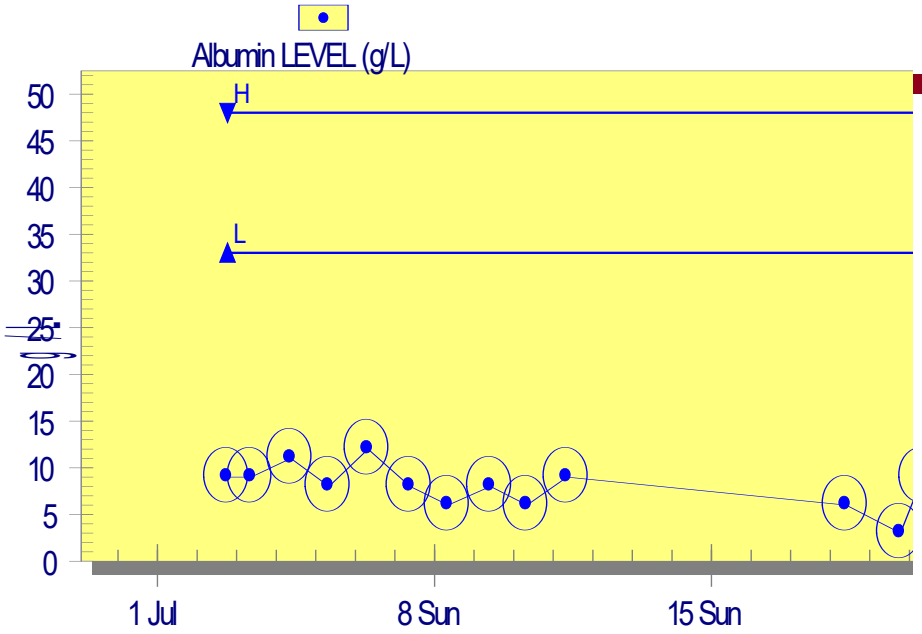
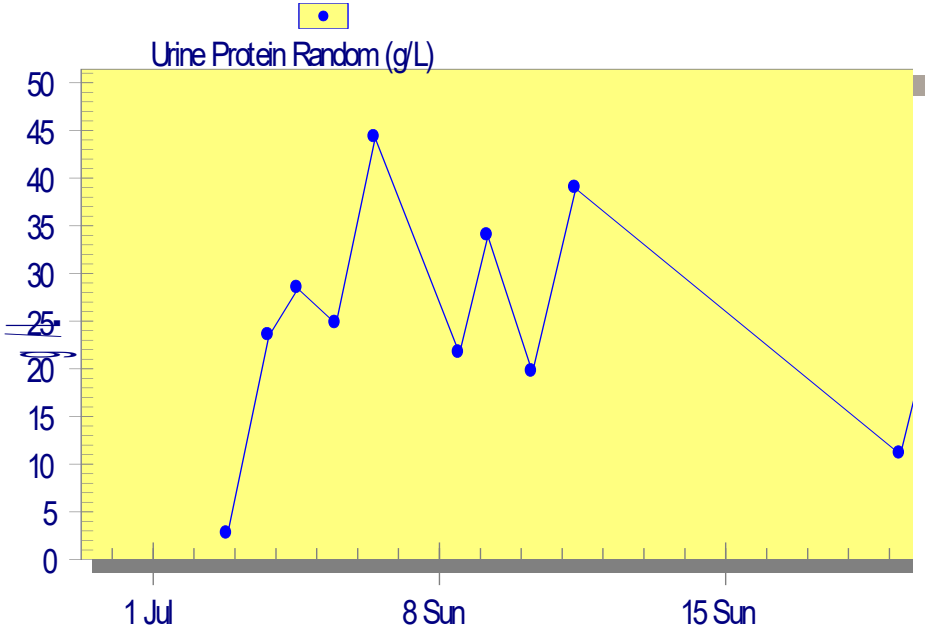
Discharge Medications

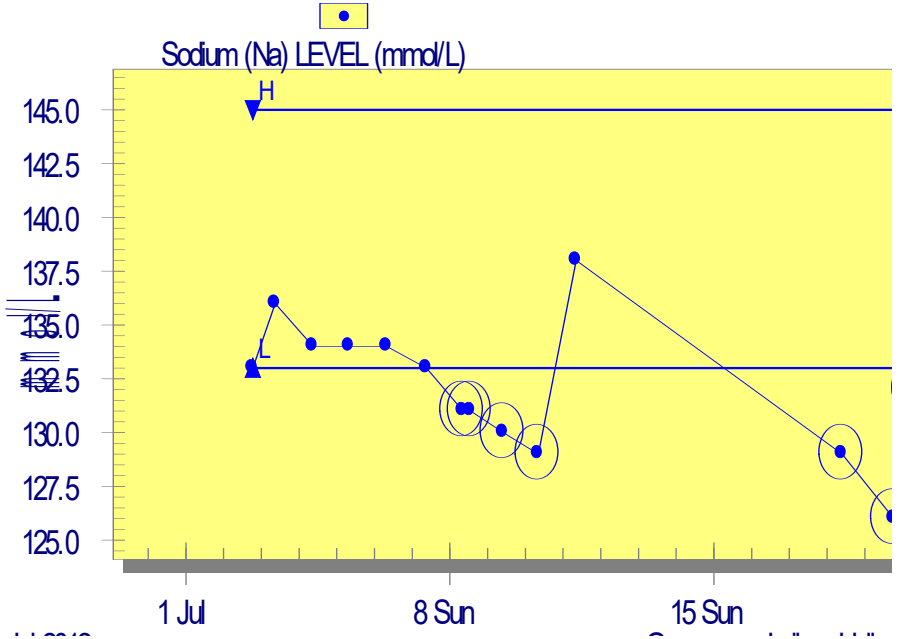
- Amlodipine 1.5 mg bid (0.2 mg/kg/day)
- Iron elemental 25 mg bid (3 mg/kg/day)
- Vitamin D 800 units daily
- Prednisone 20 mg bid (2.4 mg/kg/day) (60 mg/m^2/day)

Progress

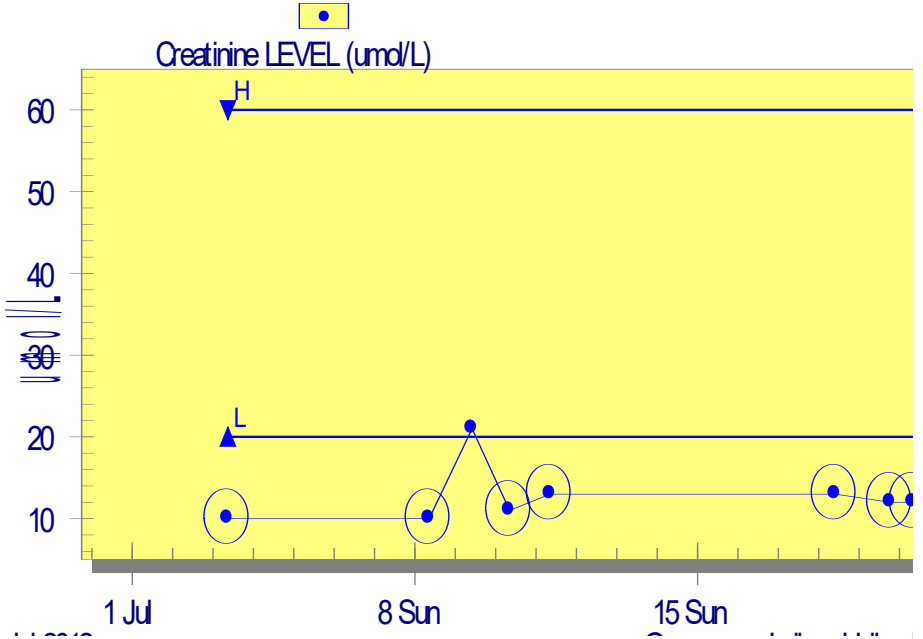




Sodium (Na) LEVEL



Creatinine LEVEL



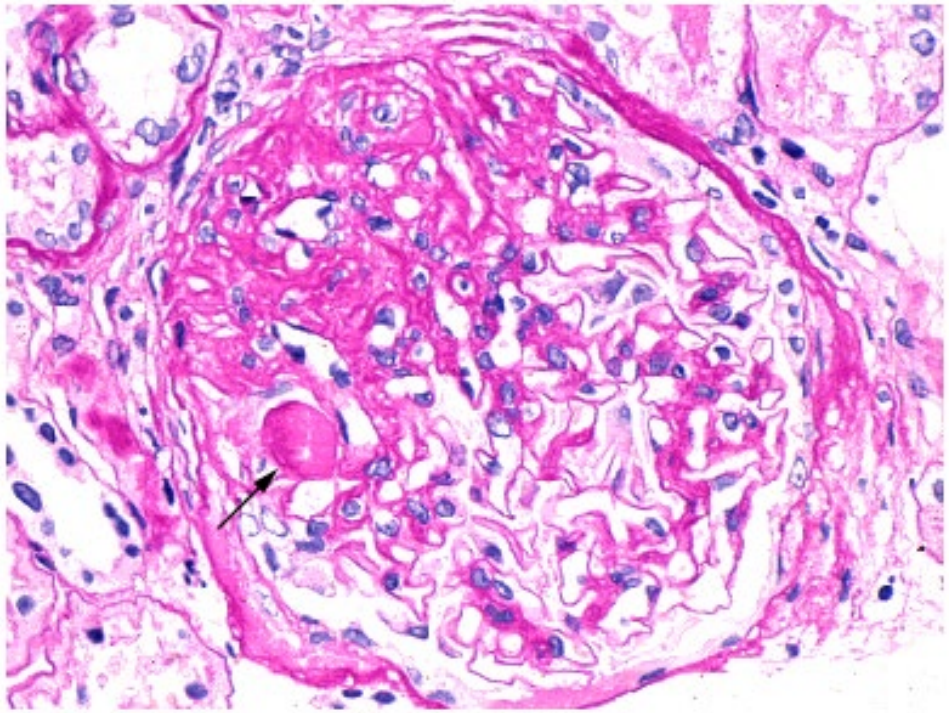
What Next?

Re-admitted

- Weight 18.2 kg (initially 16.5 kg)
- More 25% Albumin
- A diagnostic test was done…

Moderate FSGS

Elect



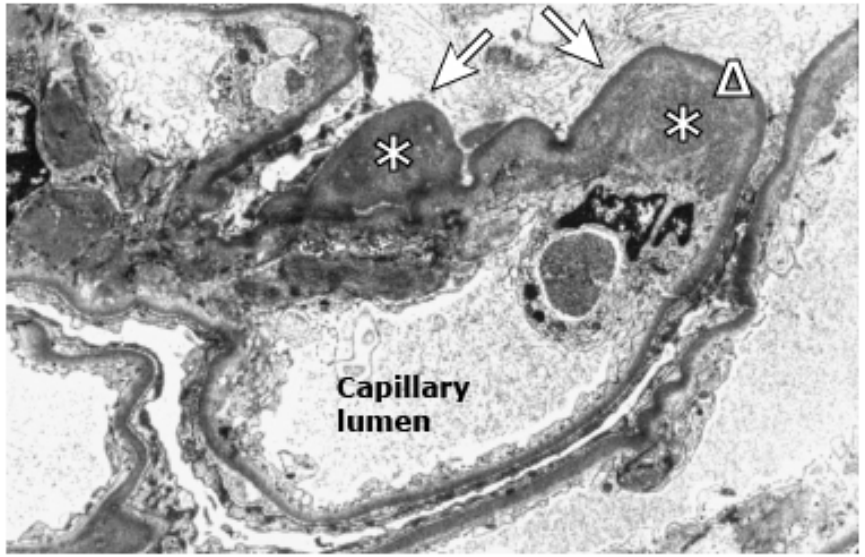
Light micrograph in focal segmental glomerulosclerosis (FSGS) shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal.

- 44 glomeruli, none of which are globally sclerosed
- 11 glomeruli show segmental sclerosis
- Mild mesangial proliferation and 2 glomeruli show segmental extracapillary proliferation or crescents
- No spikes or duplications are seen on silver stains.
- The interstitium shows very mild focal atrophy

Uptodate.com

Immunofluorescence

- IgG: negative
- IgA: negative
- IgM: 3+ focal and segmental smudgy staining
- kappa: 2+ segmental smudgy staining
- lambda: 1+ segmental smudgy staining
- fibrinogen: negative
- C3c: 1+ segmental staining
- C1q: negative



Electron micrograph in focal segmental glomerulosclerosis shows diffuse epithelial cell foot process fusion with occasional loss of the epithelial cells (arrows). The other major finding is massive subendothelial hyaline deposits (asterisk) under the glomerular basement membrane (Δ). These deposits reflect insudation of plasma proteins, not the deposition of immunoglobulins. These deposits contribute to narrowing of the capillary lumens.

- Extensive foot process effacement with prominent microvillous transformation.
- Small cytoplasmic vacuoles are seen in some podocytes, as well as fibrillary cytoplasmic densities.
- Rare, small deposits are seen in mesangial areas, but no prominent immune complex-type deposits are seen.

So…what to do next?

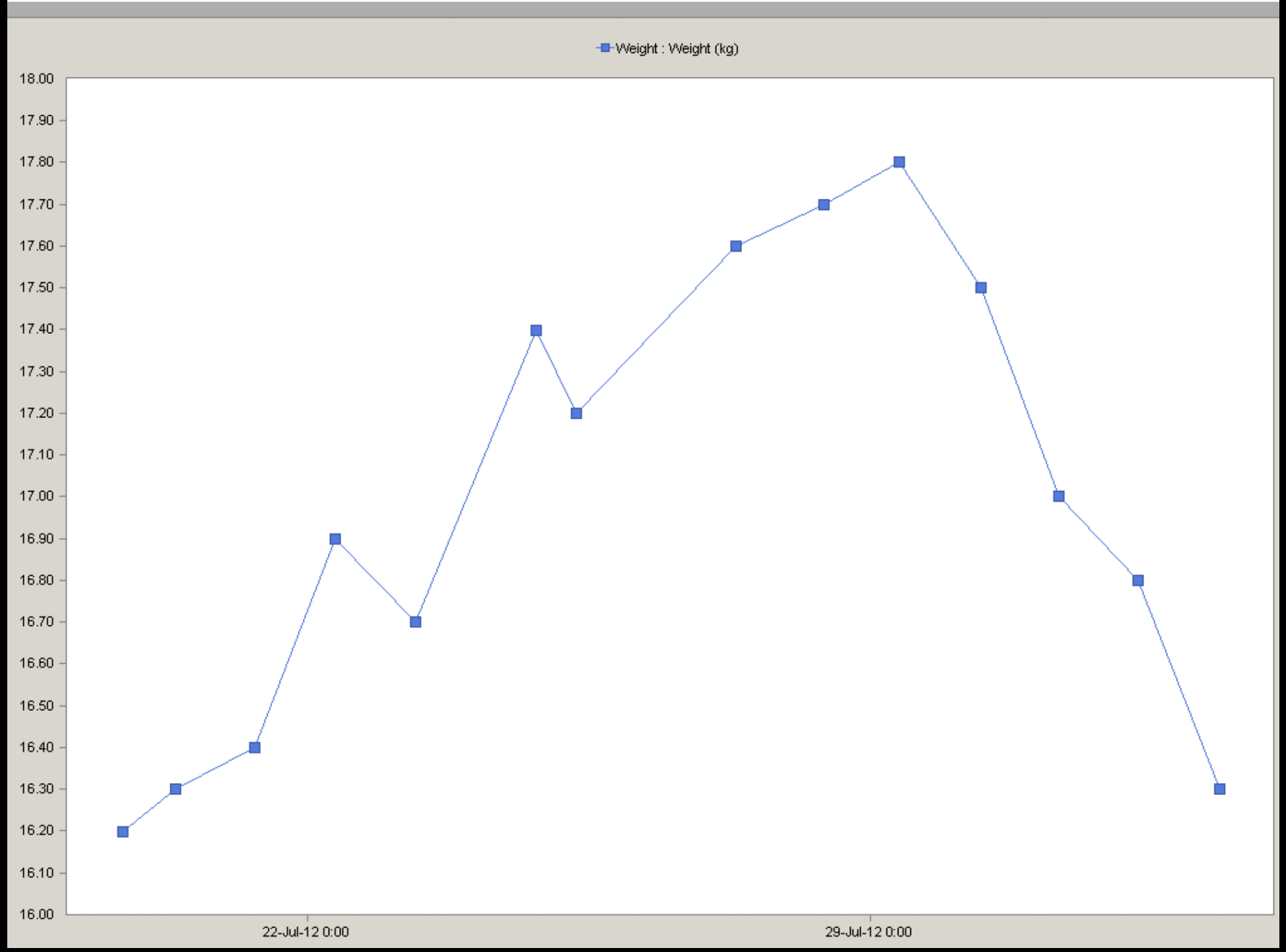
IPNA Clinical Practice Guideline
Pediatr Nephrol 2020

First-line immunosuppressive treatment in children with SRNS

- We recommend that CNI (cyclosporine or tacrolimus) should be the first-line immunosuppressive therapy in children with SRNS and started once the diagnosis is confirmed (Fig. 2) (grade B, moderate recommendation).
- We suggest tapering PDN treatment once diagnosis of SRNS is established and discontinuing PDN therapy after 6 months (grade D, weak recommendation).
- We recommend withholding or delaying CNI treatment in patients with an eGFR < 30 ml/min/1.73 m^2, AKI, and/or uncontrolled hypertension (grade X, strong recommendation).
- We recommend withholding CNI and stopping PDN treatment in patients with evidence for a monogenic form of SRNS (grade B, moderate recommendation).
- When CNIs are not available or unaffordable, we suggest using cyclophosphamide (CPH) [intravenous or po] with or without high-dose steroids (grade D, weak recommendation).
- We recommend making patients and families aware of potential side effects of immunosuppressive medication as given in Table 4 (grade X, strong recommendation).

Treatment

- Amlodipine 1.5 mg bid (0.2 mg/kg/day)
- Enalapril 3.5 mg bid (0.4 mg/kg/day)
- Cyclosporin A 40 mg bid
- Enoxaparin 15 mg daily
- Hydrochlorothiazide 18 mg bid (2 mg/kg/day)
- Iron elemental 37.5 mg bid (3 mg/kg/day)
- Penicillin 150 mg bid
- Prednisone 40 mg alt days (2.4 mg/kg/day or 60 mg/m^2/day)
- Albumin 25% 50 ml bid with furosemide 1 mg/kg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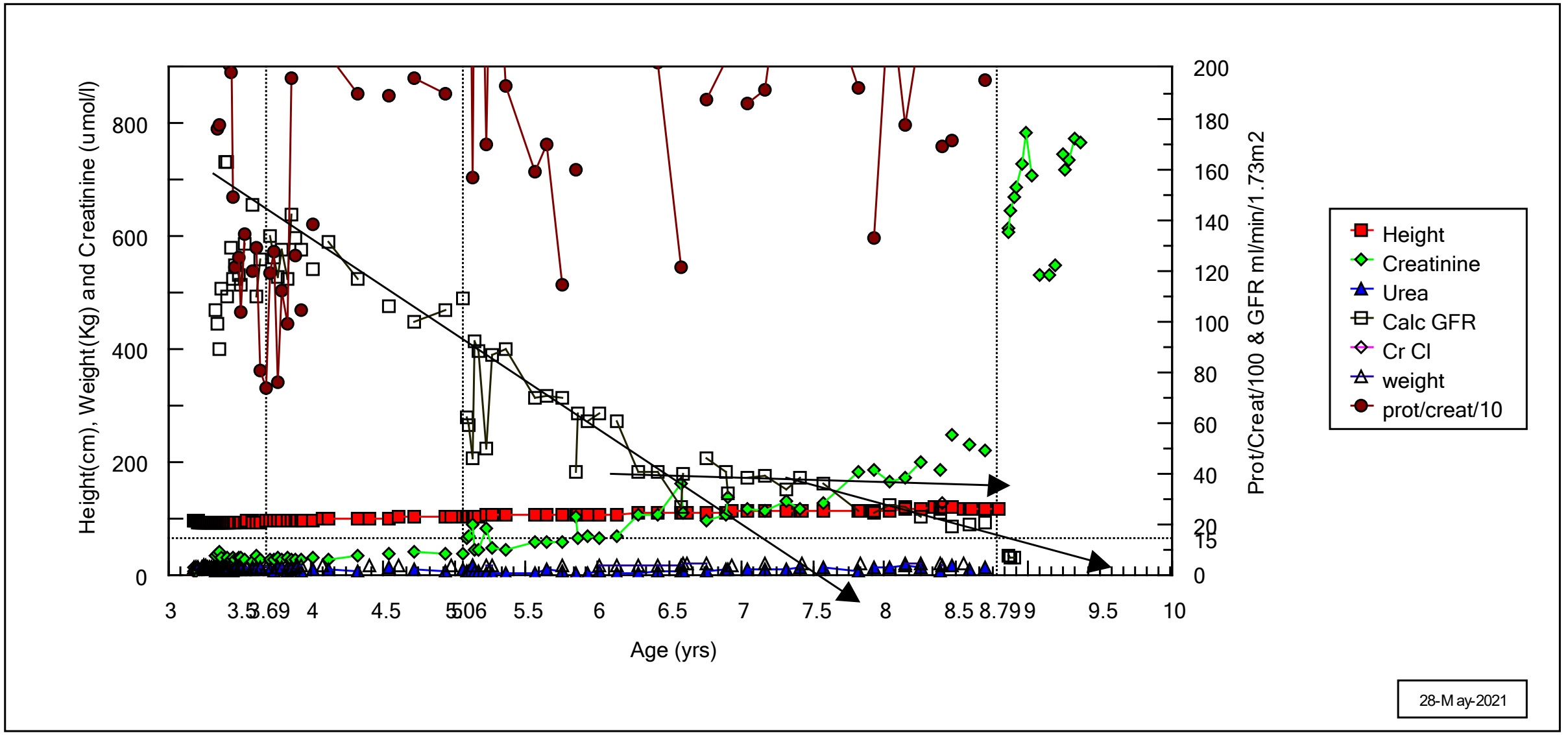
Longer Term

- What would you advise the family?

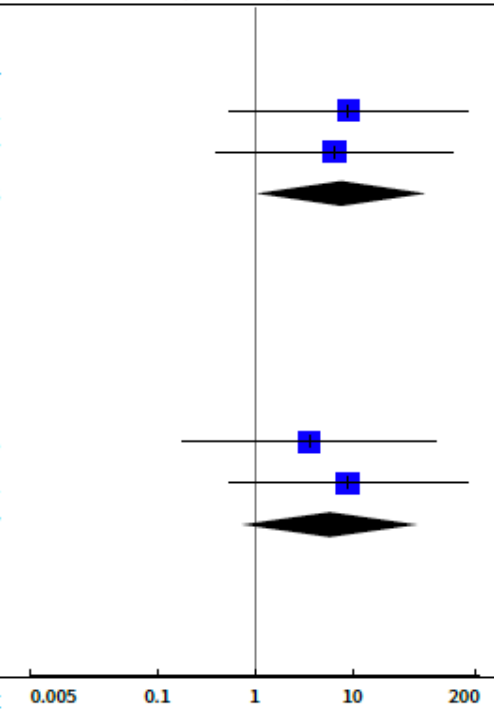

Height(cm), Weight(Kg) and Creatinine (umol/l)
Prot/Creat/100 & GFR ml/min/1.73m2
Age (yrs)
Height
Creatinine
Urea
Calc GFR
Cr Cl
weight
prot/creat/10
28-May-2021

More on Alberta’s story later

First line treatment for SRNS – all pathologies and FSGS, full remission

Analysis 1.1. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 1 Complete remission.

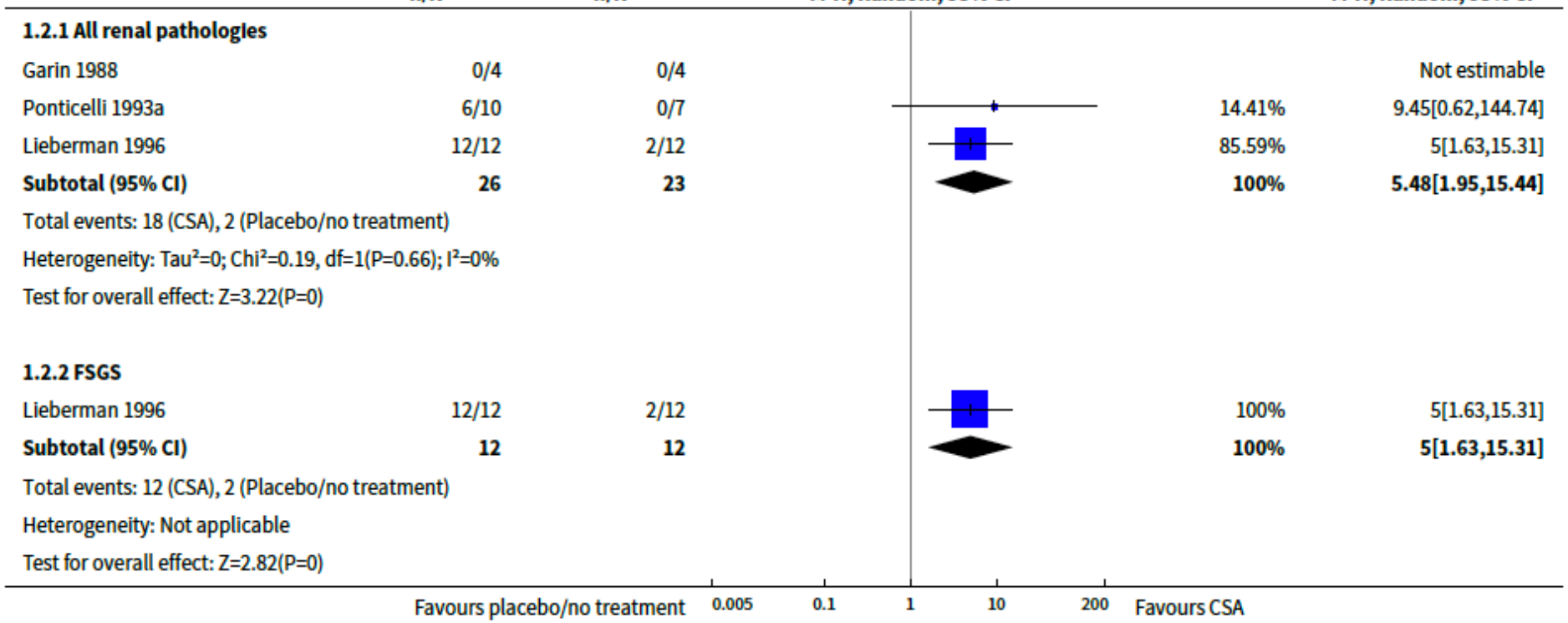
Study or subgroup	CSA n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All renal pathologies					
Garin 1988	0/4	0/4			Not estimable
Lieberman 1996	4/12	0/12		49.24%	9[0.54,150.81]
Ponticelli 1993a	4/10	0/7		50.76%	6.55[0.41,105.1]
Subtotal (95% CI)	**26**	**23**		**100%**	**7.66[1.06,55.34]**
Total events: 8 (CSA), 0 (Placebo/no treatment)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.02$, df=1(P=0.87); $I^2=0\%$					
Test for overall effect: Z=2.02(P=0.04)					
1.1.2 FSGS					
Ponticelli 1993a	1/4	0/5		47.35%	3.6[0.18,70.34]
Lieberman 1996	4/12	0/12		52.65%	9[0.54,150.81]
Subtotal (95% CI)	**16**	**17**		**100%**	**5.83[0.75,45.09]**
Total events: 5 (CSA), 0 (Placebo/no treatment)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.2$, df=1(P=0.65); $I^2=0\%$					
Test for overall effect: Z=1.69(P=0.09)					



First line treatment – complete or partial remission as outcome

Analysis 1.2. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 2 Complete or partial remission.

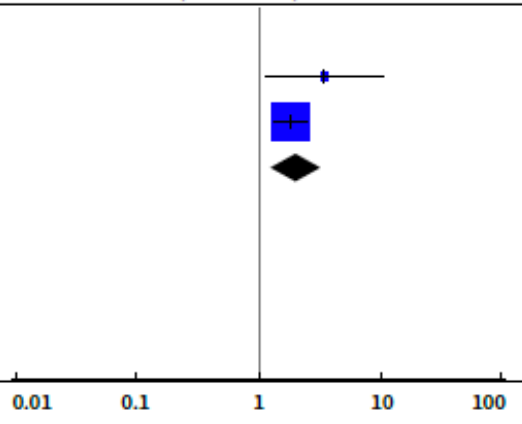
Study or subgroup	CSA n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 All renal pathologies					
Garin 1988	0/4	0/4			Not estimable
Ponticelli 1993a	6/10	0/7		14.41%	9.45[0.62,144.74]
Lieberman 1996	12/12	2/12		85.59%	5[1.63,15.31]
Subtotal (95% CI)	**26**	**23**		**100%**	**5.48[1.95,15.44]**
Total events: 18 (CSA), 2 (Placebo/no treatment)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.19$, df=1(P=0.66); $I^2=0\%$					
Test for overall effect: Z=3.22(P=0)					
1.2.2 FSGS					
Lieberman 1996	12/12	2/12		100%	5[1.63,15.31]
Subtotal (95% CI)	**12**	**12**		**100%**	**5[1.63,15.31]**
Total events: 12 (CSA), 2 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.82(P=0)					

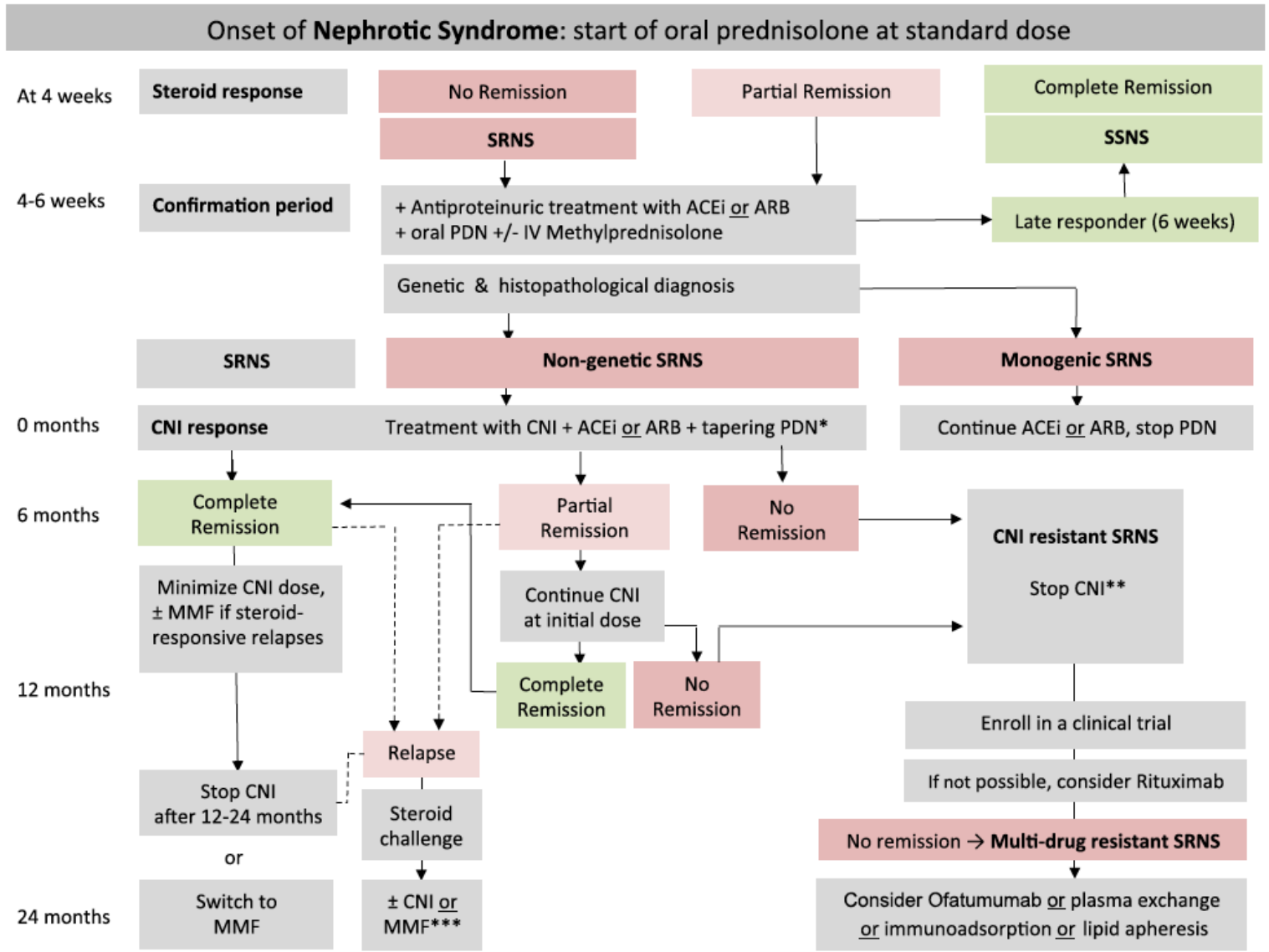


Calcineurin Inhibitor versus Cyclophosphamide

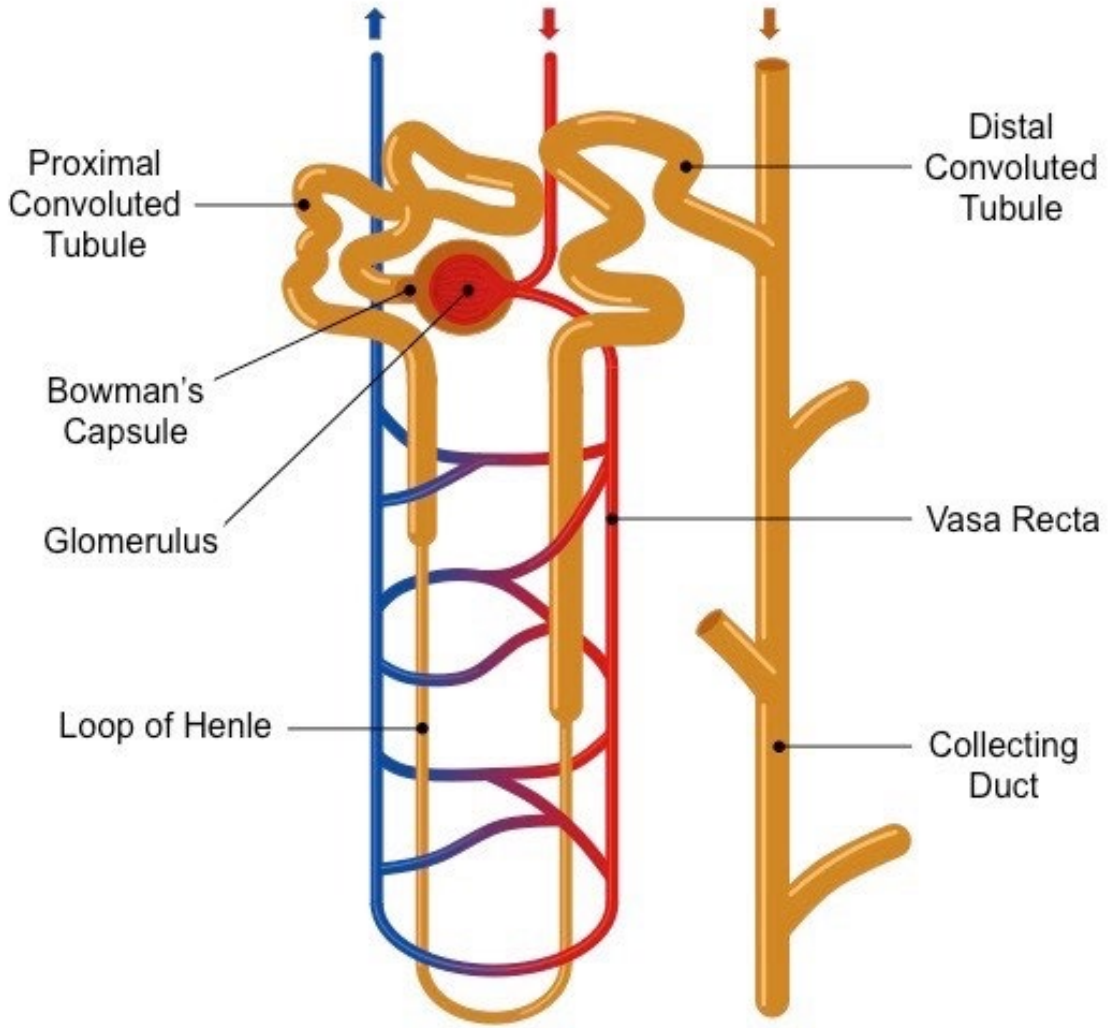
Analysis 2.1. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 1 Treatment response at 3 to 6 months.

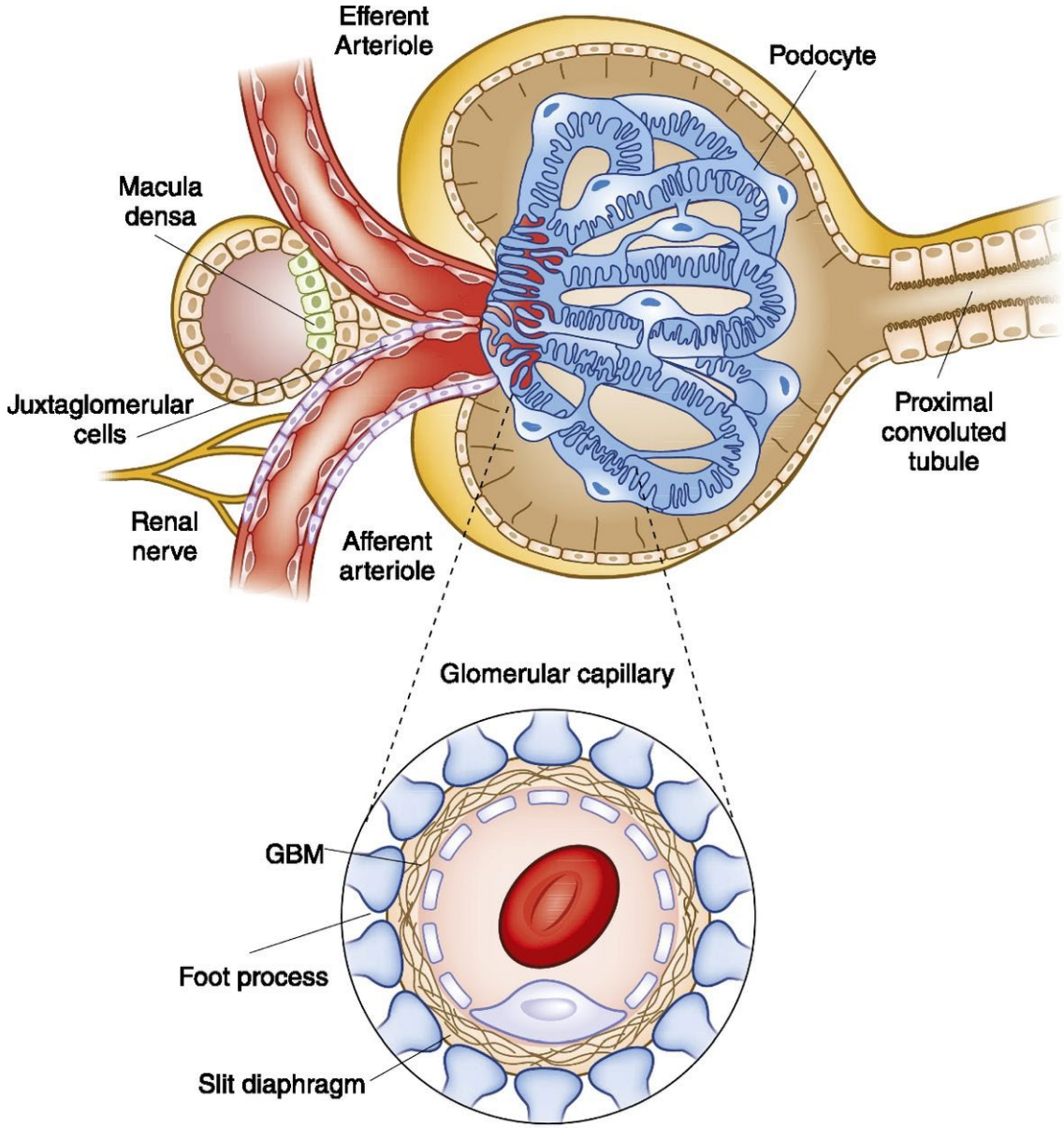
Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Complete or partial remission					
APN 2008	9/15	3/17		15.17%	3.4[1.12,10.28]
Gulati 2012	52/63	28/61		84.83%	1.8[1.34,2.42]
Subtotal (95% CI)	**78**	**78**		**100%**	**1.98[1.25,3.13]**
Total events: 61 (CNI), 31 (IV CPA)					
Heterogeneity: Tau^2=0.04; Chi^2=1.24, df=1(P=0.26); I^2=19.67%					
Test for overall effect: Z=2.92(P=0)					




Onset of Nephrotic Syndrome: start of oral prednisolone at standard dose
At 4 weeks
Steroid response
No Remission
Partial Remission
Complete Remission
SRNS
SSNS
4-6 weeks
Confirmation period
+ Antiproteinuric treatment with ACEi or ARB
+ oral PDN +/- IV Methylprednisolone
Late responder (6 weeks)
Genetic & histopathological diagnosis
SRNS
Non-genetic SRNS
Monogenic SRNS
0 months
CNI response
Treatment with CNI + ACEi or ARB + tapering PDN*
Continue ACEi or ARB, stop PDN
6 months
Complete Remission
Partial Remission
No Remission
CNI resistant SRNS
Stop CNI**
Minimize CNI dose, ± MMF if steroid-responsive relapses
Continue CNI at initial dose
12 months
Complete Remission
No Remission
Enroll in a clinical trial
Relapse
If not possible, consider Rituximab
Stop CNI after 12-24 months
Steroid challenge
No remission → Multi-drug resistant SRNS
or
24 months
Switch to MMF
± CNI or MMF***
Consider Ofatumumab or plasma exchange or immunoadsorption or lipid apheresis

UNDERSTANDING THE PATHOGENESIS





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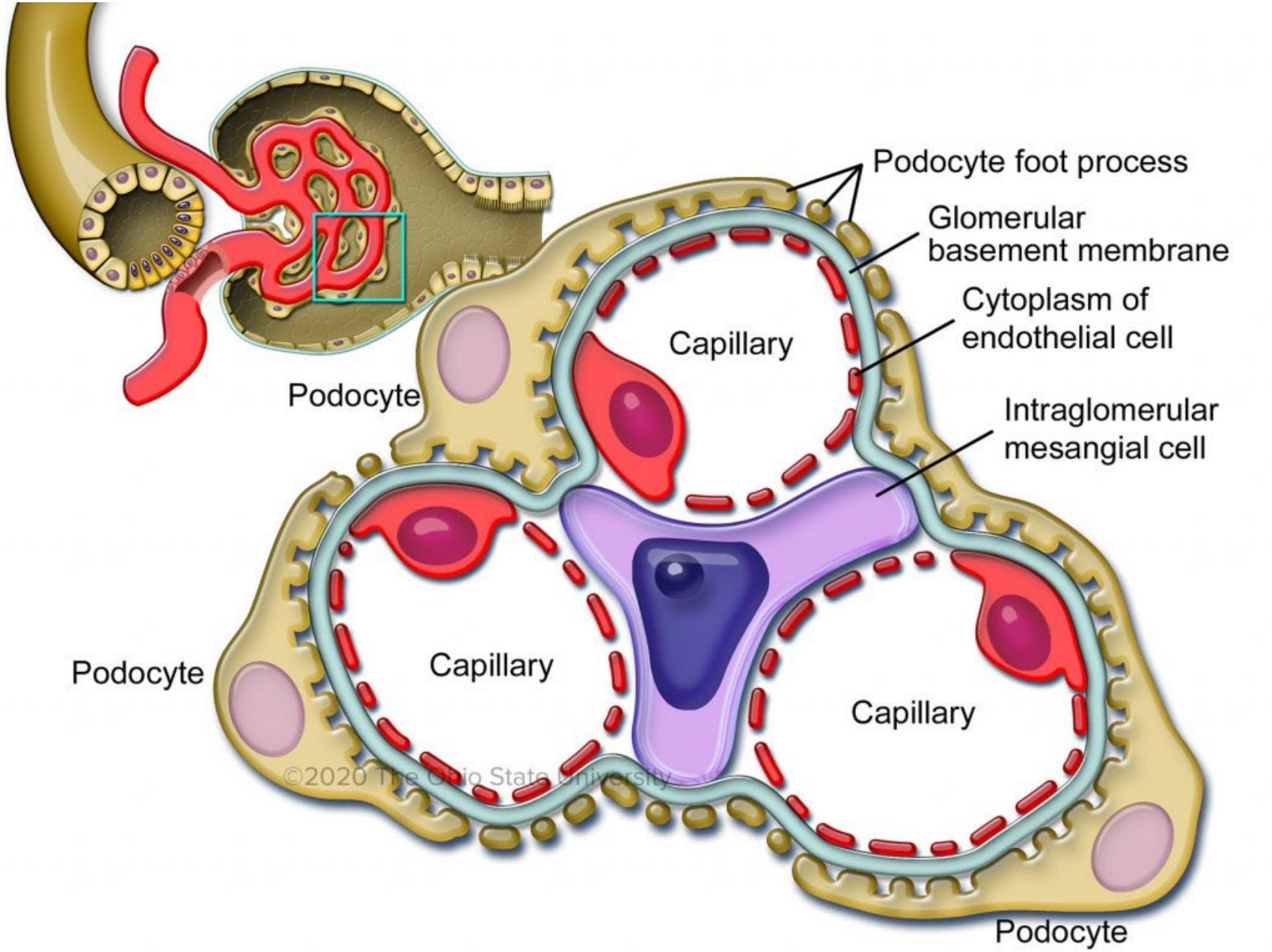

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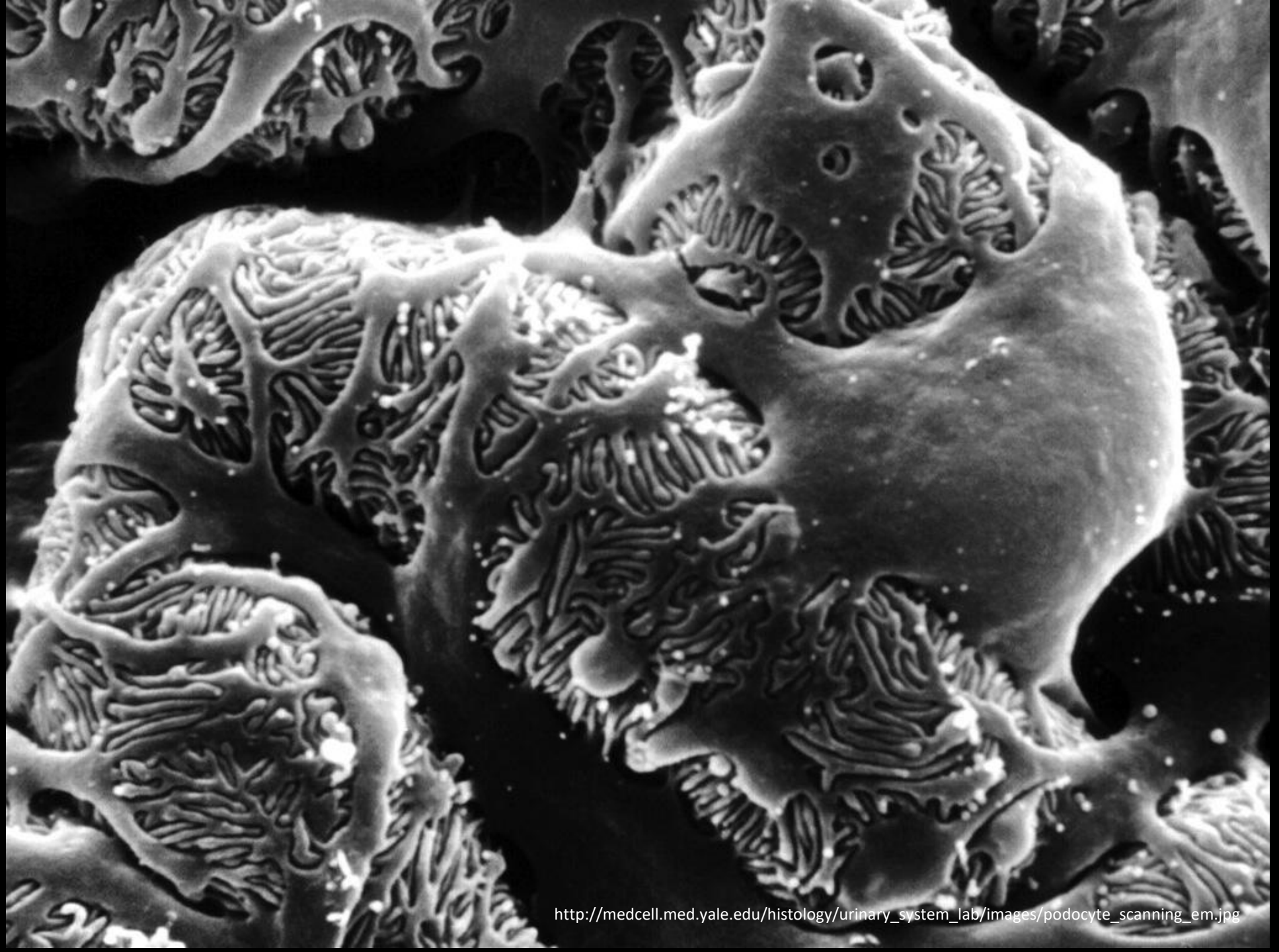
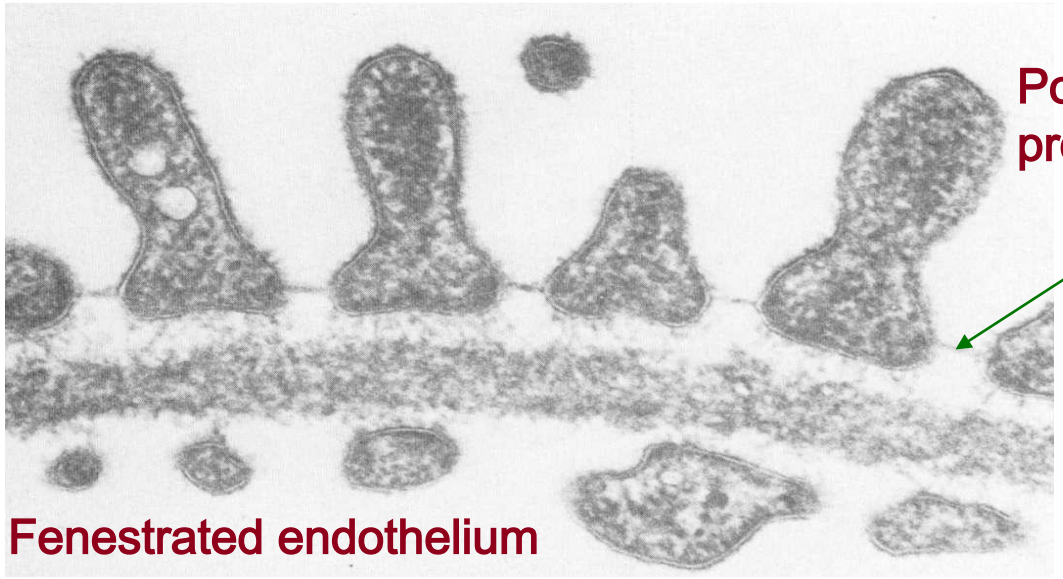


http://medcell.med.yale.edu/histology/urinary_system_lab/images/podocyte_scanning_em.jpg

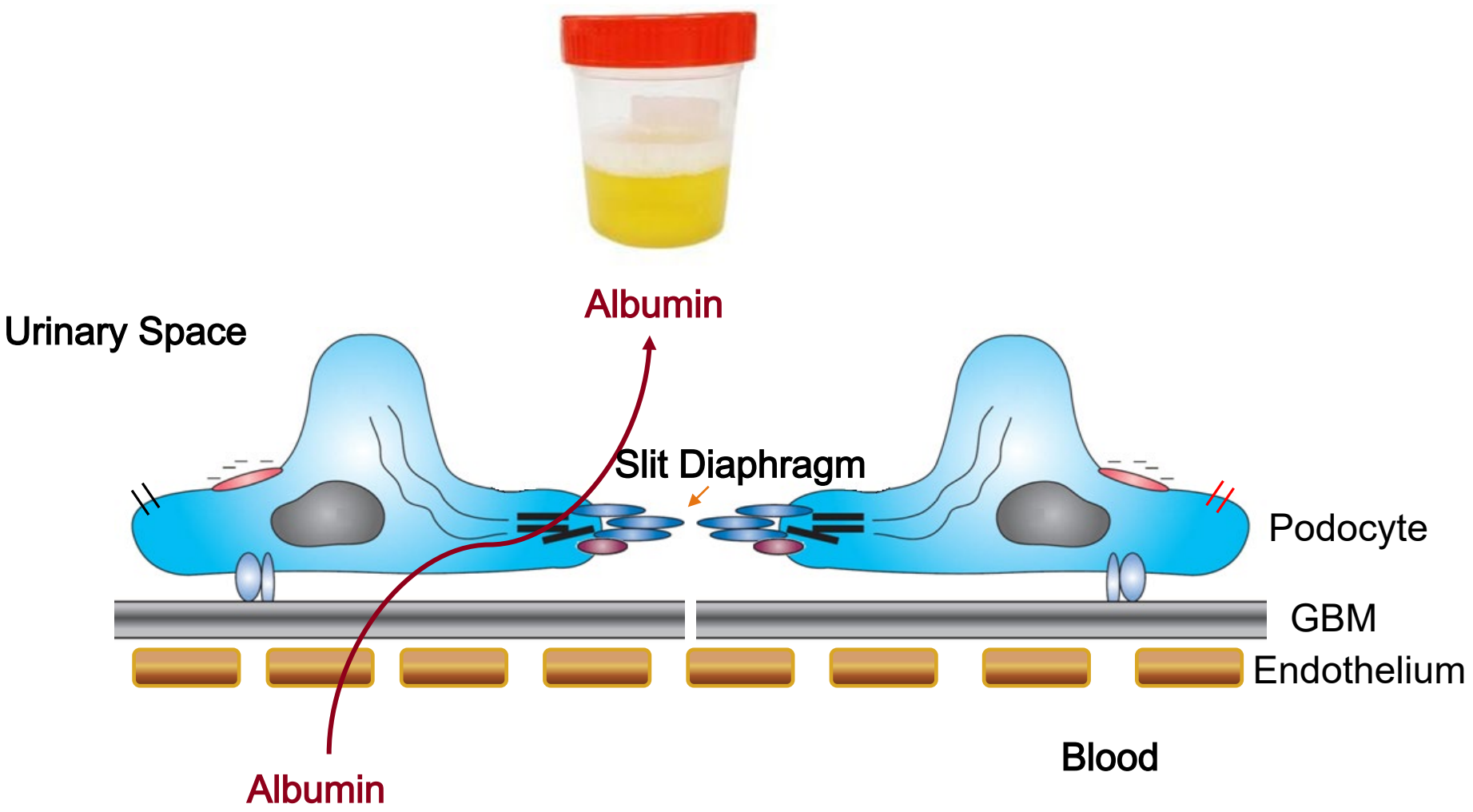
GLOMERULAR FILTRATION BARRIER

Urine



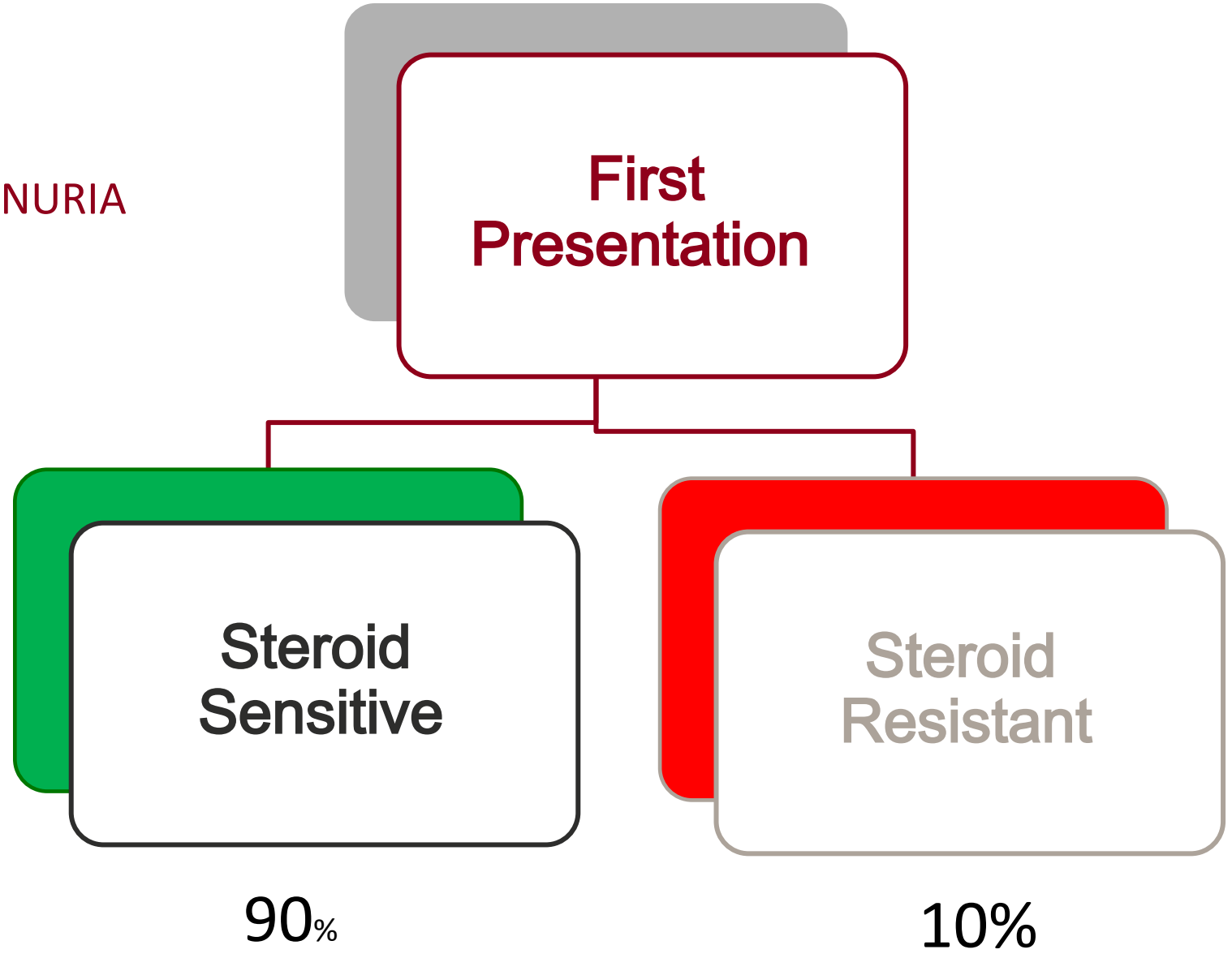
Blood

http://cours.cegep -st-jerome.qc.ca/101-902-m.f/bio903/urinaire/Images/podocytes2.gif

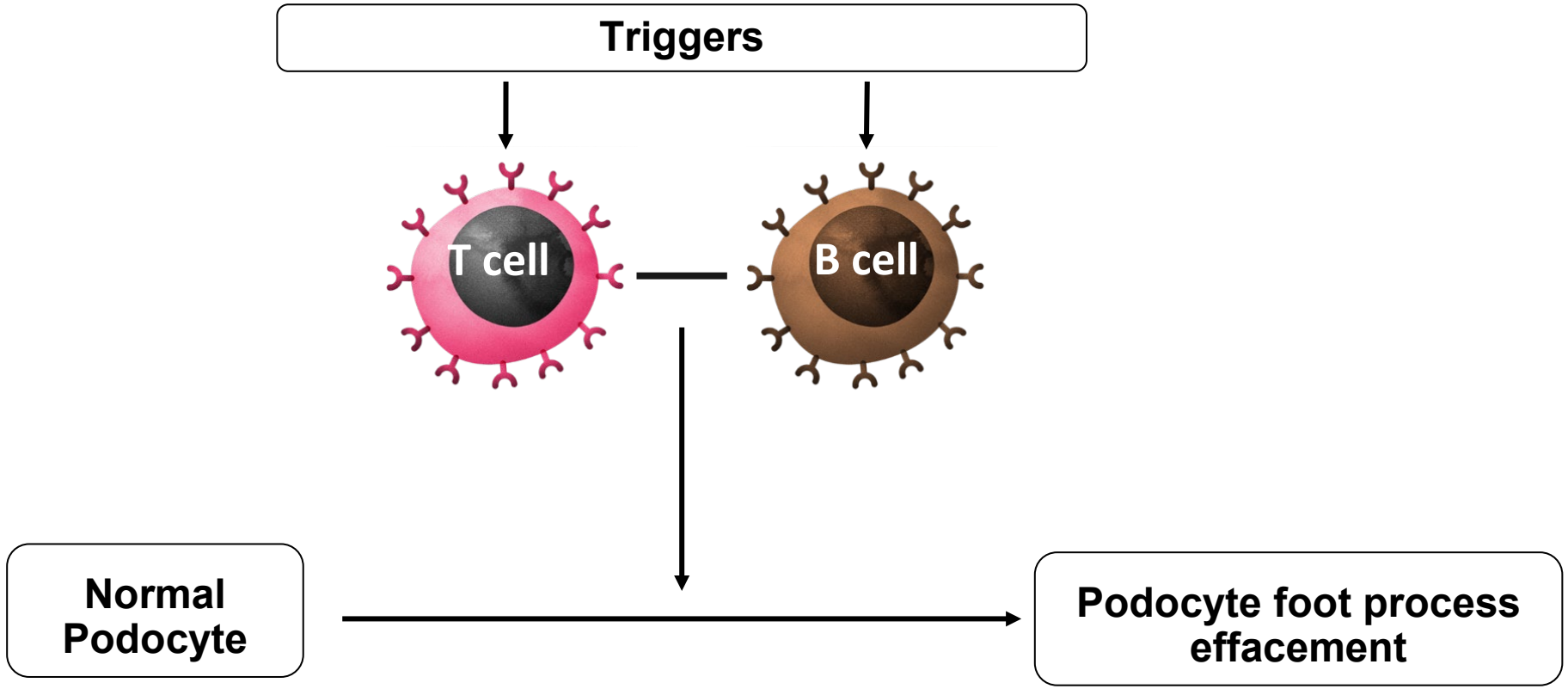


Eddy et al. Lancet 2003

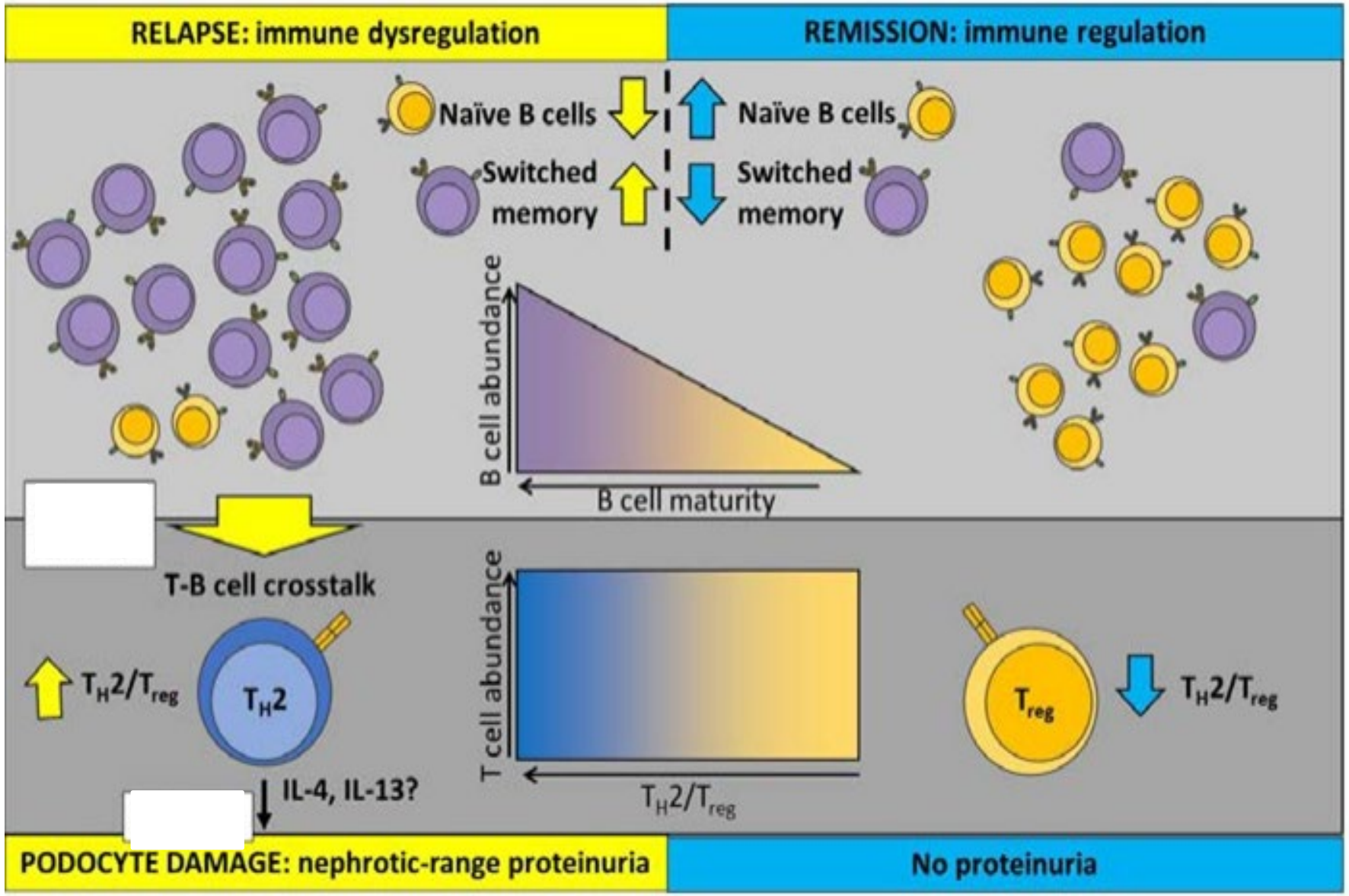
CHILD PRESENTING WITH PROTEINURIA



Immune pathogenesis of nephrotic syndrome



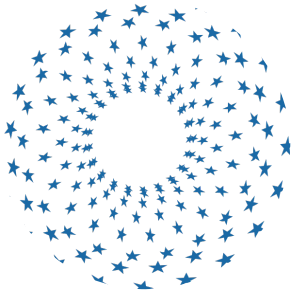
Shalhoub Lancet 1975


RELAPSE: immune dysregulation
REMISSION: immune regulation
Naïve B cells
Switched memory
Naïve B cells
Switched memory
B cell abundance
B cell maturity
T-B cell crosstalk
T_H2/T_{reg}
T_H2
IL-4, IL-13?
T cell abundance
T_H2/T_{reg}
T_{reg}
T_H2/T_{reg}
PODOCYTE DAMAGE: nephrotic-range proteinuria
No proteinuria

SUMMARY OF CURRENT UNDERSTANDING:

Structural

- Mutations affecting the structure and function of the glomerular filtration barrier



Circulating factors

- Elusive ‘glomerular permeability factor’

Immune Mediated

- T and B cells, cross talk
- Immune regulation

AGE OF PRESENTATION KEY TO DIAGNOSIS AND MANAGEMENT

<3 Months	3-12 Months	> 1 Year
• Genetic testing • Extrarenal manifestations • Congenital infection	• Genetic testing • Extrarenal manifestations • Kidney biopsy • *Idiopathic immune*	• Idiopathic immune • Genetic causes (less likely) • Kidney biopsy **not** performed

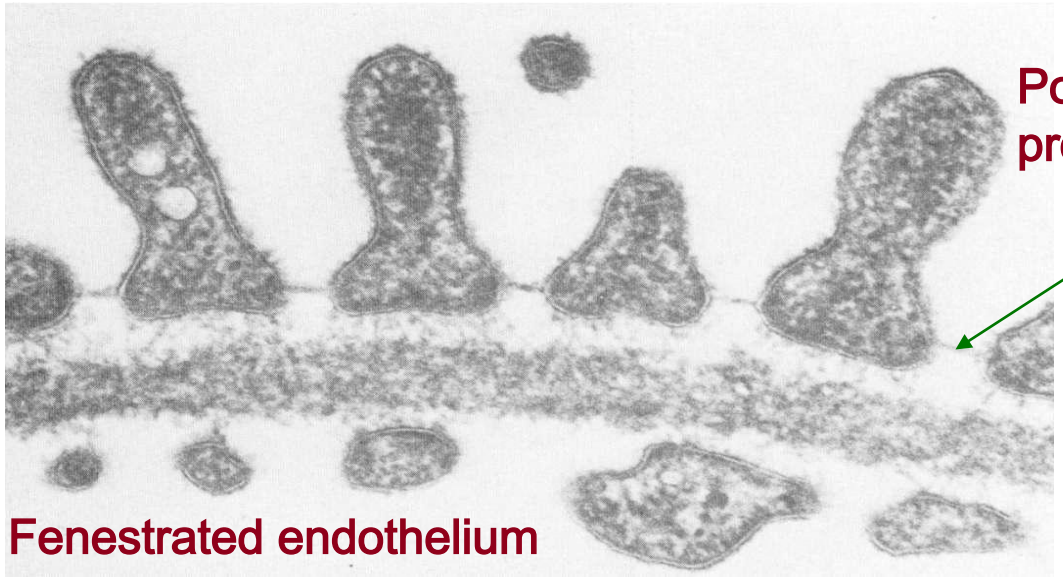
Likelihood of a monogenic cause by age:

- 0 to 3 months – 69 %
- 4 to 12 months – 50 %
- 13 months to 6 years – 25 %
- 7 to 12 years – 18 %
- 13 to 17 years – 11 %
- >18 years – 21 %

Boyer O, Nat RevNephrol2021

GLOMERULAR FILTRATION BARRIER

Urine



Blood

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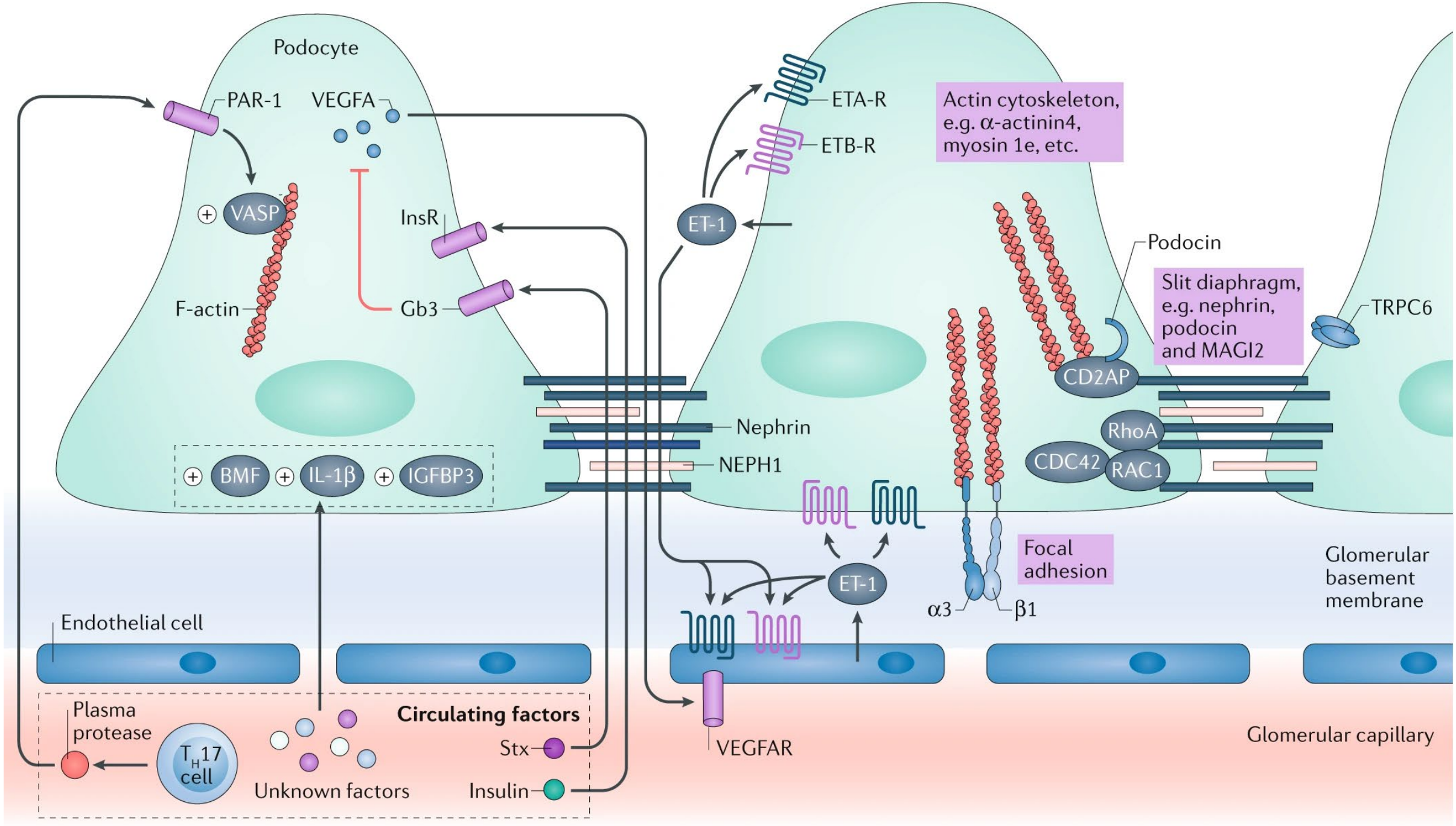
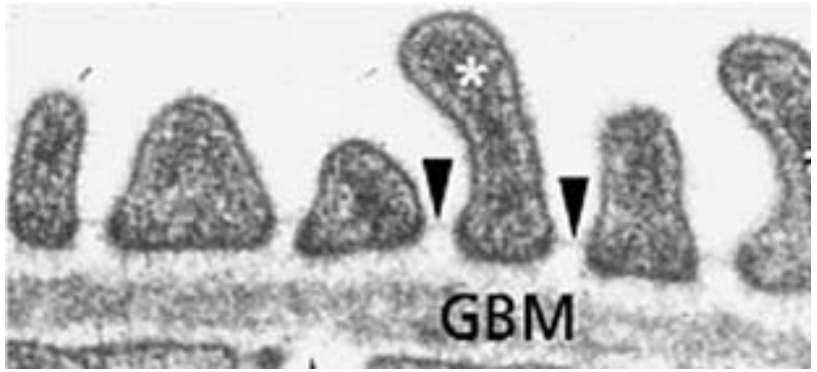
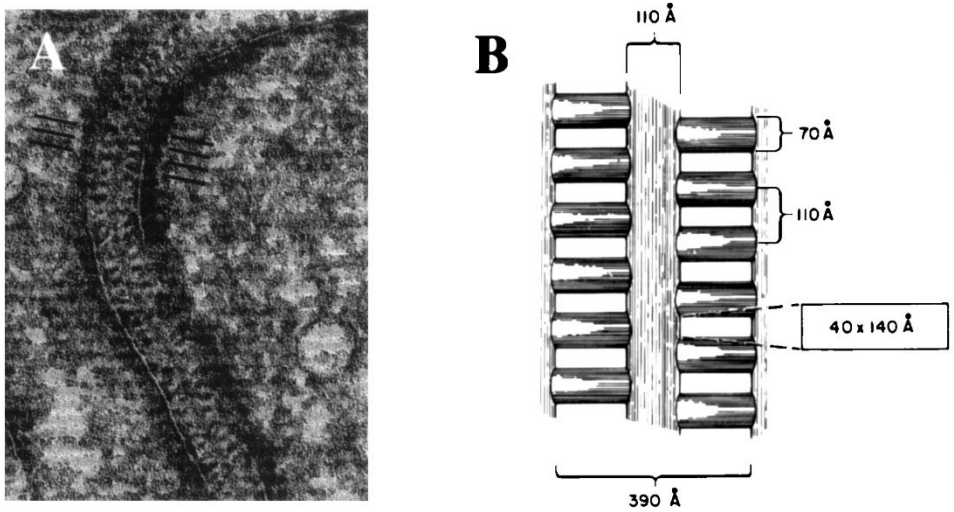
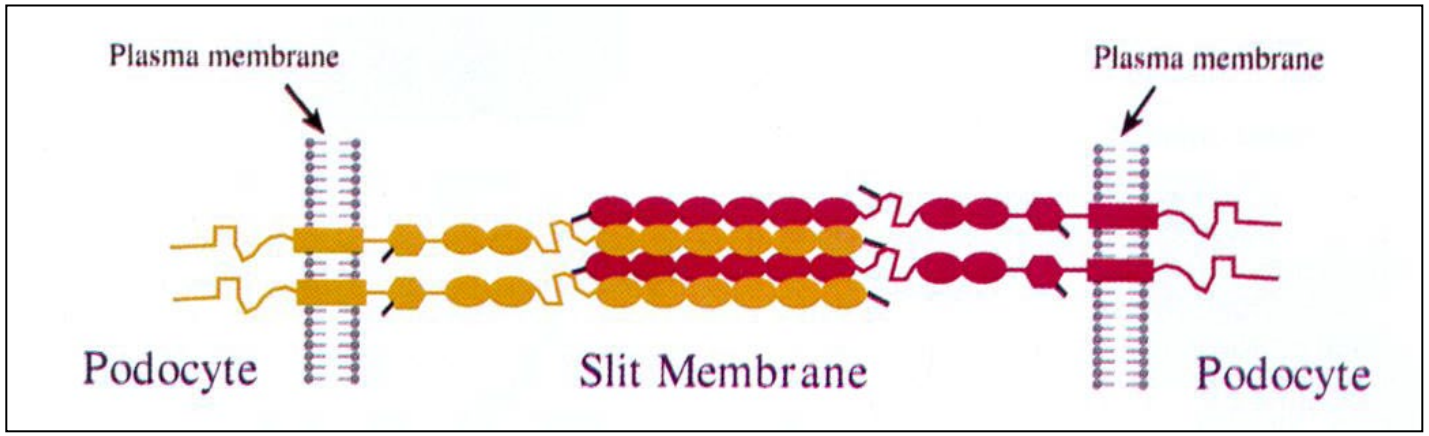

Podocyte
PAR-1
VEGFA
VASP
F-actin
InsR
Gb3
ET-1
ETA-R
ETB-R
Actin cytoskeleton, e.g. α-actinin4, myosin 1e, etc.
Podocin
Slit diaphragm, e.g. nephrin, podocin and MAGI2
TRPC6
CD2AP
RhoA
CDC42
RAC1
Nephrin
NEPH1
BMF
IL-1β
IGFBP3
ET-1
Focal adhesion
α3
β1
Glomerular basement membrane
Endothelial cell
Circulating factors
Plasma protease
T_H17 cell
Unknown factors
Stx
Insulin
VEGFAR
Glomerular capillary

Nephrin is the structural backbone of the slit diaphragm





Rodewald and Karnovsky, J Cell Biol, 1974

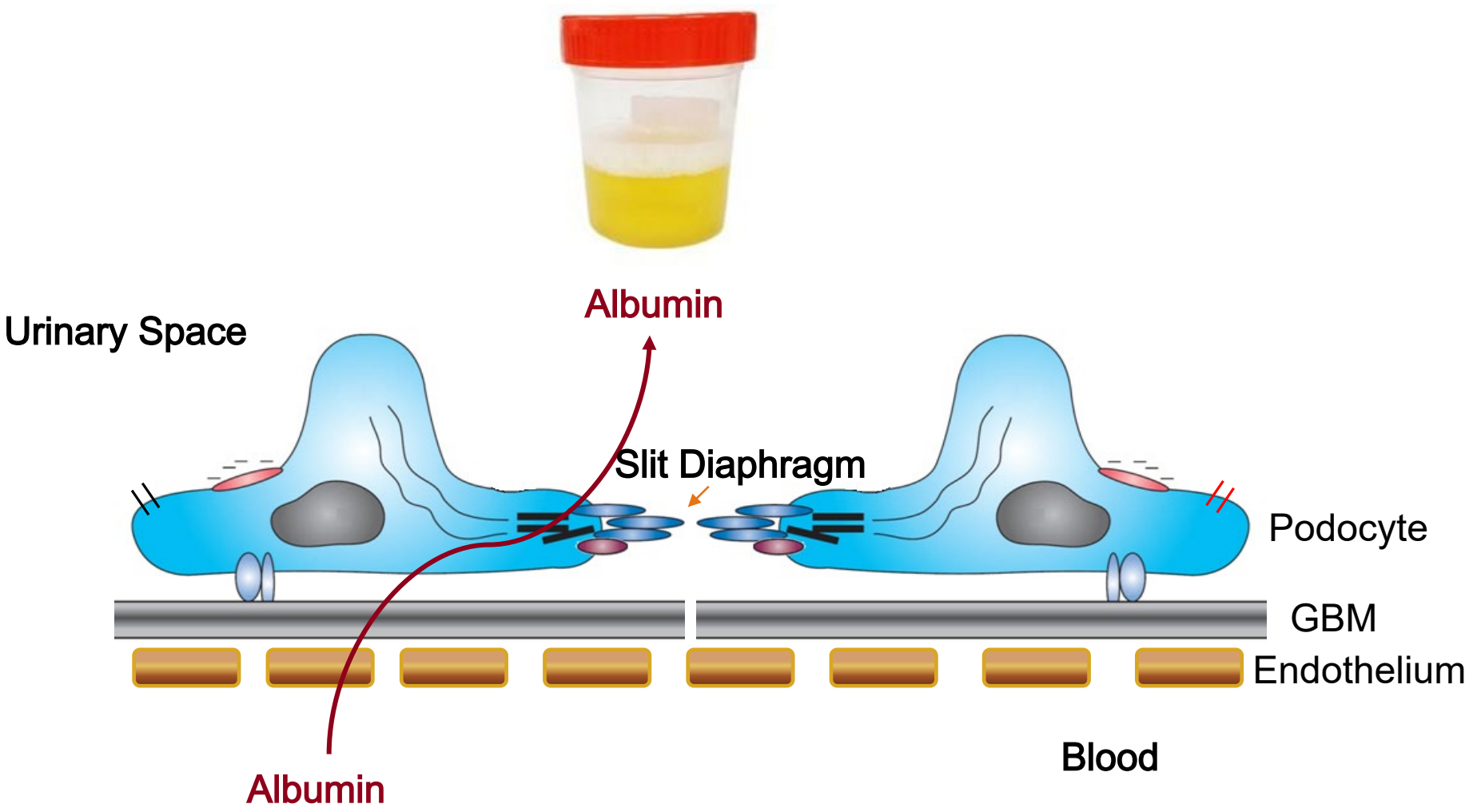


Nephrin

- Transmembrane protein
- Structural backbone of the slit diaphragm
- Homophilic interactions

Gene Symbol	Alternate Name	Inheritance	Syndrome Name	Comment
NPHS1	Nephrin	AR	*Finnish NS* **NS Type 1**	Congenital
NPHS2	Podocin	AR	**NS Type 2**	SRNS
PLCE1	NPHS3 PHOSPHOLIPASE C	AR	**NS Type 3**	Congenital SRNS
WT1	Wilm's tumour 1	AD	*Frasier* *Denys Drash* **NS Type 4**	Congenital Childhood SRNS
LAMB2	Laminin Beta-2	AR	*Pierson* **NS Type 5**	Congenital
PTPRO	GLEPP1, PTPU2	AR	**NS Type 6**	Childhood
ACTN4	Actinin Alpha-4	AD or AR	FSGS 1	SRNS, CKD as adult
TRPC6	Transient receptor potential ion channel 6	AD	FSGS 2	SRNS, ?Later onset
CD2AP	CD2 associated protein	AR	FSGS 3	Early Onset
APOL1	Apolipoprotein L1		FSGS 4	Increased risk of FSGS in Africans
INF2	Inverted formin 2	AD	FSGS 5	SRNS Adolescence or Adult

Gene	Inheritance	Accession no.	Disease
MMACHC	AR	NM_015506.3	Cobalamin C deficiency, TMA, and nephrotic syndrome
*MYO1E**	AR	NM_004998	Familial SRNS
NEU1	AR	NM_000434.4	Nephrosialidosis (sialidosis type II + childhood NS)
NPHP4	AR	NM_015102.5	Nephronophthisis with FSGS and nephrotic range proteinuria
*NPHS1**	AR	NM_004646	CNS/SRNS
*NPHS2**	AR	NM_014625	CNS, SRNS
NUP85	AR	NM_024844.5	SRNS
*NUP93**	AR	NM_014669	Childhood SRNS
*NUP107**	AR	NM_020401	Childhood SRNS
NUP160	AR	NM_015231.2	SRNS
NUP205	AR	NM_015135	Childhood SRNS
NXF5	XR	NM_032946	FSGS with co-segregating heart block disorder
*OCRL**	XR	NM_000276	Dent's disease-2, Lowe syndrome, ± FSGS, ± nephrotic range proteinuria
OSGEP	AR	NM_017807.4	NS with primary microcephaly
PAX2	AD	NM_003987	Adult-onset FSGS without extrarenal manifestations
PDSS2	AR	NM_020381	Leigh syndrome
PLCe1	AR	NM_016341	CNS/SRNS
PMM2	AR	NM_000303	Congenital disorder of glycosylation
*PODXL**	AD	NM_005397	FSGS
PTPRO	AR	NM_030667	NS
SCARB2	AR	NM_005506	Action myoclonus renal failure syndrome ± hearing loss
SGPL1	AR	NM_003901.4	Primary adrenal insufficiency and SRNS
SMARCAL1	AR	NM_014140	Schimke immuno-osseous dysplasia
SYNPO	AD	NM_007286	Sporadic FSGS (promoter mutations)
TBC1D8B	XR	NM_017752.3	Early-onset SRNS with FSGS
TNS2	AR	NM_170754.3	SSNS/SDNS (with MCD/FSGS/DMS on biopsy)
TP53RK	AR	NM_033550.4	NS with primary microcephaly
TPRKB	AR	NM_001330389.1	NS with primary microcephaly
*TRPC6**	AD	NM_004621	Familial and sporadic SRNS (mainly adult)
TTC21B	AR	NM_024753	FSGS with tubulointerstitial involvement
WDR73	AR	NM_032856	Galloway-Mowat syndrome (microcephaly and SRNS)
*WT1**	AD	NM_024426	Sporadic SRNS (children: may be associated with abnormal genitalia); Denys-Drash and Frasier syndrome
XPO5	AR	NM_020750	Childhood SRNS
ZMPSTE24	AR	NM_005857	Mandibuloacral dysplasia with FSGS
MYH9	AD/assoc.	NM_002473	MYH9-related disease; Epstein and Fechtner syndromes
*APOL1**	G1, G2 risk alleles	NM_003661	Increased susceptibility to FSGS and ESRD in African Americans, Hispanic Americans and in individuals



Eddy et al. Lancet 2003

PODONET

SALEEM

BACK TO THE CASE

"...most important teachers and discriminating critics."

-D. Ellis

KEY MESSAGES

1. Rare disease, diagnosis often missed, significant complications
2. Importance of glomerular filtration barrier, pathology does not predict response or prognosis
3. No alternative to prednisone to induce remission, steroid toxicity is a big problem, evidence for steroid sparing agents is poor
4.

Canadian Childhood Nephrotic Syndrome Project Team, Funding and Partners

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Tho Al-Aubodah
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MSc Student:
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PhD Candidate:
Areefa Alladin (Samuel lab)

Patient Partners

Claudia Harding
Jiffin Joseph

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

UNIVERSITY OF CALGARY

Roy & Vi Baay
Chair in Kidney Research

The Kidney Foundation of Canada
The foundation of kidney care.

NEPHCURE Kidney International
Saving Kidneys • Saving Lives

CAPN
Canadian Association of Pediatric Nephrologists
Association des Néphrologues Pédiatriques du Canada

Contact us: childneph@ucalgary.ca

Questions

https://www.cbc.ca/news/canada/calgary/alberta-children-s-hospital-covid-surgery-1.6180991

CHALLENGES AND OPPORTUNITIES IN CHILDHOOD NEPHROTIC SYNDROME

Steroid resistant

Susan M. Samuel, MD FRCPC MSc

Professor, Canada Research Chair

3– Day Paediatric Nephrology Workshop
19 – 21 June 2023
University College Hospital
Ibadan, Nigeria

UNIVERSITY OF CALGARY

CHILDNEPH

OUTLINE

1. Clinical case and features of SSNS
2. Challenges in the management of SSNS
3. Insights into the pathogenesis of NS
4. Case presentation and management of NS

Nephrotic Syndrome

Constellation of symptoms and signs

- > 3 g/L protein on dipstick
- Confirmed with a urine protein to creatinine ratio of 2154 mg/mmol
- Blood tests revealed serum albumin of 9 g/L
- No other abnormalities in clinical evaluation
- A diagnosis of childhood nephrotic syndrome was made

CLINICAL PRESENTATION

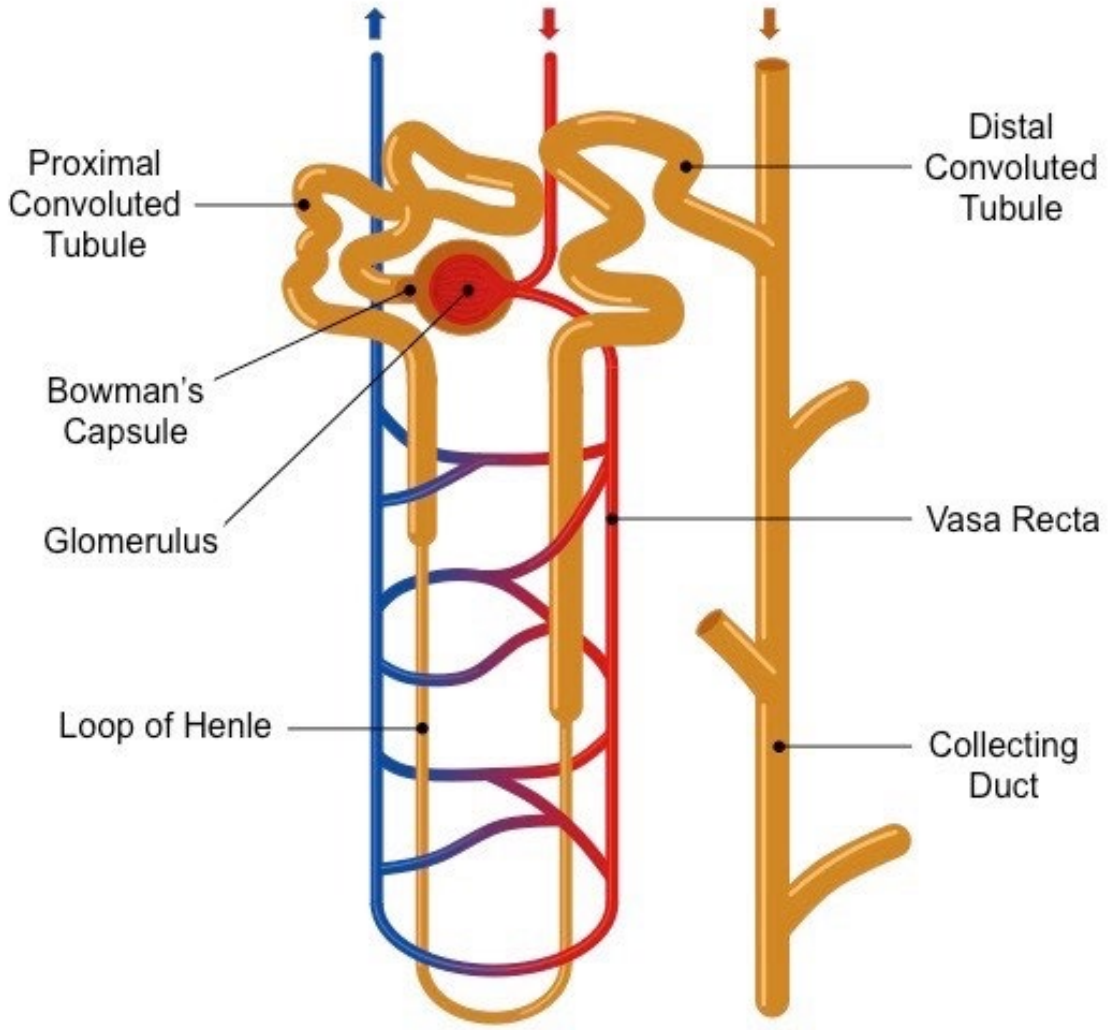
- Nephrotic range proteinuria
- Low serum albumin <30 g/L
- Gravity dependent edema

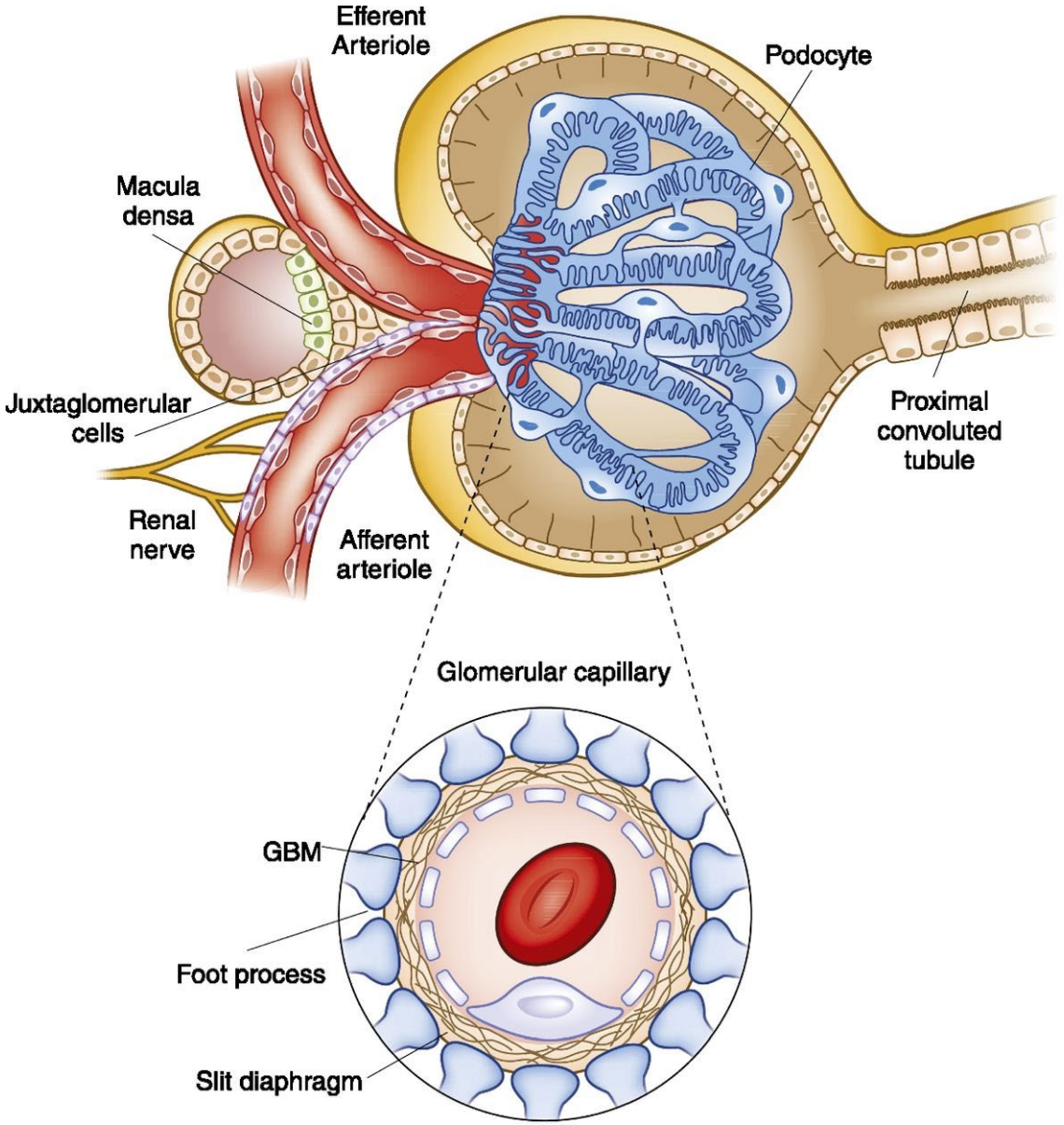
- Urine
  - Primarily albuminuria
  - Minimal blood or casts
- Blood
  - High cholesterol
  - Normal C3

NEPHROTIC RANGE PROTEINURIA

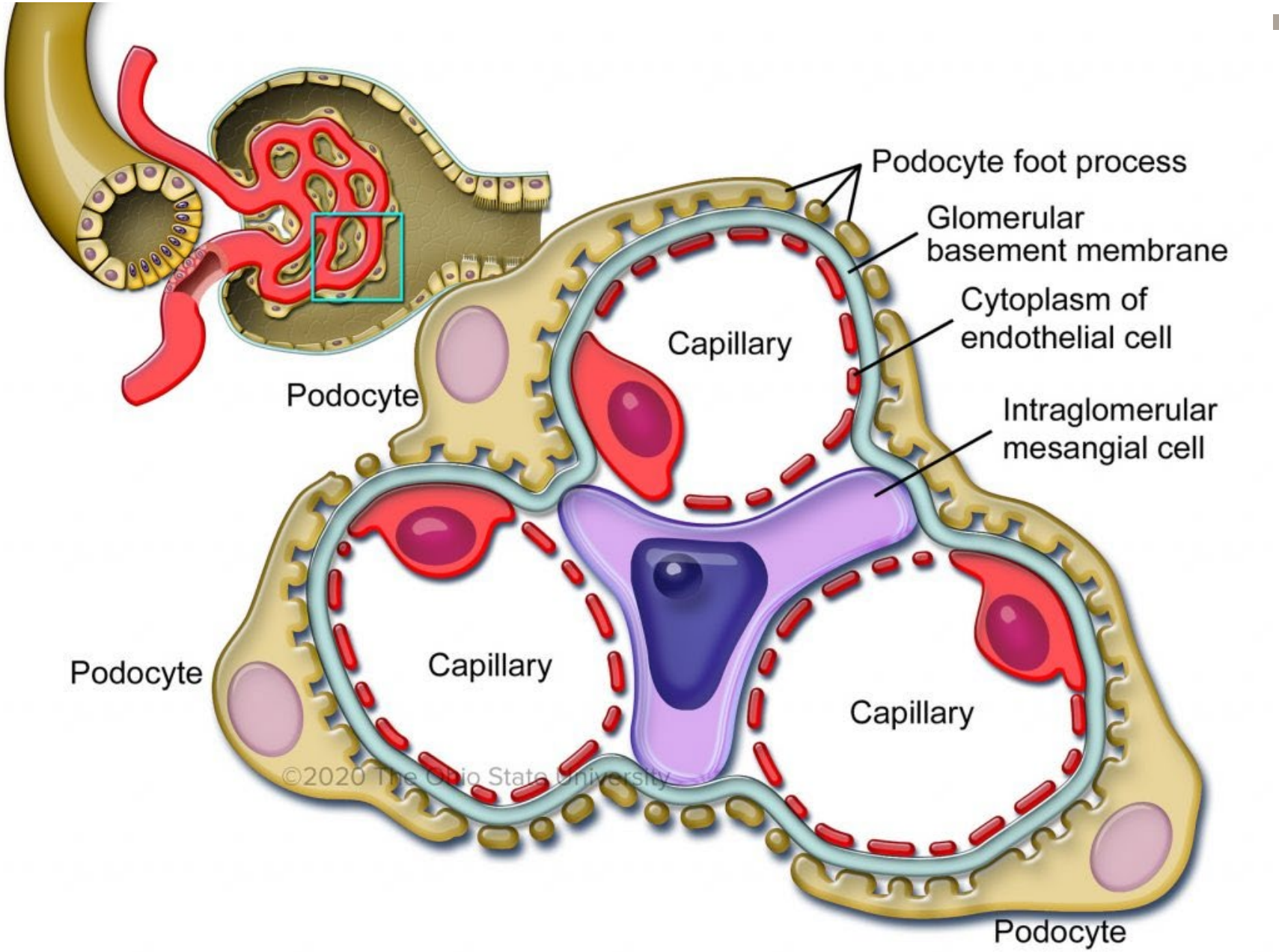
Measurement method	First morning spot urine	24 hour urine
Urine dipstick or urine protein	3+ (300-1000 mg/dL) or 4+ (≥ 1000 mg/dL)	≥ 1000 mg/m^2 per day > 40 mg/m^2/hour
Urine protein to creatinine ratio	≥ 200 mg/mmol (≥2 mg/mg)	≥ 200 mg/mmol (≥ 2 mg/mg)

UNDERSTANDING THE PATHOGENESIS





https://ib.bioninja.com.au/higher -level/topic-11-animal-physiology/113-the-kidney-and-osmoregu/nephrons.html
https://cjasn.asnjournals.org/content/9/8/1461.figures-only



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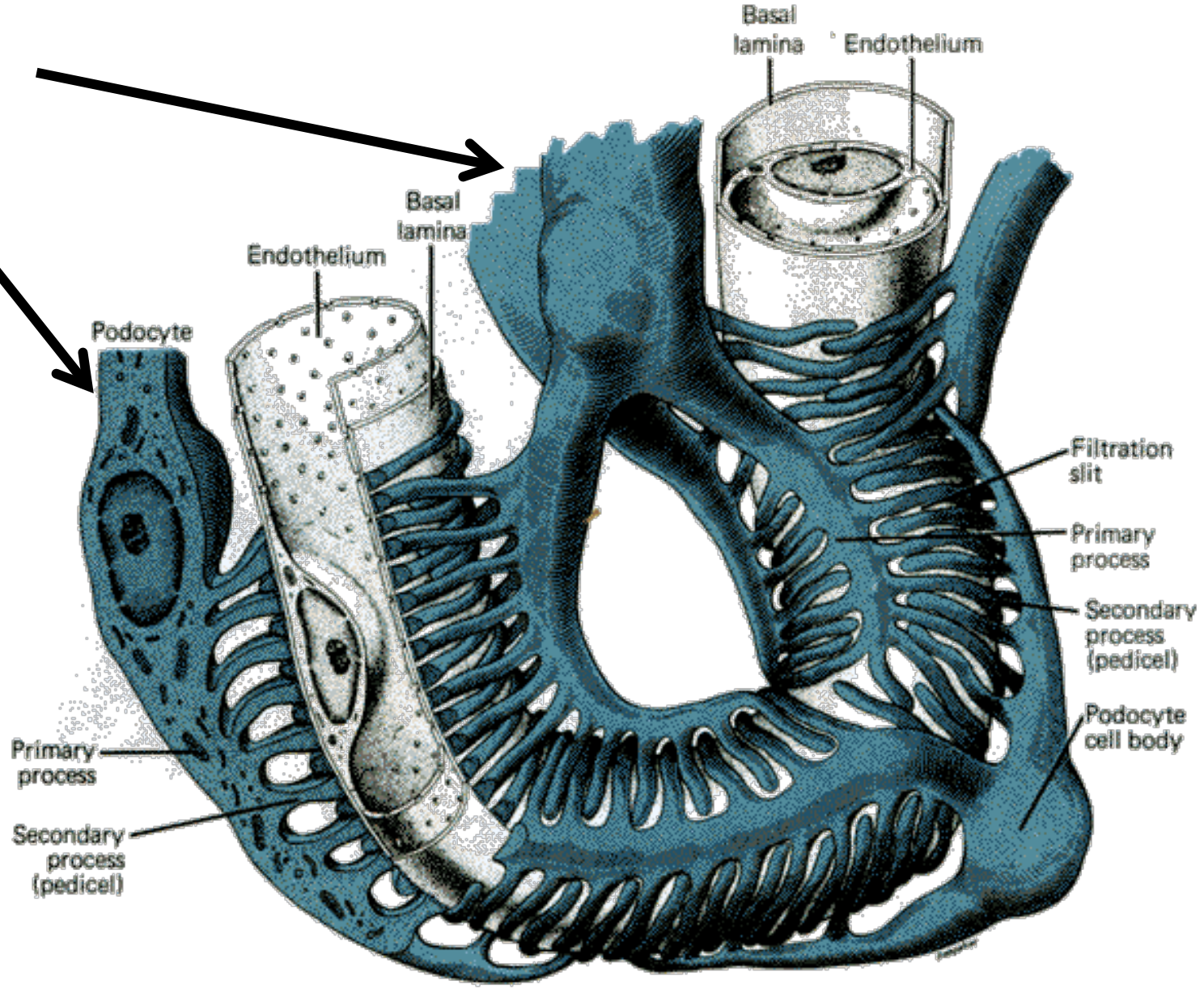
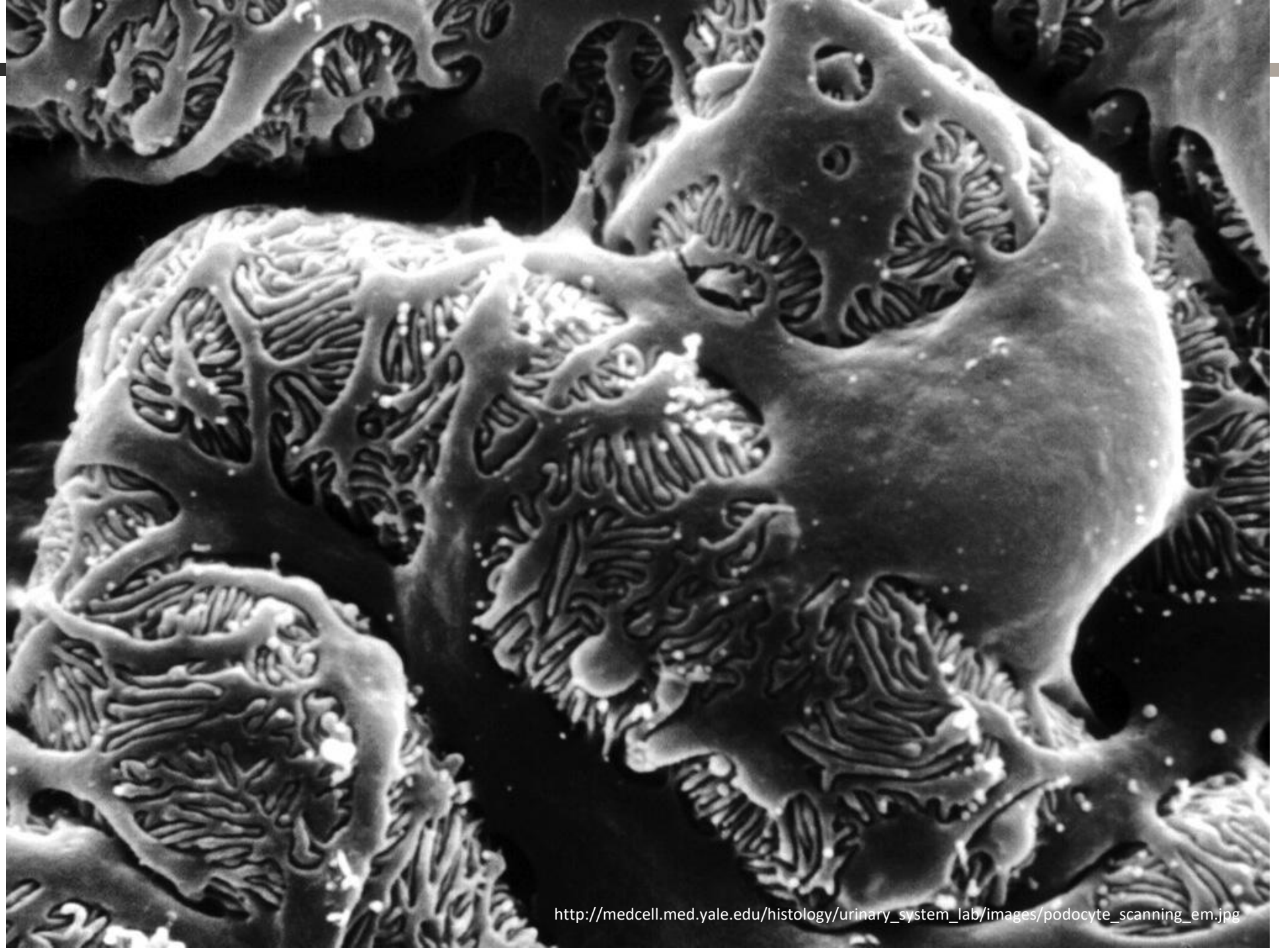
Podocytes



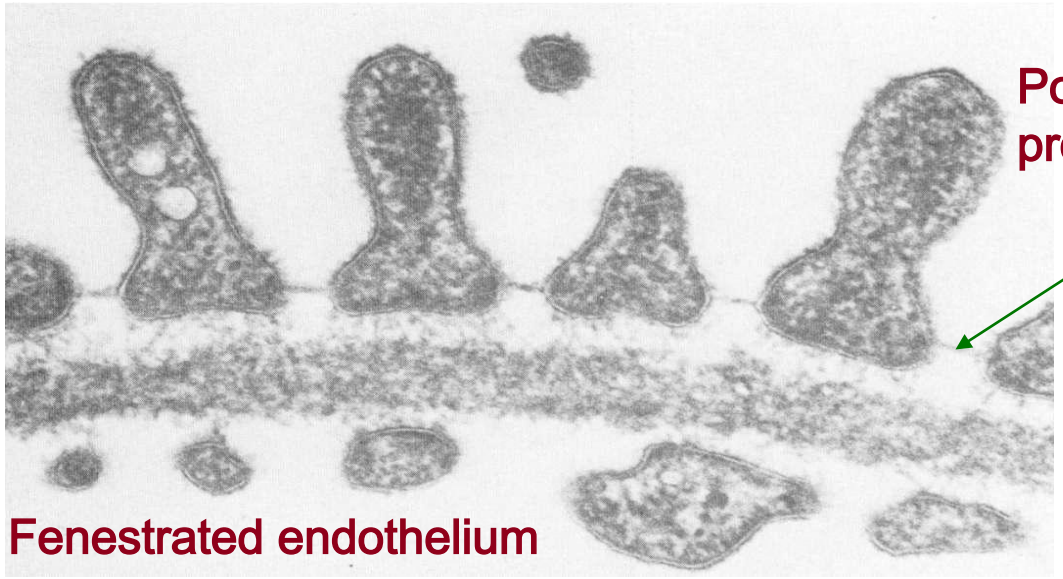
http://cours.cegep-st-jerome.qc.ca/101-902-m.f/bio903/urinaire/Images/podocytes2.gif



http://medcell.med.yale.edu/histology/urinary_system_lab/images/podocyte_scanning_em.jpg

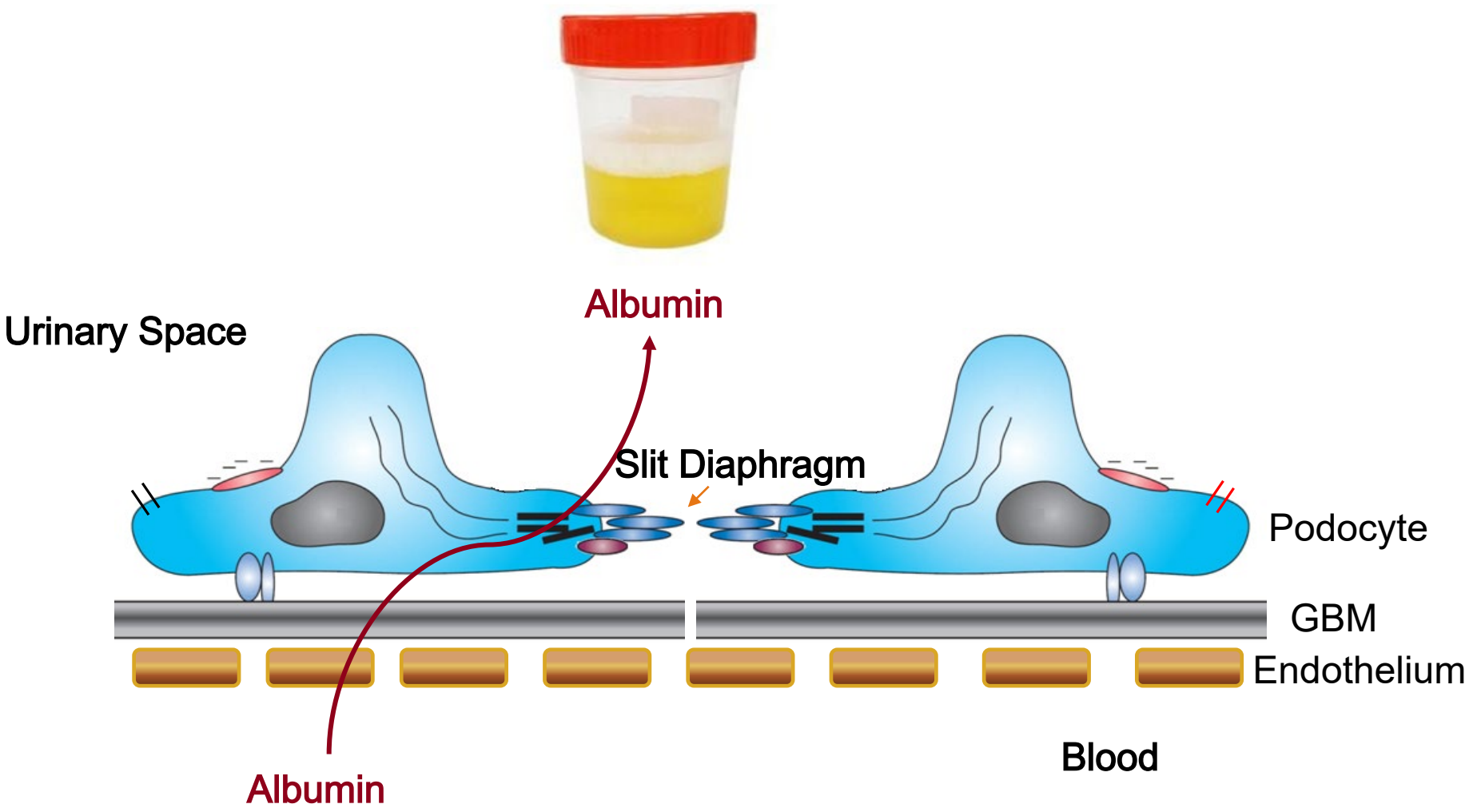
GLOMERULAR FILTRATION BARRIER

Urine



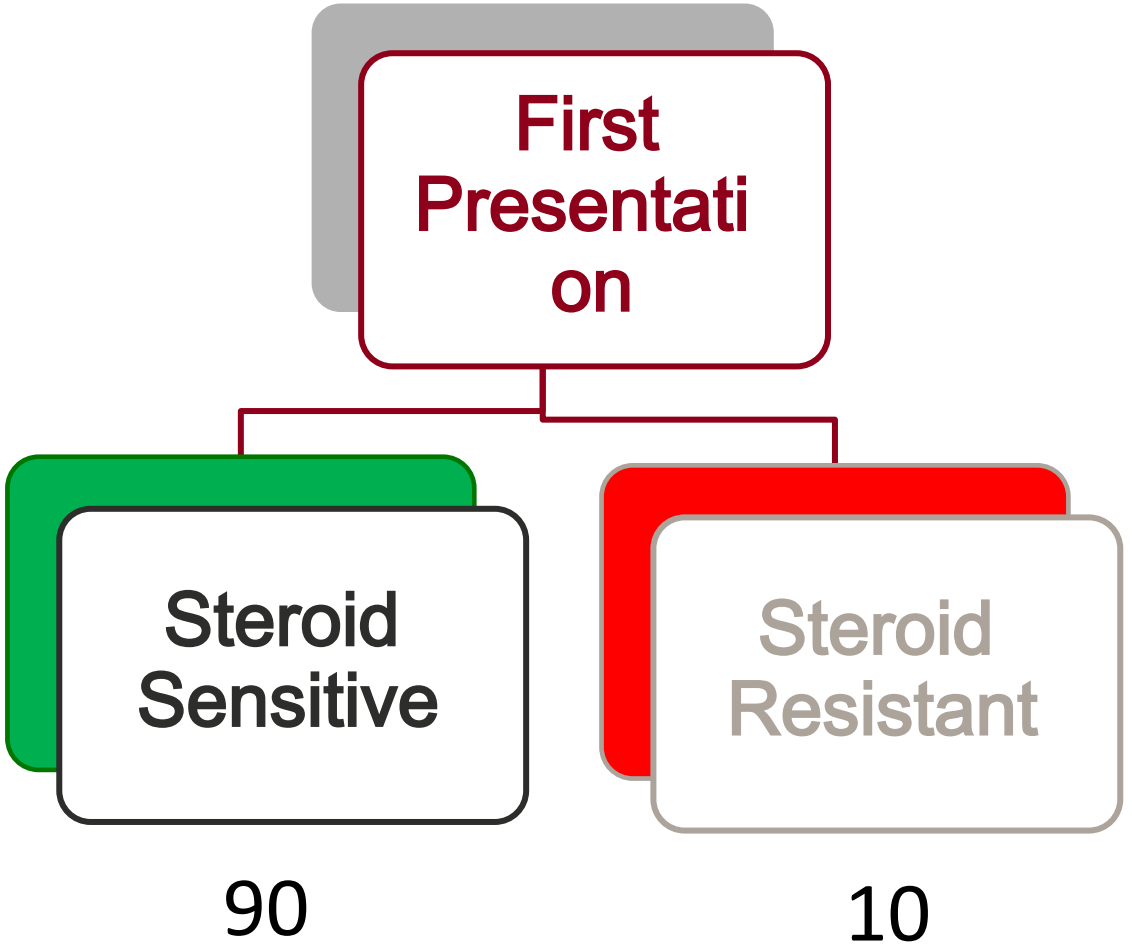
Blood

http://cours.cegep -st-jerome.qc.ca/101-902-m.f/bio903/urinaire/Images/podocytes2.gif

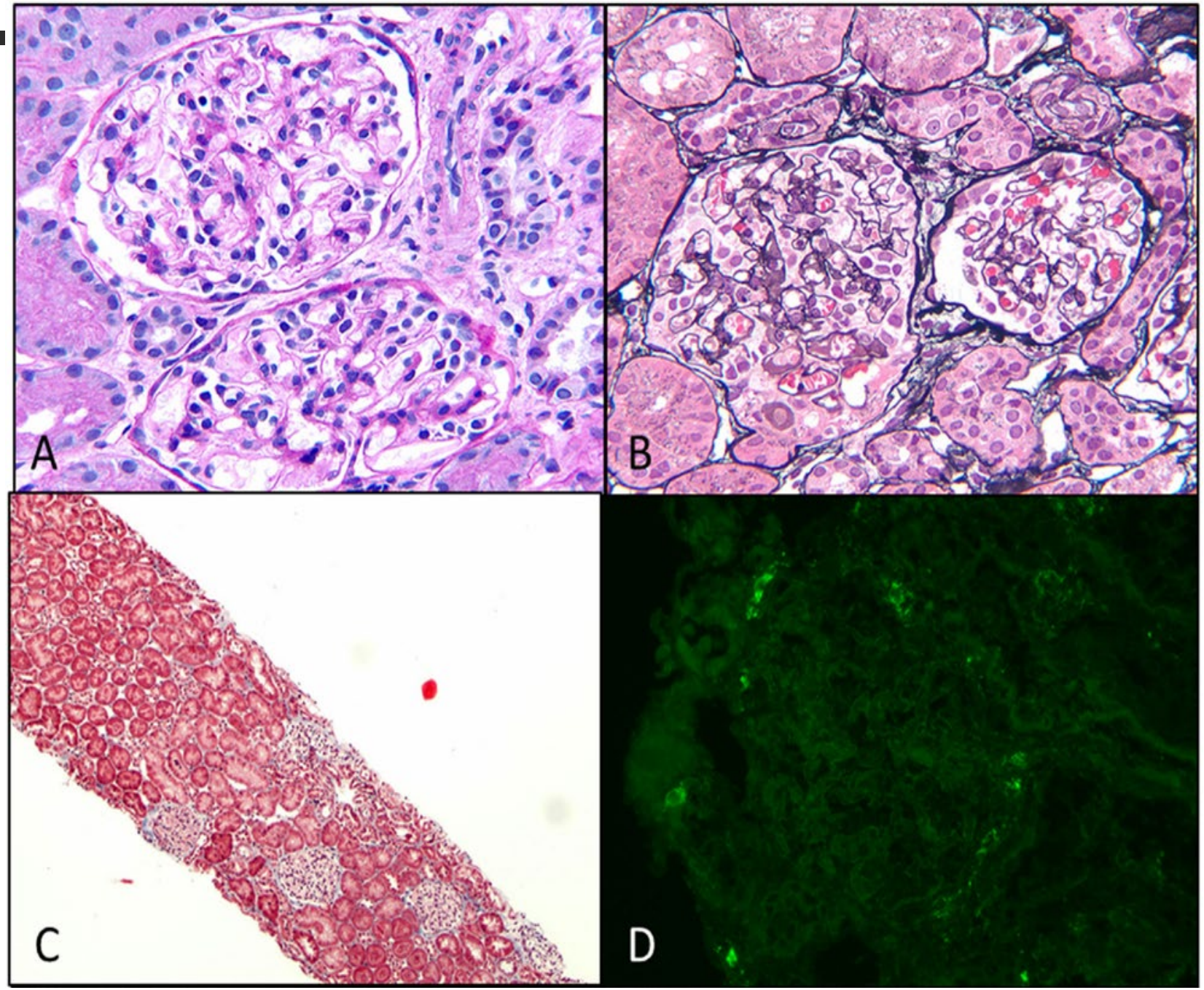


Eddy et al. Lancet 2003

CHILD PRESENTING WITH PROTEINURIA

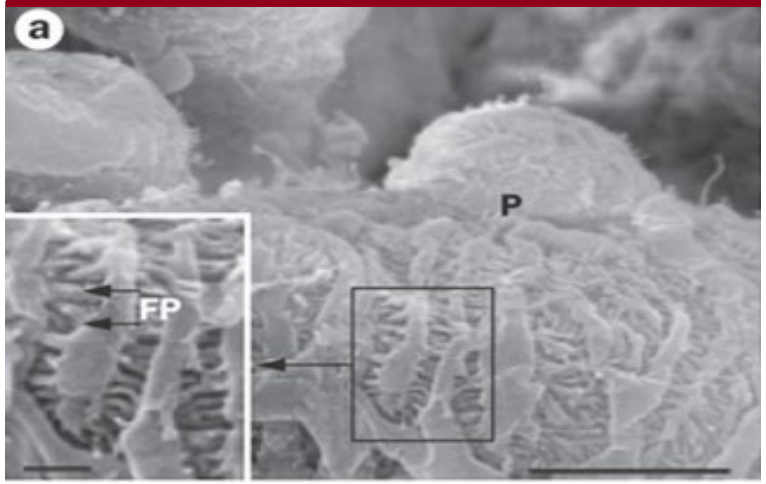


MINIMAL CHANGE DISEASE

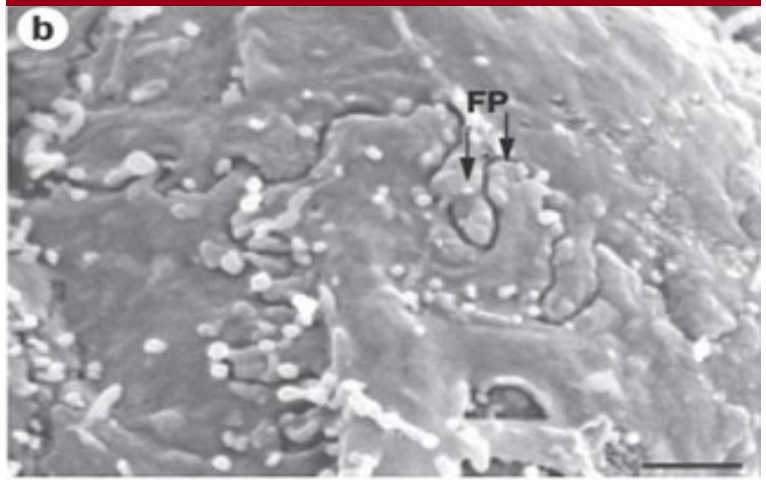


Ranganathan S. Front Pediatr
2016

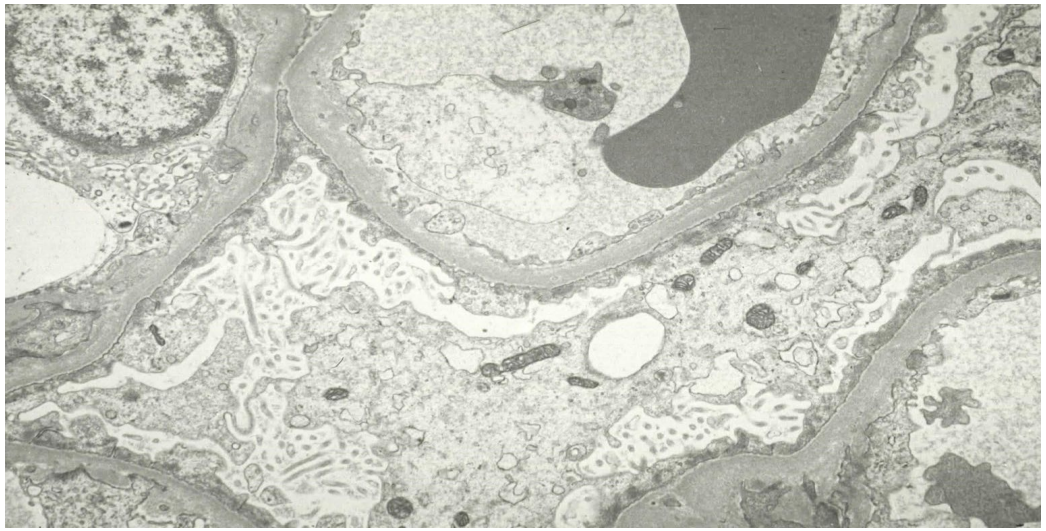
HEALTHY

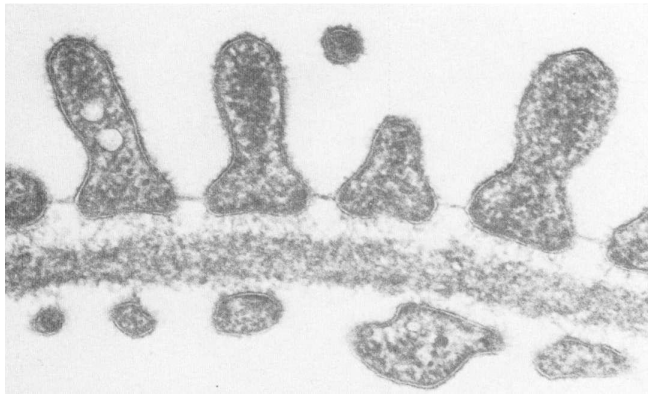


Podocyte effacement



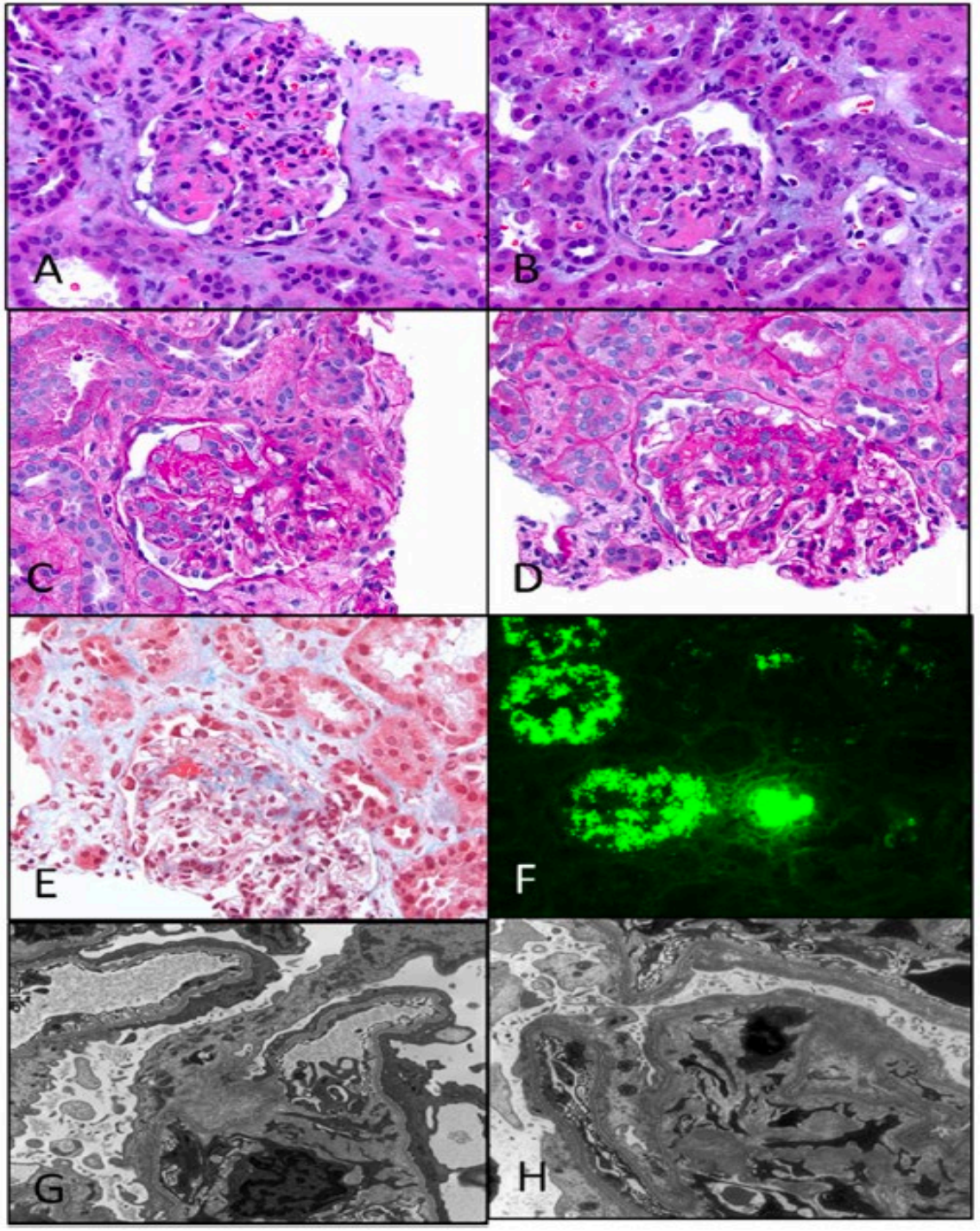
MINIMAL CHANGE DISEASE - PODOCYTE EFFACEMENT



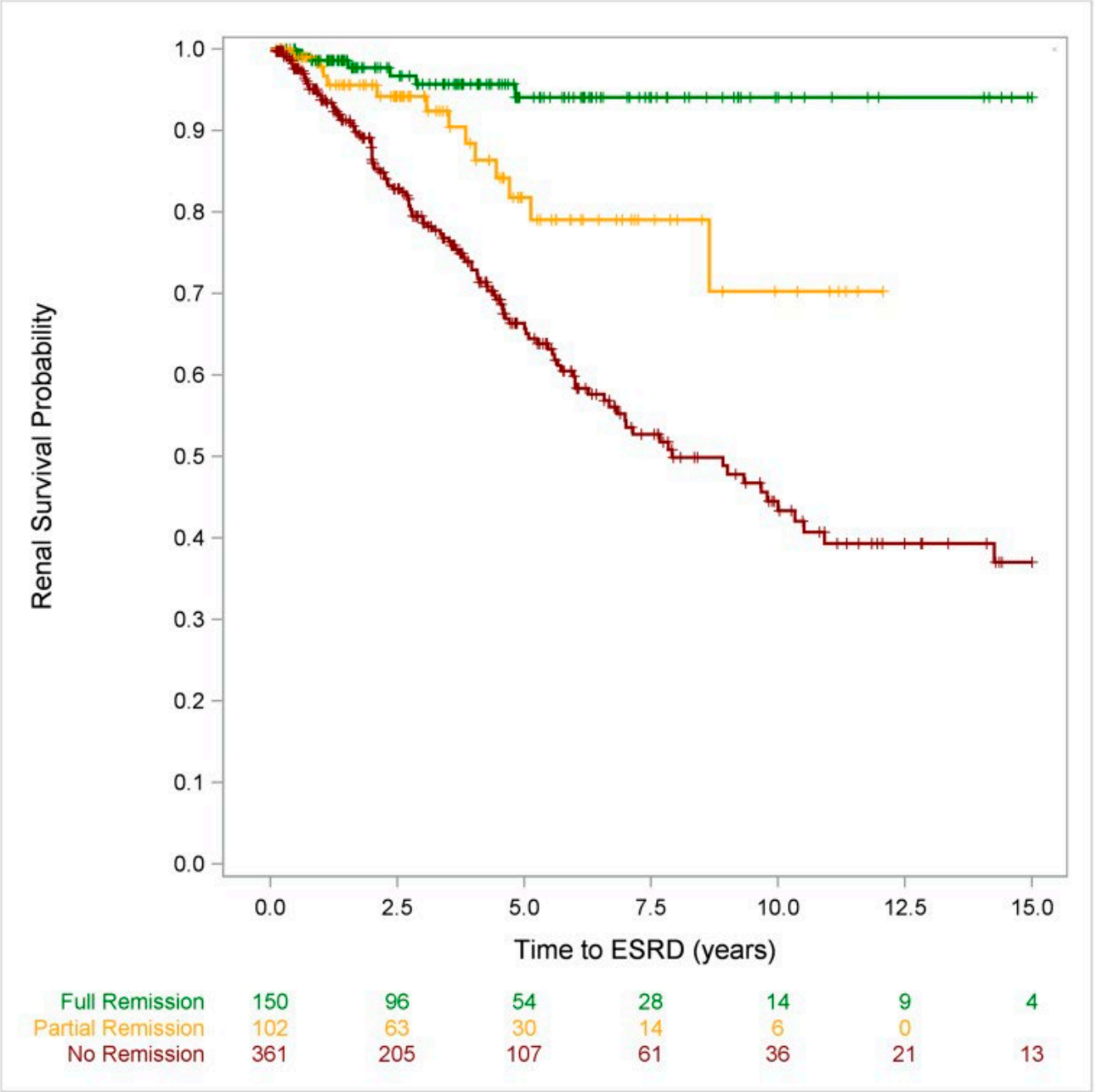


Tryggvason et al. NEJM 2006

Focal segmental glomerulosclerosis

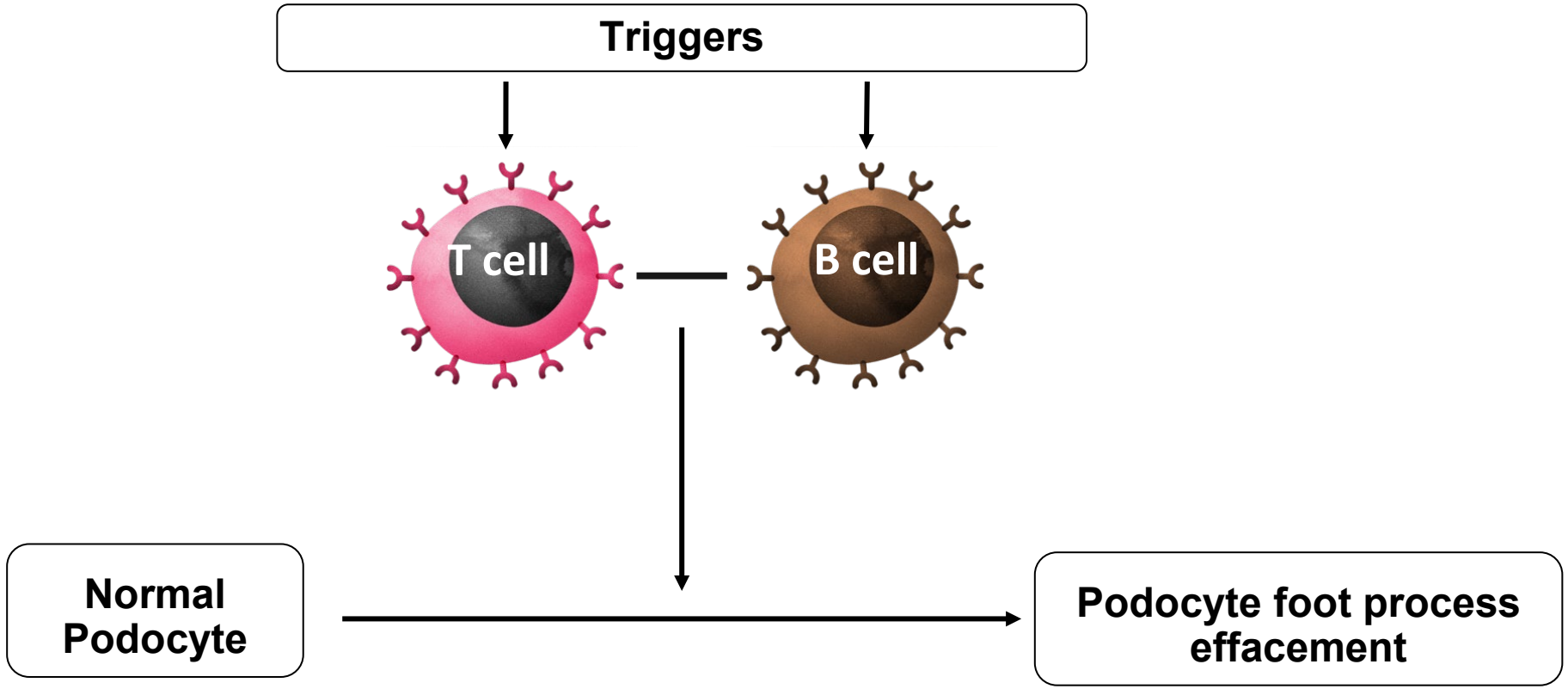


Long term outcomes Podonet Registry

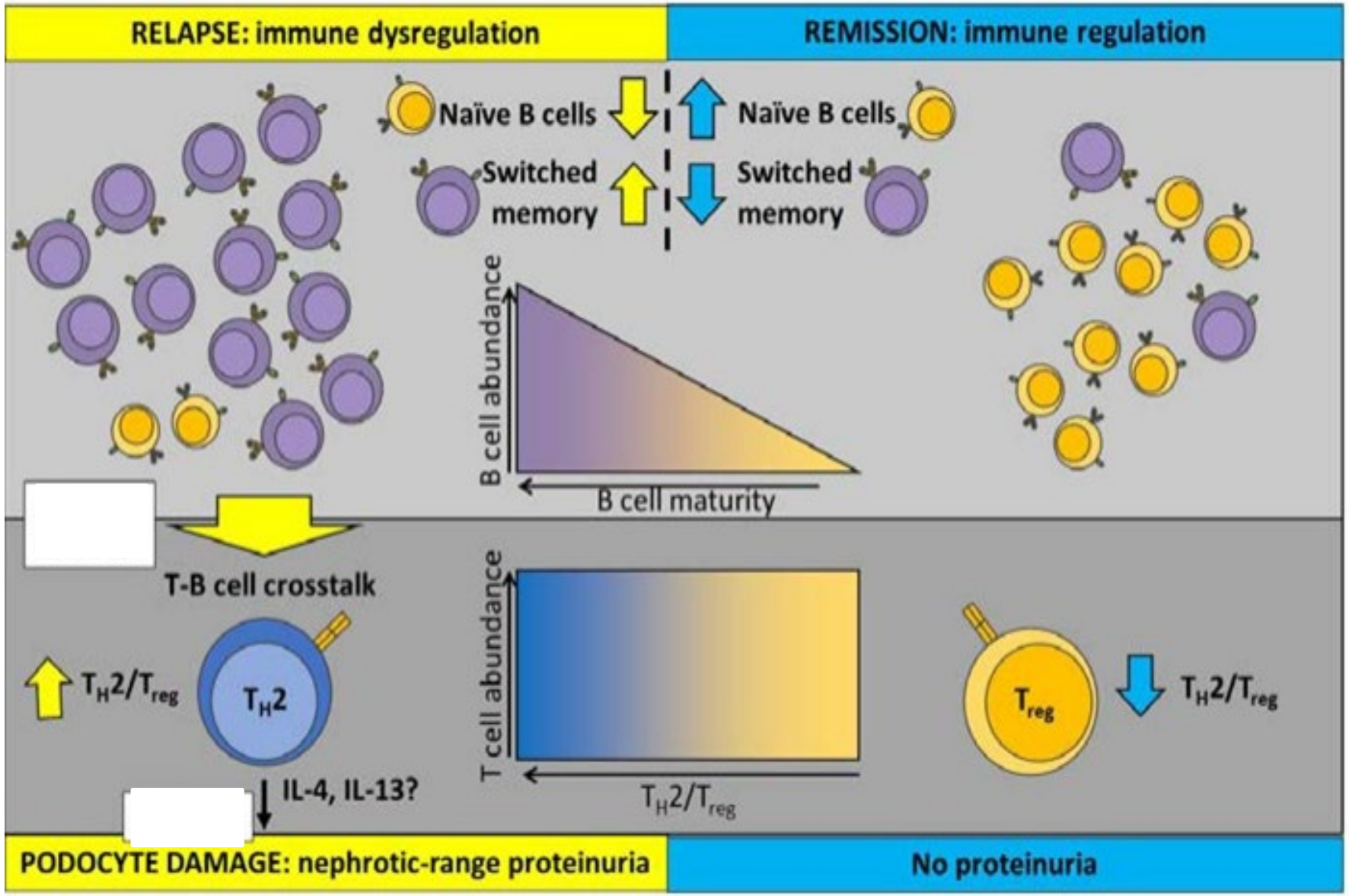


Trautmann JASN 2017

Immune pathogenesis of nephrotic syndrome



Shalhoub Lancet 1975

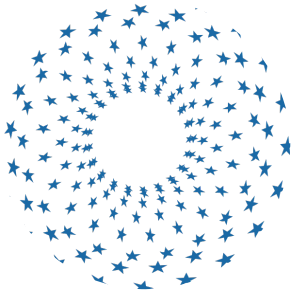


Takano et al. Used with permission

SUMMARY OF CURRENT UNDERSTANDING:

Structural

- Mutations affecting the structure and function of the glomerular filtration barrier



Circulating factors

- Elusive ‘glomerular permeability factor’

Immune Mediated

- T and B cells, cross talk
- Immune regulation

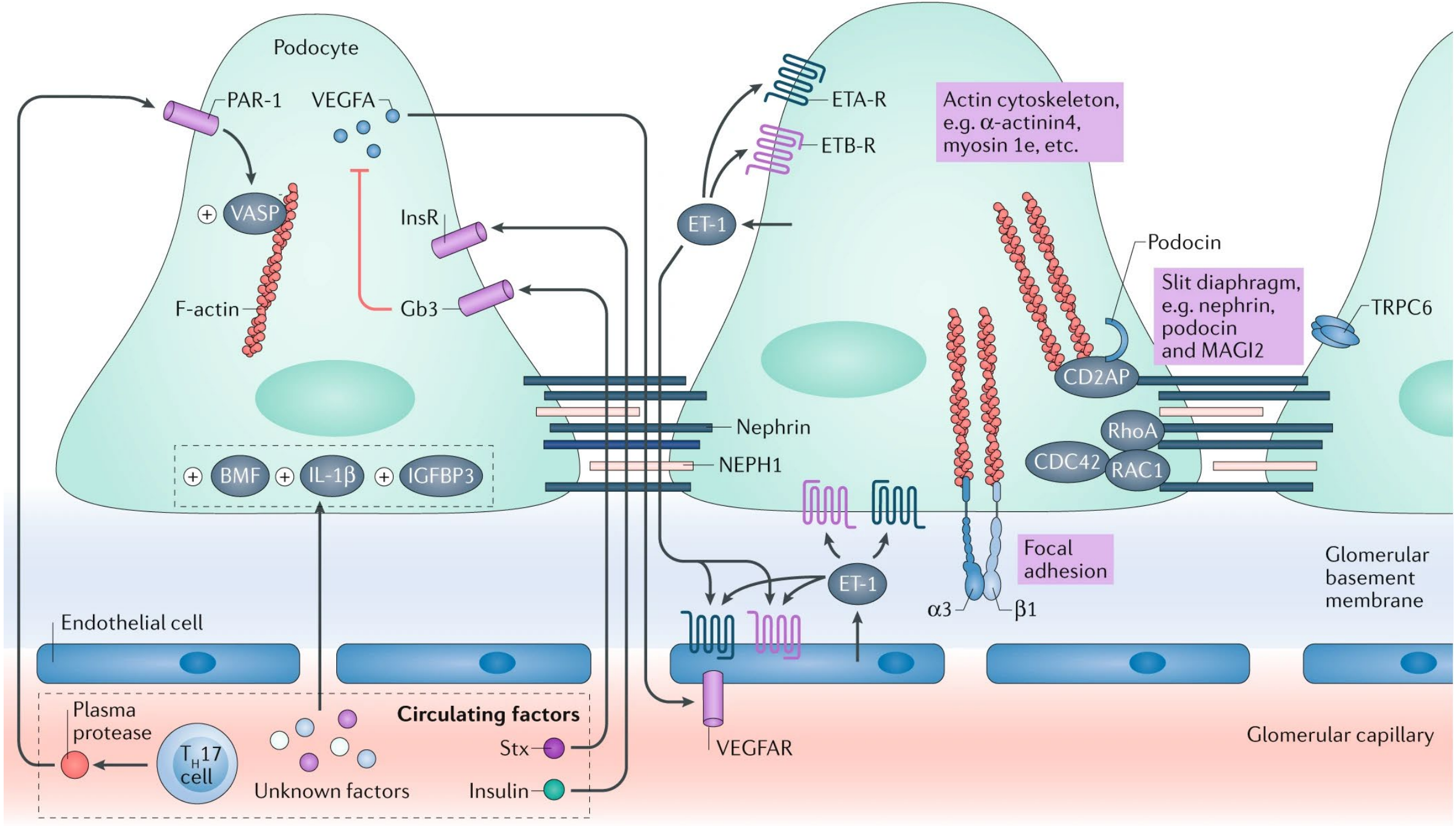
AGE OF PRESENTATION KEY TO DIAGNOSIS AND MANAGEMENT

<3 Months	3-12 Months	> 1 Year
• Genetic testing • Extrarenal manifestations • Congenital infection	• Genetic testing • Extrarenal manifestations • Kidney biopsy • *Idiopathic immune*	• Idiopathic immune • Genetic causes (less likely) • Kidney biopsy **not** performed

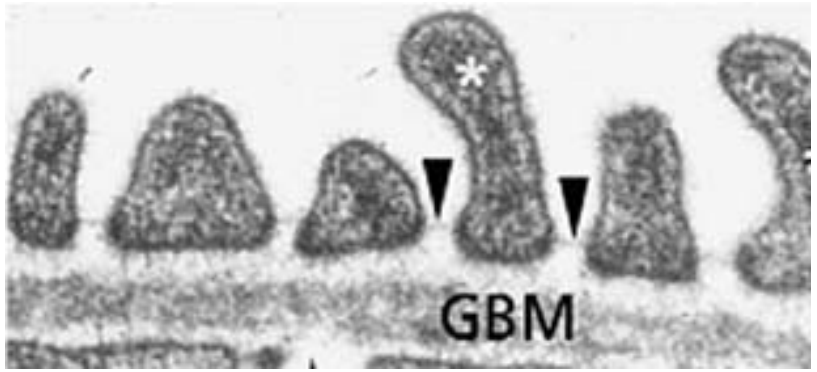
Likelihood of a monogenic cause by age:

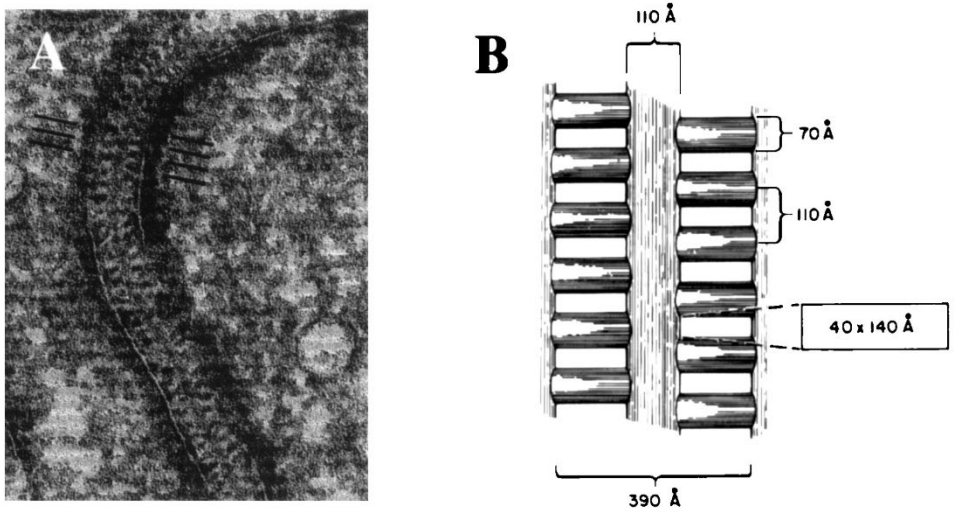
- 0 to 3 months – 69 %
- 4 to 12 months – 50 %
- 13 months to 6 years – 25 %
- 7 to 12 years – 18 %
- 13 to 17 years – 11 %
- >18 years – 21 %

Boyer O, Nat RevNephrol2021

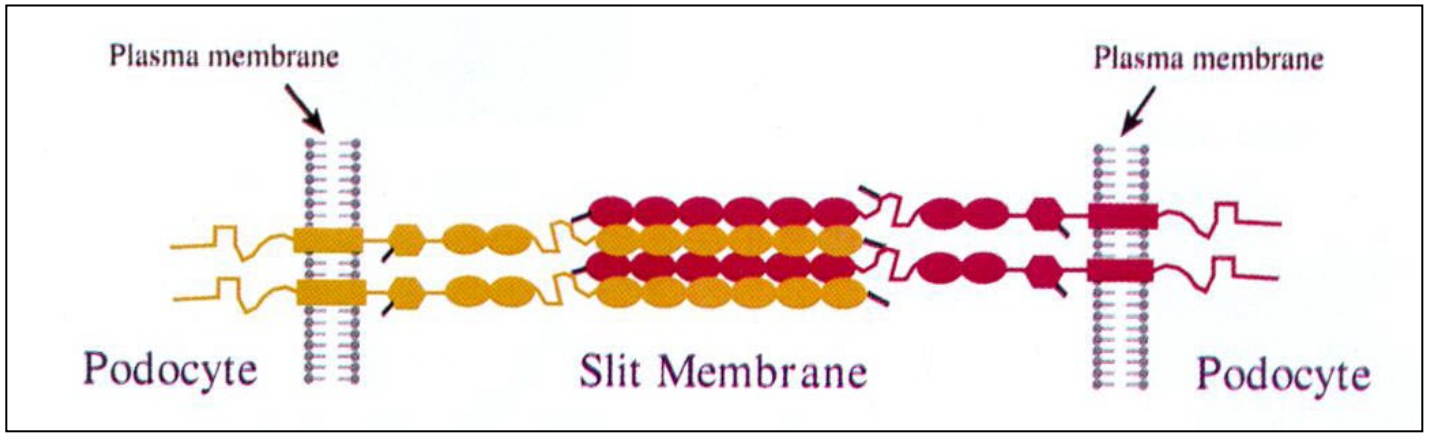

Podocyte
PAR-1
VEGFA
VASP
F-actin
InsR
Gb3
ET-1
ETA-R
ETB-R
Actin cytoskeleton, e.g. α-actinin4, myosin 1e, etc.
Podocin
Slit diaphragm, e.g. nephrin, podocin and MAGI2
TRPC6
CD2AP
RhoA
CDC42
RAC1
Nephrin
NEPH1
BMF
IL-1β
IGFBP3
ET-1
Focal adhesion
α3
β1
Glomerular basement membrane
Endothelial cell
Circulating factors
Plasma protease
T_H17 cell
Unknown factors
Stx
Insulin
VEGFAR
Glomerular capillary

Nephrin is the structural backbone of the slit diaphragm





Rodewald and Karnovsky, J Cell Biol, 1974



Nephrin

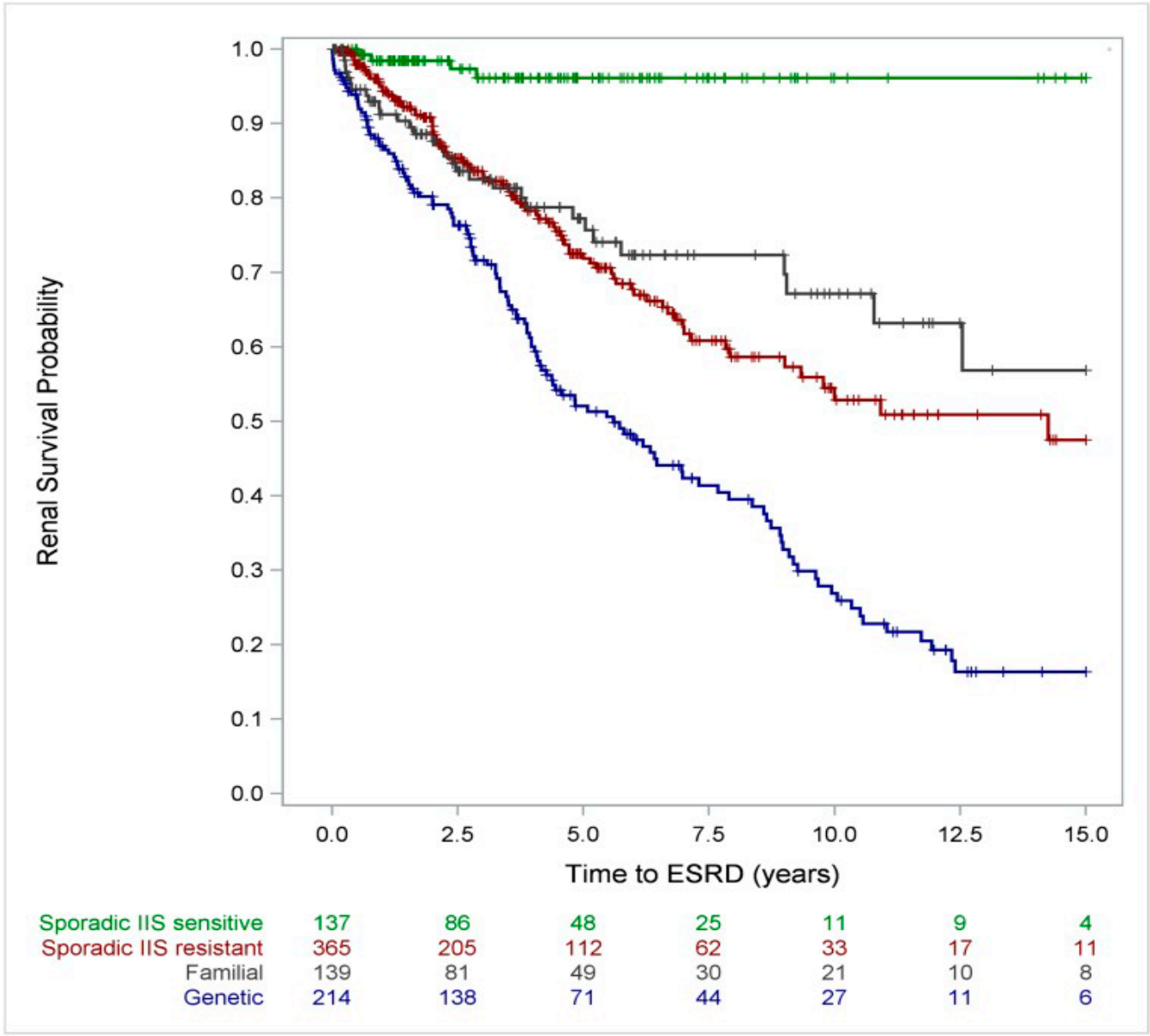
- Transmembrane protein
- Structural backbone of the slit diaphragm
- Homophilic interactions

Gene Symbol	Alternate Name	Inheritance	Syndrome Name	Comment
NPHS1	Nephrin	AR	*Finnish NS* **NS Type 1**	Congenital
NPHS2	Podocin	AR	**NS Type 2**	SRNS
PLCE1	NPHS3 PHOSPHOLIPASE C	AR	**NS Type 3**	Congenital SRNS
WT1	Wilm's tumour 1	AD	*Frasier* *Denys Drash* **NS Type 4**	Congenital Childhood SRNS
LAMB2	Laminin Beta-2	AR	*Pierson* **NS Type 5**	Congenital
PTPRO	GLEPP1, PTPU2	AR	**NS Type 6**	Childhood
ACTN4	Actinin Alpha-4	AD or AR	FSGS 1	SRNS, CKD as adult
TRPC6	Transient receptor potential ion channel 6	AD	FSGS 2	SRNS, ?Later onset
CD2AP	CD2 associated protein	AR	FSGS 3	Early Onset
APOL1	Apolipoprotein L1		FSGS 4	Increased risk of FSGS in Africans
INF2	Inverted formin 2	AD	FSGS 5	SRNS Adolescence or Adult

Gene	Inheritance	Accession no.	Disease
MMACHC	AR	NM_015506.3	Cobalamin C deficiency, TMA, and nephrotic syndrome
*MYO1E**	AR	NM_004998	Familial SRNS
NEU1	AR	NM_000434.4	Nephrosialidosis (sialidosis type II + childhood NS)
NPHP4	AR	NM_015102.5	Nephronophthisis with FSGS and nephrotic range proteinuria
*NPHS1**	AR	NM_004646	CNS/SRNS
*NPHS2**	AR	NM_014625	CNS, SRNS
NUP85	AR	NM_024844.5	SRNS
*NUP93**	AR	NM_014669	Childhood SRNS
*NUP107**	AR	NM_020401	Childhood SRNS
NUP160	AR	NM_015231.2	SRNS
NUP205	AR	NM_015135	Childhood SRNS
NXF5	XR	NM_032946	FSGS with co-segregating heart block disorder
*OCRL**	XR	NM_000276	Dent's disease-2, Lowe syndrome, ± FSGS, ± nephrotic range proteinuria
OSGEP	AR	NM_017807.4	NS with primary microcephaly
PAX2	AD	NM_003987	Adult-onset FSGS without extrarenal manifestations
PDSS2	AR	NM_020381	Leigh syndrome
PLCe1	AR	NM_016341	CNS/SRNS
PMM2	AR	NM_000303	Congenital disorder of glycosylation
*PODXL**	AD	NM_005397	FSGS
PTPRO	AR	NM_030667	NS
SCARB2	AR	NM_005506	Action myoclonus renal failure syndrome ± hearing loss
SGPL1	AR	NM_003901.4	Primary adrenal insufficiency and SRNS
SMARCAL1	AR	NM_014140	Schimke immuno-osseous dysplasia
SYNPO	AD	NM_007286	Sporadic FSGS (promoter mutations)
TBC1D8B	XR	NM_017752.3	Early-onset SRNS with FSGS
TNS2	AR	NM_170754.3	SSNS/SDNS (with MCD/FSGS/DMS on biopsy)
TP53RK	AR	NM_033550.4	NS with primary microcephaly
TPRKB	AR	NM_001330389.1	NS with primary microcephaly
*TRPC6**	AD	NM_004621	Familial and sporadic SRNS (mainly adult)
TTC21B	AR	NM_024753	FSGS with tubulointerstitial involvement
WDR73	AR	NM_032856	Galloway-Mowat syndrome (microcephaly and SRNS)
*WT1**	AD	NM_024426	Sporadic SRNS (children: may be associated with abnormal genitalia); Denys-Drash and Frasier syndrome
XPO5	AR	NM_020750	Childhood SRNS
ZMPSTE24	AR	NM_005857	Mandibuloacral dysplasia with FSGS
MYH9	AD/assoc.	NM_002473	MYH9-related disease; Epstein and Fechtner syndromes
*APOL1**	G1, G2 risk alleles	NM_003661	Increased susceptibility to FSGS and ESRD in African Americans, Hispanic Americans and in individuals

Determinant of outcomes

- Immunosuppression sensitivity
- Identification of a genetic mutation



Trautmann JASN 2017

CASE

Patient Alberta – 3 year old girl

- History of presenting illness
  - Unwell for 2 weeks with fatigue
  - 10 days of facial oedema
  - Some loose stools
  - No rash

- **Past History**
  - Pneumonia

Examination

- Oedema – puffy eyes
- 16.5 kg (90^{th} centile)
- 98.5 cm (90^{th} centile)
- 110/63 mm Hg (95^{th} centile 109/68 mmHg)

What would you do next?

- A diagnostic test was done.

Investigations

- Urinalysis
  - SG 1.020
  - Protein >3 g/L
  - Blood Moderate
  - RBCs 6 – 10 cells/hpf
  - WBCs 3 – 5 cells/hpf
  - Casts None

Investigations - 2

Haemoglobin	89	g/L
MCV	62	fL
WBC	10.6	$x10^9/L$
Creatinine	10	umol/L
Urea	4.1	mmol/L
Sodium	133	mmol/L
Albumin	9	g/L
Urine PCR	2104	mg/mmol

Other Investigations

Cholesterol	10.44	mmol/L		
C_3	1.22	g/L	Ref Range	0.6 – 1.6
C_4	0.32	g/L		0.1 – 0.4
IgA	0.57	g/L		0.35 – 2.4
ANCA	neg			
Anti-MPO	<2.0	KEU/L	<5	
Anti-PR3	<2.0	KEU/L	<5	
ANA	neg			

What would you do next?

Initial Management

- Low Na diet

- IV Methylprednisolone 150 mg (225 mg/m^2/dose) one dose
- Prednisone 17 mg bid (2 mg/kg/day) (50 mg/m^2/day)
- Iron elemental 25 mg bid (3 mg/kg/day)
- Albumin 65 ml (25%) x 4 (1 g/kg/dose)
  plus fuorsemide 1 mg/kg half way through infusion

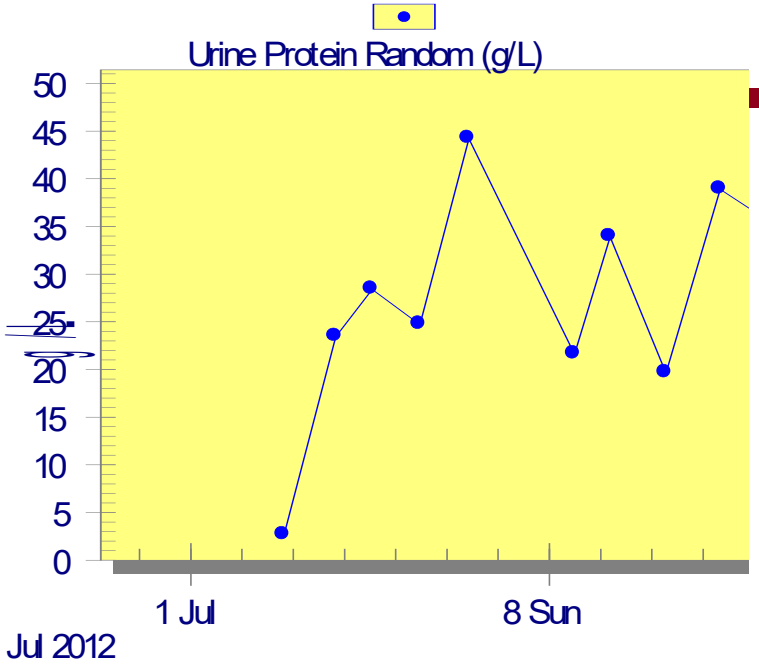
Careful History and Physical Exam

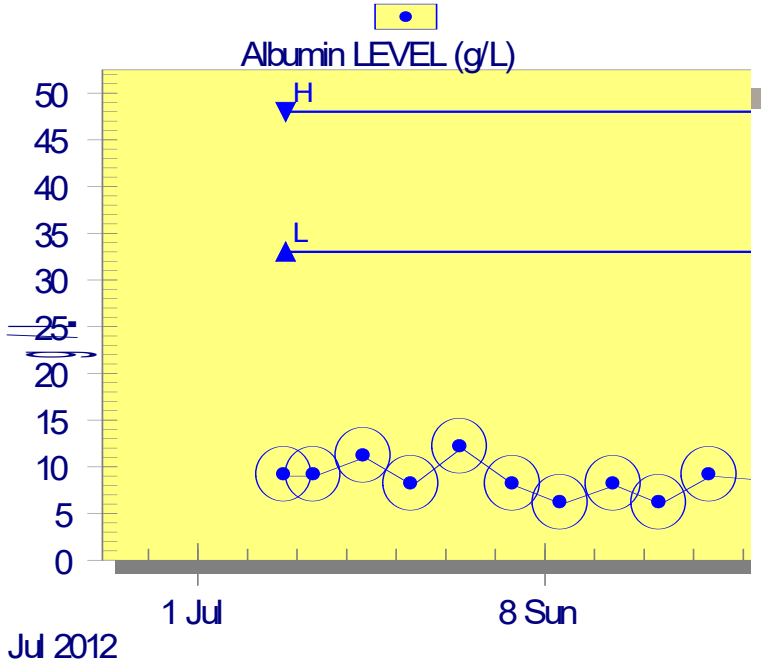
- History
  - Family history, consanguinity, birth history
  - Risk factors (secondary causes sickle cell, HIV, Hep B, malaria, parvovirus B19, CMV, syphilis, TB)
  - Other glomerular diseases (SLE, membranous, C3 GN)
  - Infections, adrenal insufficiency

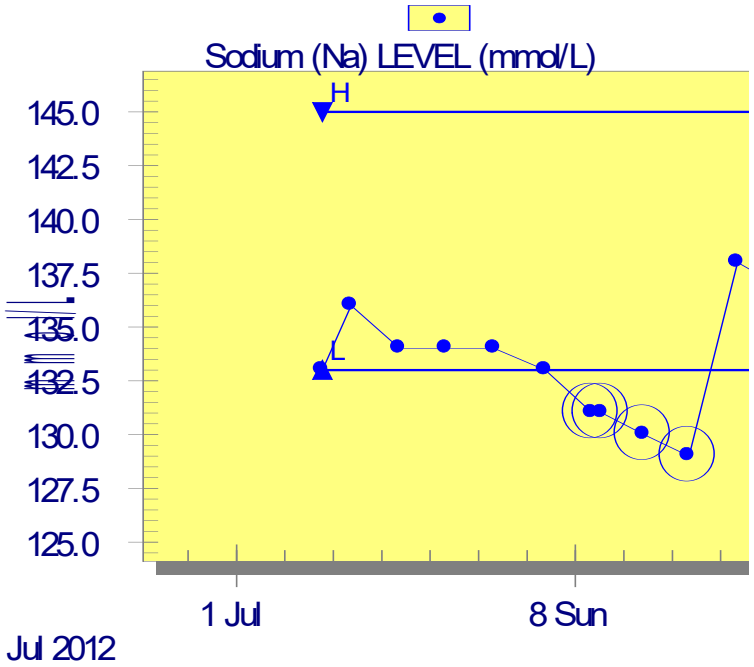
- Physical exam
  - Skeletal, neuro, eye, ear, congenital anomalies, ambiguous genitalia
  - Pubertal exam

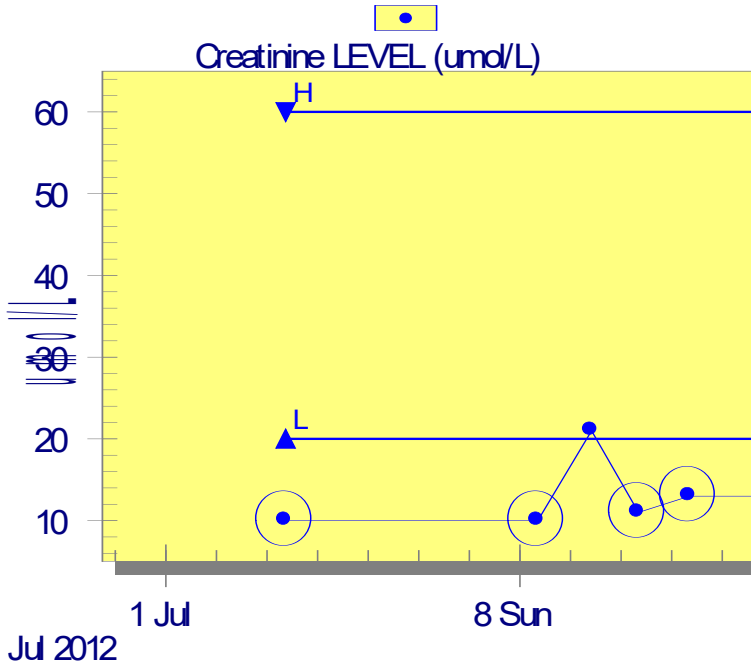
Other laboratory tests

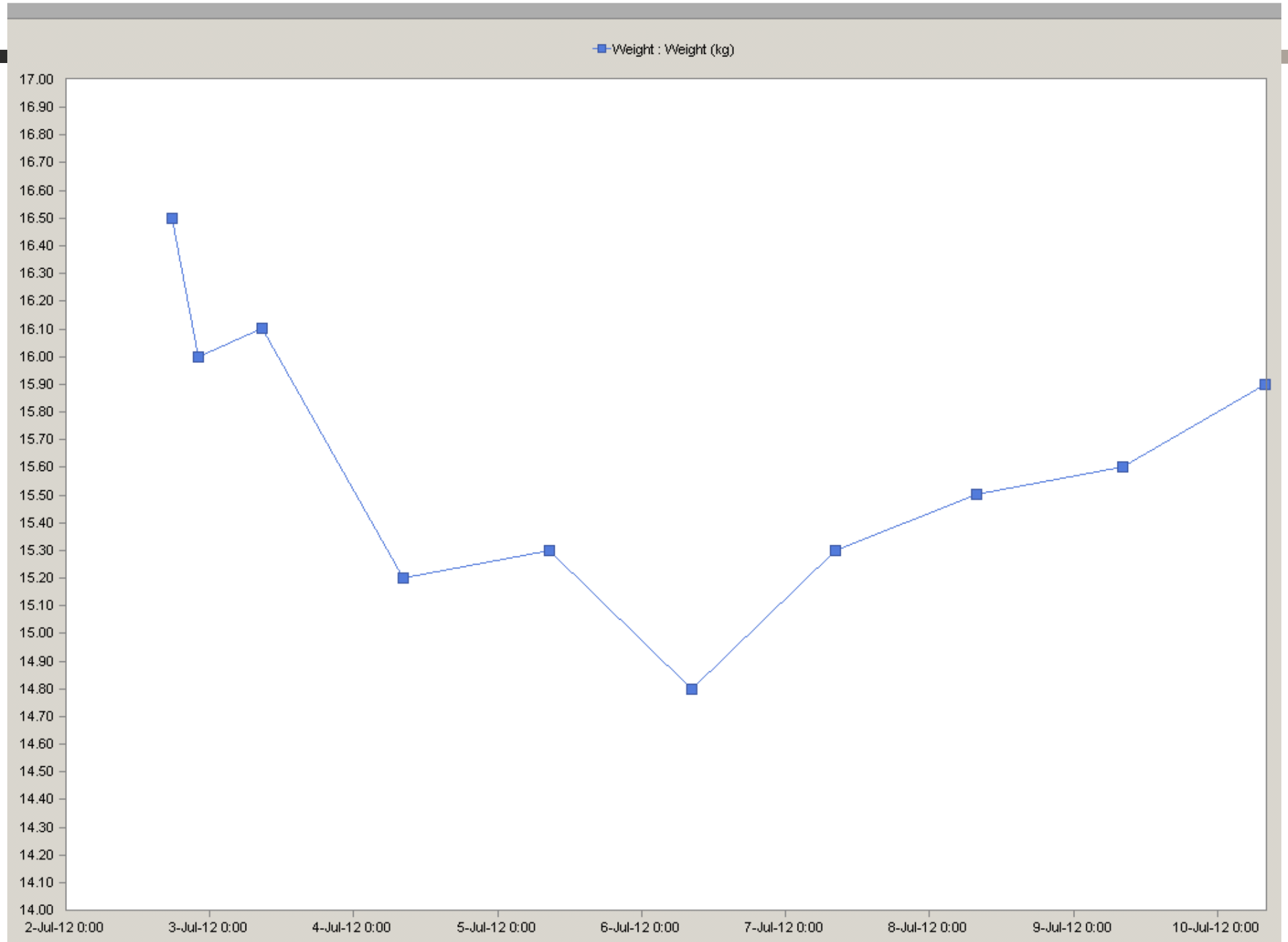
- Genetic testing (test for known panel of genes, whole exome sequencing)
  - Only ~30% will have an identified mutation
- Liver tests, lipid profile, clotting
- TSH
- Viral tests (Hep Bs Ag, anti-HCV-IgG, syphilis, HIV)
- Chest Xray
- Renal ultrasound


Urine Protein Random (g/L)
50
45
40
35
30
25
20
15
10
5
0
1 Jul
8 Sun
Jul 2012


Albumin LEVEL (g/L)
H
L
50
45
40
35
30
25
20
15
10
5
0
1 Jul
8 Sun
Jul 2012


Sodium (Na) LEVEL (mmol/L)
H
L
145.0
142.5
140.0
137.5
135.0
132.5
130.0
127.5
125.0
1 Jul
8 Sun
Jul 2012

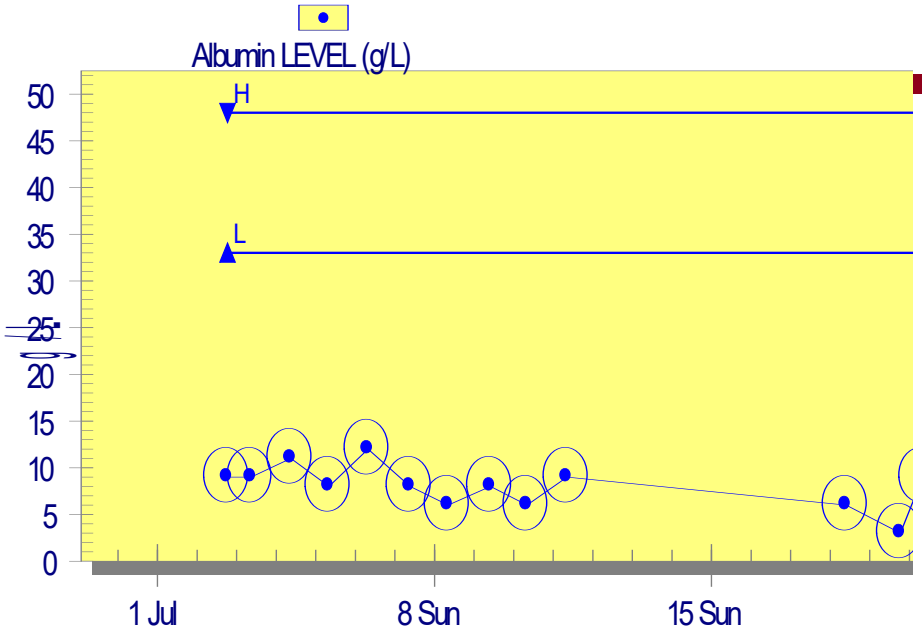

Creatinine LEVEL (umol/L)
H
L
60
50
40
30
20
10
1 Jul
8 Sun
Jul 2012

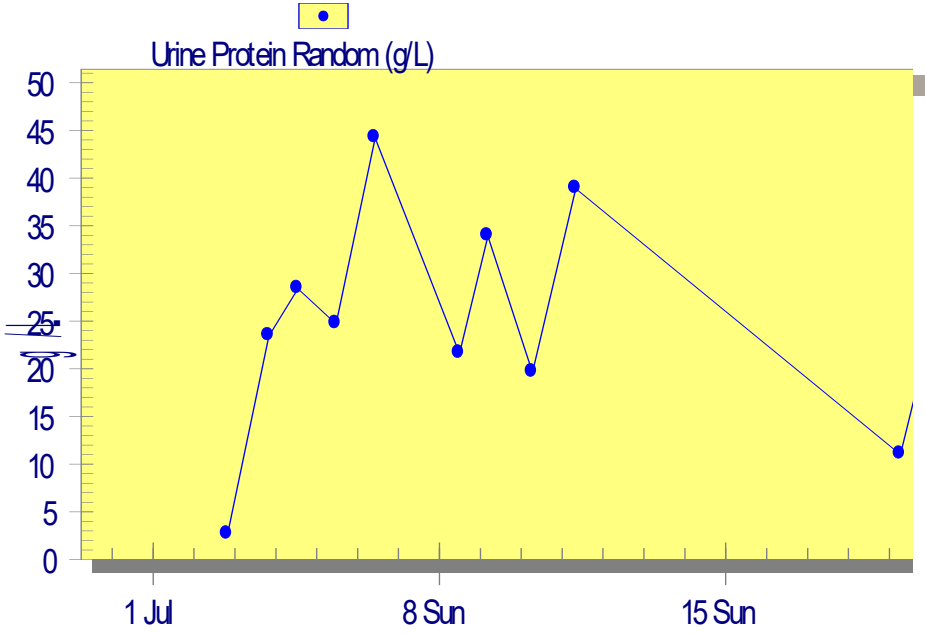

Weight : Weight (kg)
17.00
16.90
16.80
16.70
16.60
16.50
16.40
16.30
16.20
16.10
16.00
15.90
15.80
15.70
15.60
15.50
15.40
15.30
15.20
15.10
15.00
14.90
14.80
14.70
14.60
14.50
14.40
14.30
14.20
14.10
14.00
2-Jul-12 0:00
3-Jul-12 0:00
4-Jul-12 0:00
5-Jul-12 0:00
6-Jul-12 0:00
7-Jul-12 0:00
8-Jul-12 0:00
9-Jul-12 0:00
10-Jul-12 0:00

Discharge Medications

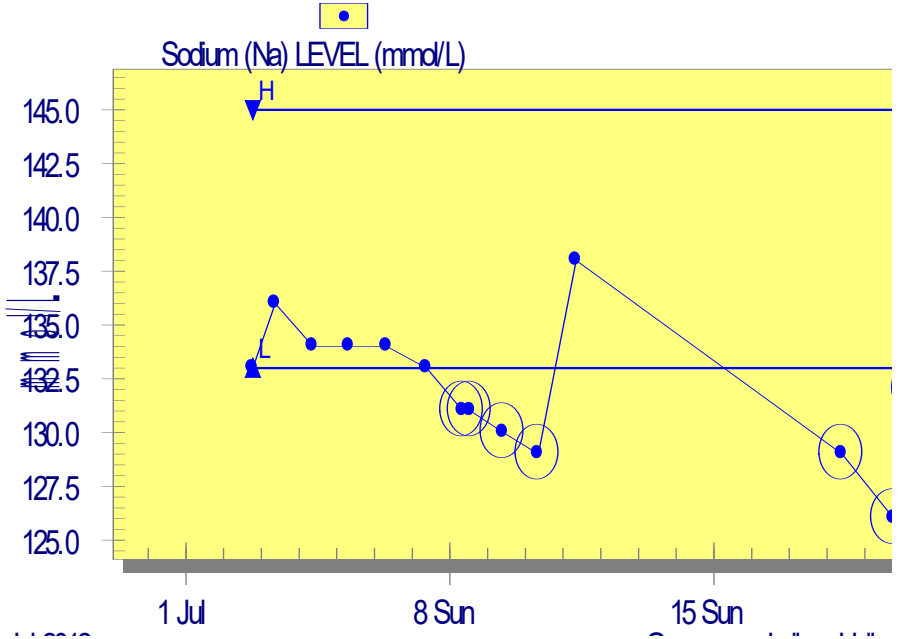
- Amlodipine 1.5 mg bid (0.2 mg/kg/day)
- Iron elemental 25 mg bid (3 mg/kg/day)
- Vitamin D 800 units daily
- Prednisone 20 mg bid (2.4 mg/kg/day) (60 mg/m^2/day)

Progress…4 weeks later

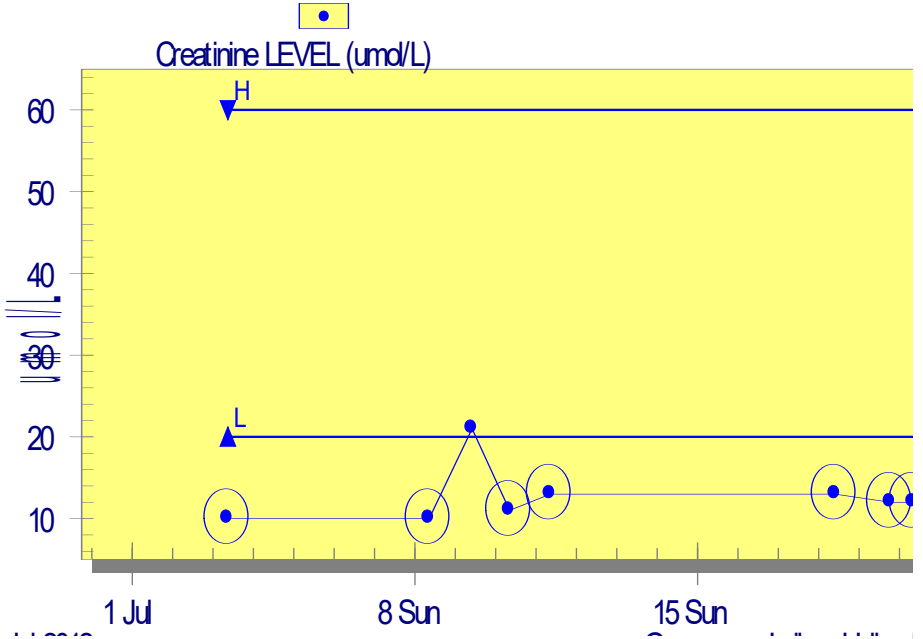




Sodium (Na) LEVEL



Creatinine LEVEL



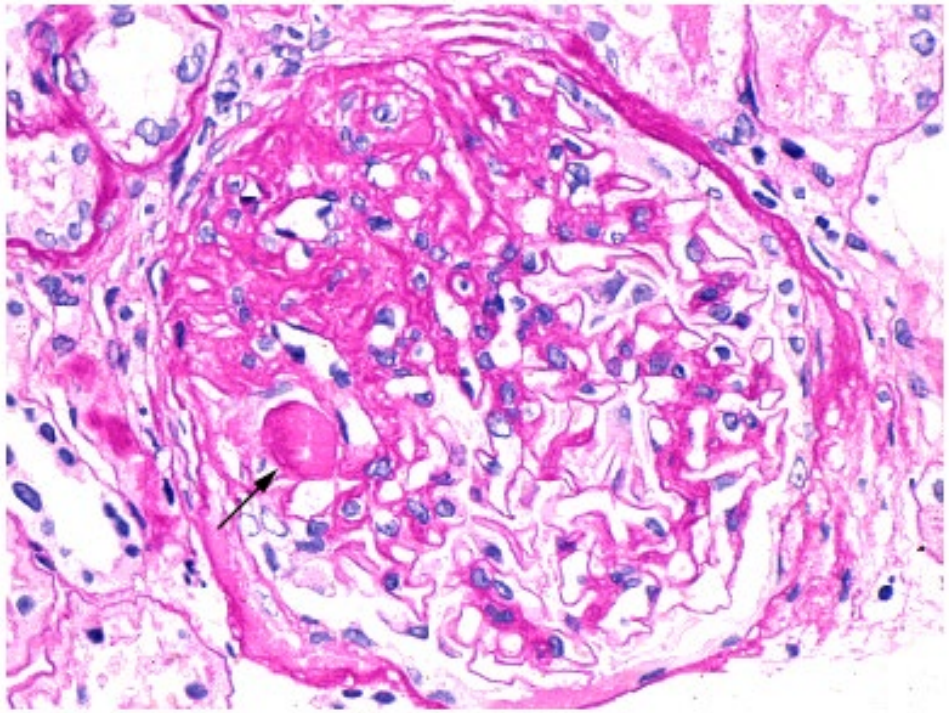
What Next?

Re-admitted

- Weight 18.2 kg (initially 16.5 kg)
- More 25% Albumin
- Another diagnostic test was done…

Moderate FSGS

Elect



Light micrograph in focal segmental glomerulosclerosis (FSGS) shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal.

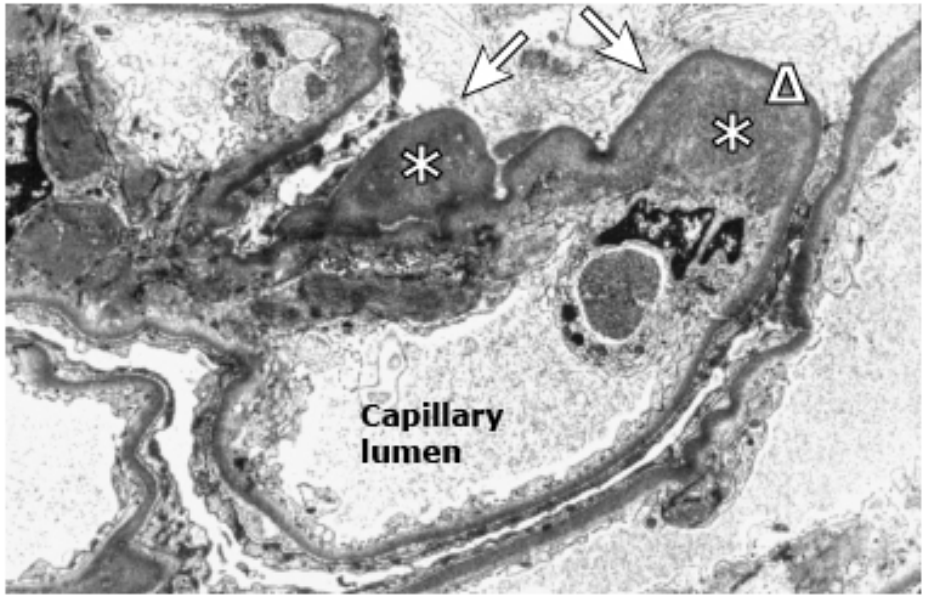
- 44 glomeruli, none of which are globally sclerosed
- 11 glomeruli show segmental sclerosis
- Mild mesangial proliferation and 2 glomeruli show segmental extracapillary proliferation or crescents
- No spikes or duplications are seen on silver stains.
- The interstitium shows very mild focal atrophy

Uptodate.com

Immunofluorescence

- IgG: negative
- IgA: negative
- IgM: 3+ focal and segmental smudgy staining
- kappa: 2+ segmental smudgy staining
- lambda: 1+ segmental smudgy staining
- fibrinogen: negative
- C3c: 1+ segmental staining
- C1q: negative

Electron microscopy



Electron micrograph in focal segmental glomerulosclerosis shows diffuse epithelial cell foot process fusion with occasional loss of the epithelial cells (arrows). The other major finding is massive subendothelial hyaline deposits (asterisk) under the glomerular basement membrane (Δ). These deposits reflect insudation of plasma proteins, not the deposition of immunoglobulins. These deposits contribute to narrowing of the capillary lumens.

So…what to do next?

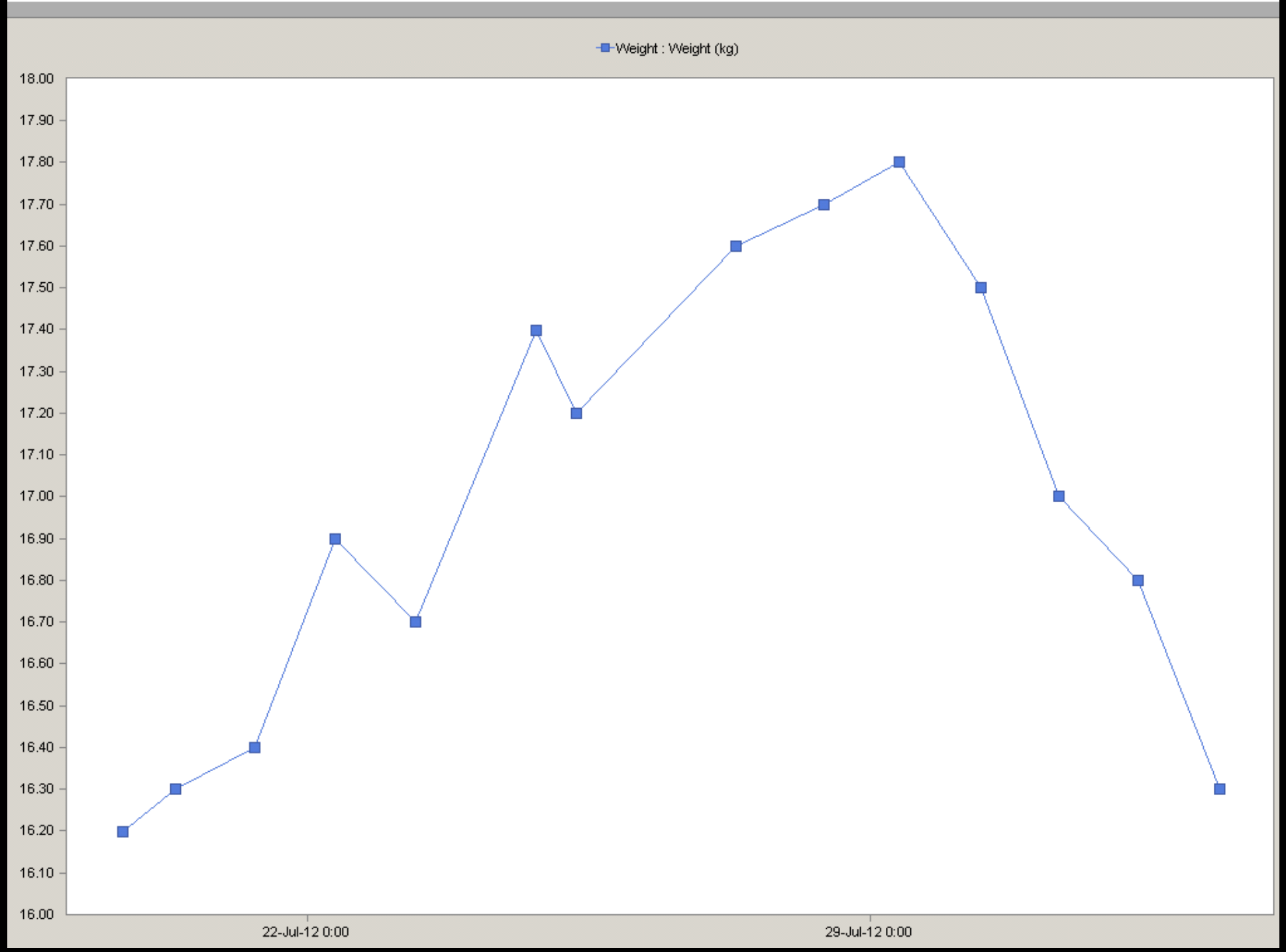
IPNA Clinical Practice Guideline
Pediatr Nephrol 2020

First-line immunosuppressive treatment in children with SRNS

- We recommend that CNI (cyclosporine or tacrolimus) should be the first-line immunosuppressive therapy in children with SRNS and started once the diagnosis is confirmed (Fig. 2) (grade B, moderate recommendation).
- We suggest tapering PDN treatment once diagnosis of SRNS is established and discontinuing PDN therapy after 6 months (grade D, weak recommendation).
- We recommend withholding or delaying CNI treatment in patients with an eGFR < 30 ml/min/1.73 m^2, AKI, and/or uncontrolled hypertension (grade X, strong recommendation).
- We recommend withholding CNI and stopping PDN treatment in patients with evidence for a monogenic form of SRNS (grade B, moderate recommendation).
- When CNIs are not available or unaffordable, we suggest using cyclophosphamide (CPH) [intravenous or po] with or without high-dose steroids (grade D, weak recommendation).
- We recommend making patients and families aware of potential side effects of immunosuppressive medication as given in Table 4 (grade X, strong recommendation).

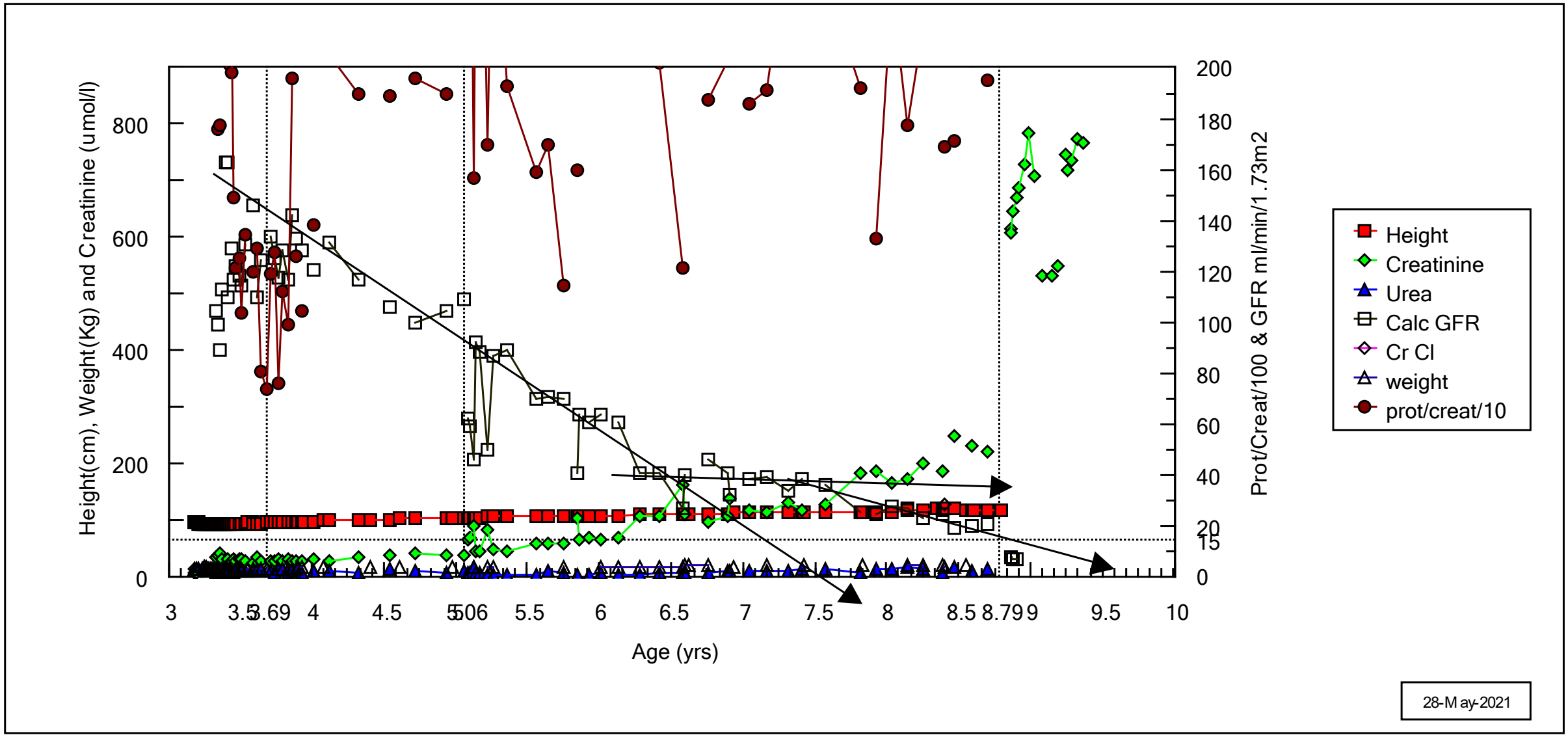
Treatment

- Amlodipine 1.5 mg bid (0.2 mg/kg/day)
- Enalapril 3.5 mg bid (0.4 mg/kg/day)
- Cyclosporin A 40 mg bid
- Enoxaparin 15 mg daily
- Hydrochlorothiazide 18 mg bid (2 mg/kg/day)
- Iron elemental 37.5 mg bid (3 mg/kg/day)
- Penicillin 150 mg bid
- Prednisone 40 mg alt days (2.4 mg/kg/day or 60 mg/m^2/day)
- Albumin 25% 50 ml bid with furosemide 1 mg/kg


Weight : Weight (kg)
18.00
17.90
17.80
17.70
17.60
17.50
17.40
17.30
17.20
17.10
17.00
16.90
16.80
16.70
16.60
16.50
16.40
16.30
16.20
16.10
16.00
22-Jul-12 0:00
29-Jul-12 0:00

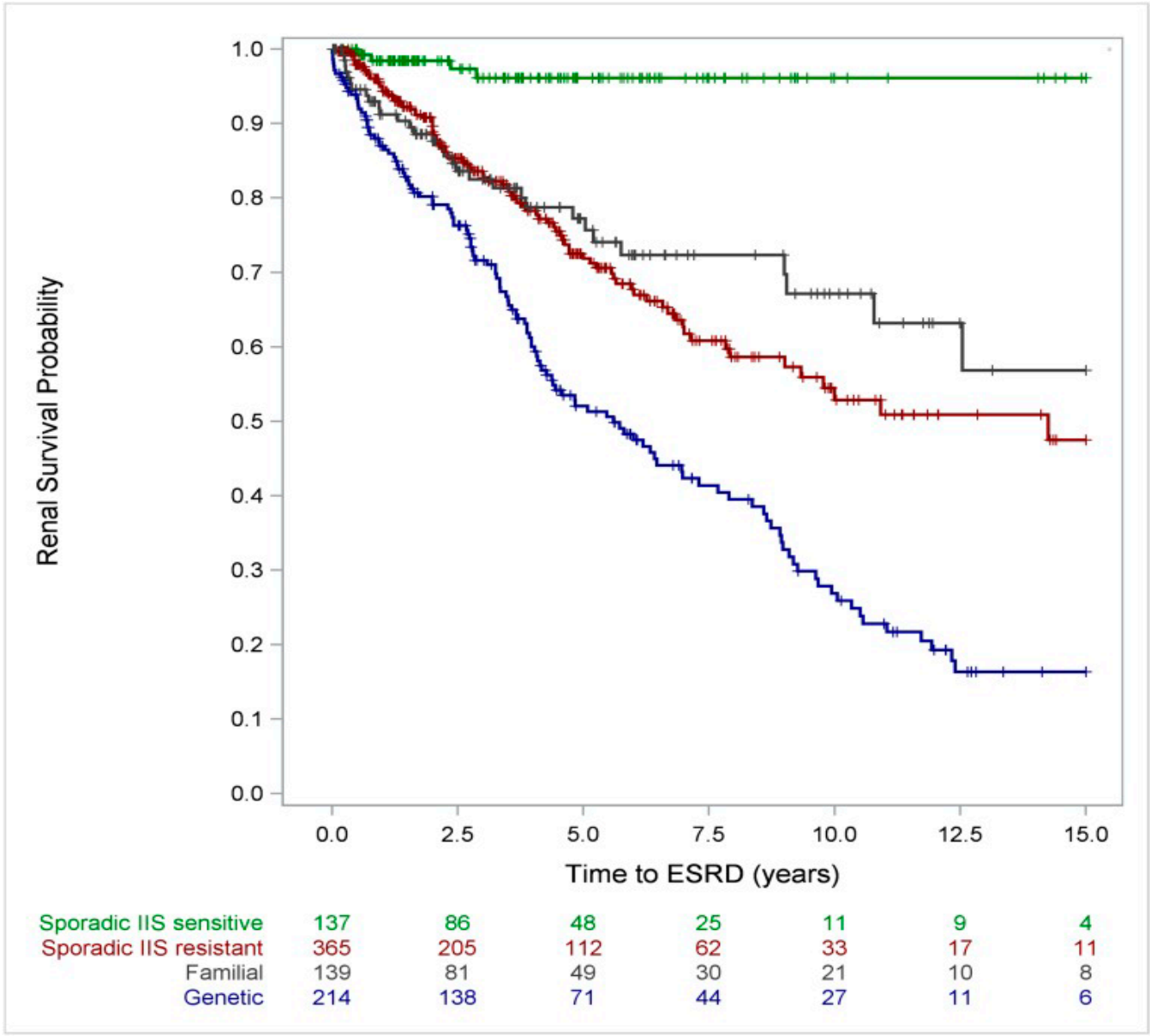
Longer Term

- What would you advise the family?


Height(cm), Weight(Kg) and Creatinine (umol/l)
Prot/Creat/100 & GFR ml/min/1.73m2
Age (yrs)
Height
Creatinine
Urea
Calc GFR
Cr Cl
weight
prot/creat/10
28-May-2021

Determinant of outcomes

- Immunosuppression sensitivity
- Identification of a genetic mutation

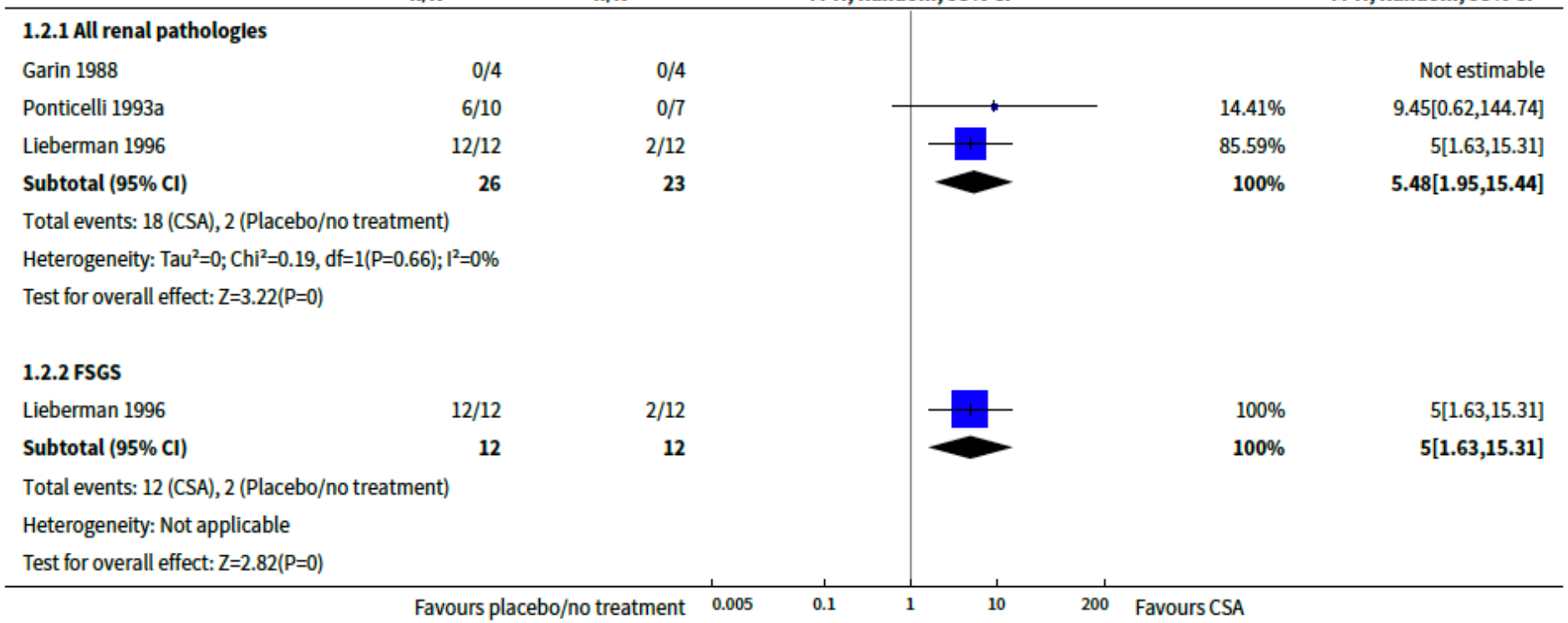


Trautmann JASN 2017

First line treatment – complete or partial remission as outcome

Analysis 1.2. Comparison 1 Cyclosporin versus placebo/no treatment, Outcome 2 Complete or partial remission.

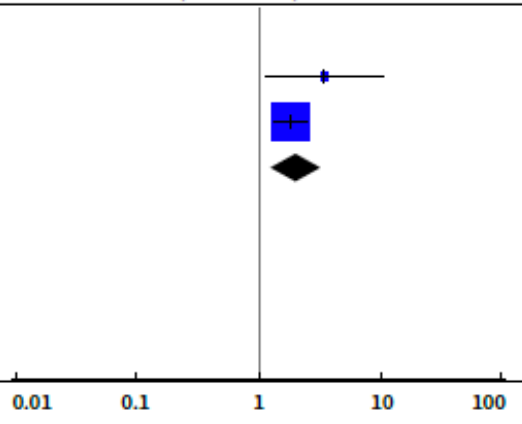
Study or subgroup	CSA n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 All renal pathologies					
Garin 1988	0/4	0/4			Not estimable
Ponticelli 1993a	6/10	0/7		14.41%	9.45[0.62,144.74]
Lieberman 1996	12/12	2/12		85.59%	5[1.63,15.31]
Subtotal (95% CI)	**26**	**23**		**100%**	**5.48[1.95,15.44]**
Total events: 18 (CSA), 2 (Placebo/no treatment)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.19$, df=1(P=0.66); $I^2=0\%$					
Test for overall effect: Z=3.22(P=0)					
1.2.2 FSGS					
Lieberman 1996	12/12	2/12		100%	5[1.63,15.31]
Subtotal (95% CI)	**12**	**12**		**100%**	**5[1.63,15.31]**
Total events: 12 (CSA), 2 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.82(P=0)					

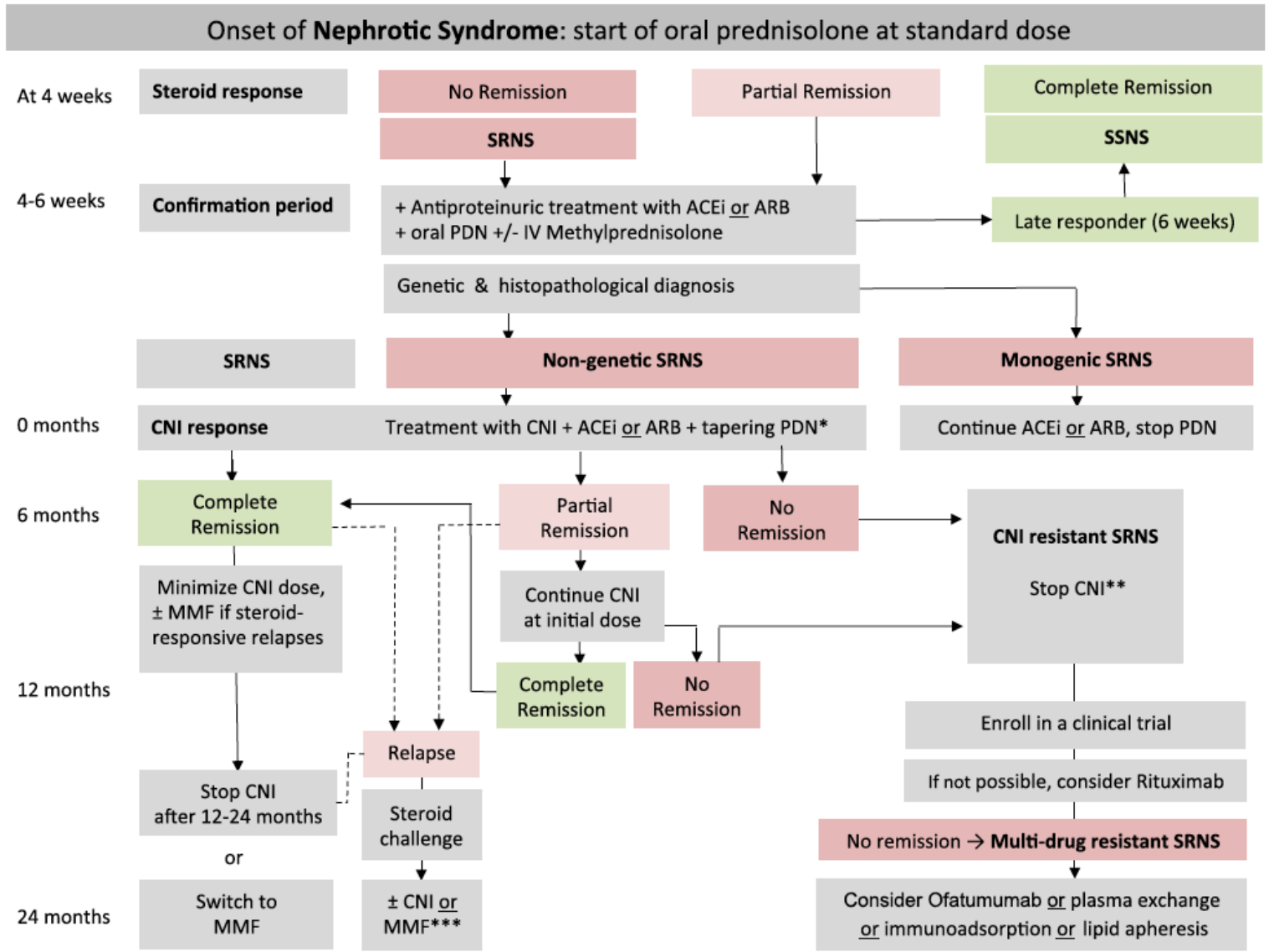


Calcineurin Inhibitor versus Cyclophosphamide

Analysis 2.1. Comparison 2 Calcineurin inhibitor versus IV cyclophosphamide, Outcome 1 Treatment response at 3 to 6 months.

Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Complete or partial remission					
APN 2008	9/15	3/17		15.17%	3.4[1.12,10.28]
Gulati 2012	52/63	28/61		84.83%	1.8[1.34,2.42]
Subtotal (95% CI)	**78**	**78**		**100%**	**1.98[1.25,3.13]**
Total events: 61 (CNI), 31 (IV CPA)					
Heterogeneity: Tau^2=0.04; Chi^2=1.24, df=1(P=0.26); I^2=19.67%					
Test for overall effect: Z=2.92(P=0)					




Onset of Nephrotic Syndrome: start of oral prednisolone at standard dose
At 4 weeks
Steroid response
No Remission
Partial Remission
Complete Remission
SRNS
SSNS
4-6 weeks
Confirmation period
+ Antiproteinuric treatment with ACEi or ARB
+ oral PDN +/- IV Methylprednisolone
Late responder (6 weeks)
Genetic & histopathological diagnosis
SRNS
Non-genetic SRNS
Monogenic SRNS
0 months
CNI response
Treatment with CNI + ACEi or ARB + tapering PDN*
Continue ACEi or ARB, stop PDN
6 months
Complete Remission
Partial Remission
No Remission
CNI resistant SRNS
Stop CNI**
Minimize CNI dose, ± MMF if steroid-responsive relapses
Continue CNI at initial dose
12 months
Complete Remission
No Remission
Enroll in a clinical trial
Relapse
If not possible, consider Rituximab
Stop CNI after 12-24 months
Steroid challenge
No remission → Multi-drug resistant SRNS
or
24 months
Switch to MMF
± CNI or MMF***
Consider Ofatumumab or plasma exchange or immunoadsorption or lipid apheresis

KEY MESSAGES

1. Rare disease, diagnosis often missed, significant complications
2. Importance of glomerular filtration barrier and importance of the immune system
3. Remission of proteinuria most important determinant of outcome
4. Careful management with ACEi, calcineurin inhibitors, CKD management, preparation for transplant, and beware of relapse

Questions

https://www.cbc.ca/news/canada/calgary/alberta-children-s-hospital-covid-surgery-1.6180991

SLE

Systemic Lupus erythematosus

Marinka Twilt, MD, MScE, PhD

Alberta Children's Hospital

Agenda

- Juvenile SLE
- ACR SLE criteria
- Case
- NLE
- MCTD

SLE

- Caused by a loss of “Tolerance”
- Anti-body mediated disease
- Some congenital forms of SLE (e.g. homozygous anti-C1q deficiency)
- **Anti-dsDNA Antibody**
- Involvement of skin, blood/marrow, and kidneys in majority.

SLE

- Pediatric presentation >>>> severe than adult presentation
- More frequent organ involvement
- More frequent severe organ involvement

SLE Classification criteria

- ACR Criteria (**for classification**) - most recently modified in 1997
- Classification requires any 4 criteria
- 76.6% sensitivity, and 93.4% specificity in children.

ACR criteria (11)

- Malar rash (fixed erythema, flat or raised, sparing nasolabial folds)
- Discoid rash (raised erythematous patches with keratotic scaling and follicular plugging)
- Photosensitivity (rash from exposure to sunlight)
- Oral or Nasopharyngeal ulceration (usually painless)
- Arthritis (non-erosive, involving at least 2 peripheral joints)
- Serositis (pleuritis, pleural effusion, pericarditis, pericardial effusion)
- Renal disorder (proteinuria > 0.5 g/d, or cellular casts)
- Neurologic disorder (seizures or psychosis, without other explanation)
- Hematologic disorder (hemolytic anemia, leukopenia (< 4.0), lymphopenia (< 1.5), or thrombocytopenia)
- Immunologic disorder (dsDNA, Sm, LAC, ACl, or false positive RPR)
- Positive ANA

jSLE

- *Epidemiology:*
  - Incidence ~ 1 / 100 000;
  - Prevalence ~ 2-25/100 000
  - Typical (pediatric) age of onset in early adolescence
  - 5:1 F to M ratio

Manifestations

ACR criteria are common manifestations.

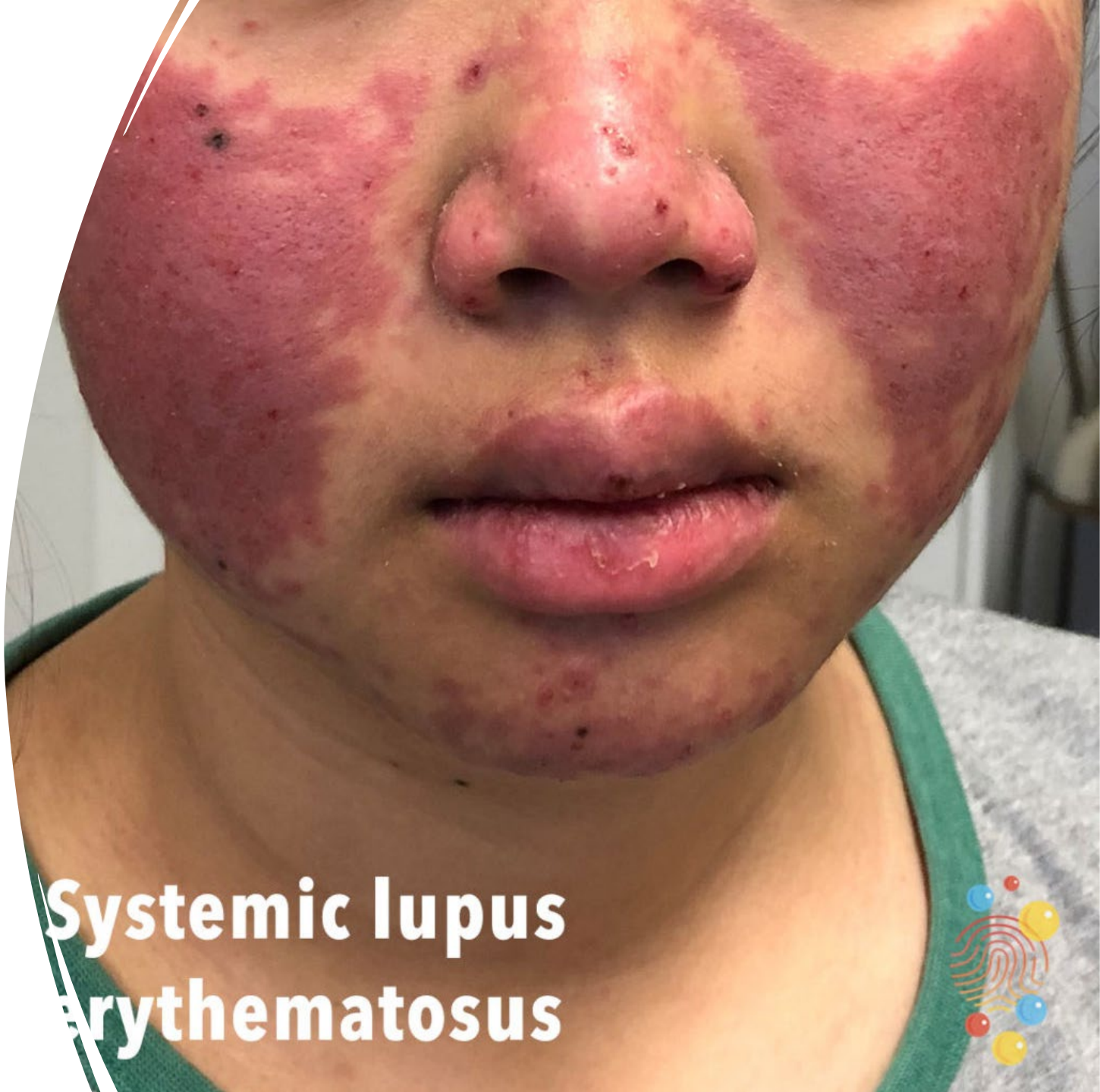
- Systemic: fevers, malaise, fatigue, lymphadenopathy, weight loss.
- Rashes: malar, photosensitive, discoid, others (many types; any rash can be SLE), oral / nasal ulceration.
- Sicca Symptoms: dry mouth (excessive cariogenesis), dry eyes (ulcerations).
- MSK: myositis, arthralgia, arthritis (typically non-erosive, symmetric, small joint).

Manifestations

- End-Organ:
  - Neuropsychiatric (seizures, psychosis || anxiety, depression, headaches*)
  - Cardiopulmonary (effusions, hemorrhages, endocarditis)
  - Vascular (vasculitis, Raynaud phenomenon)
  - Thromboembolic (stroke, coronary sinus venous thrombosis, DVT/PE) – related to APLs
  - Glomerulonephritis (5 classes; affects 20-75%, with 20-50% developing ESRD).

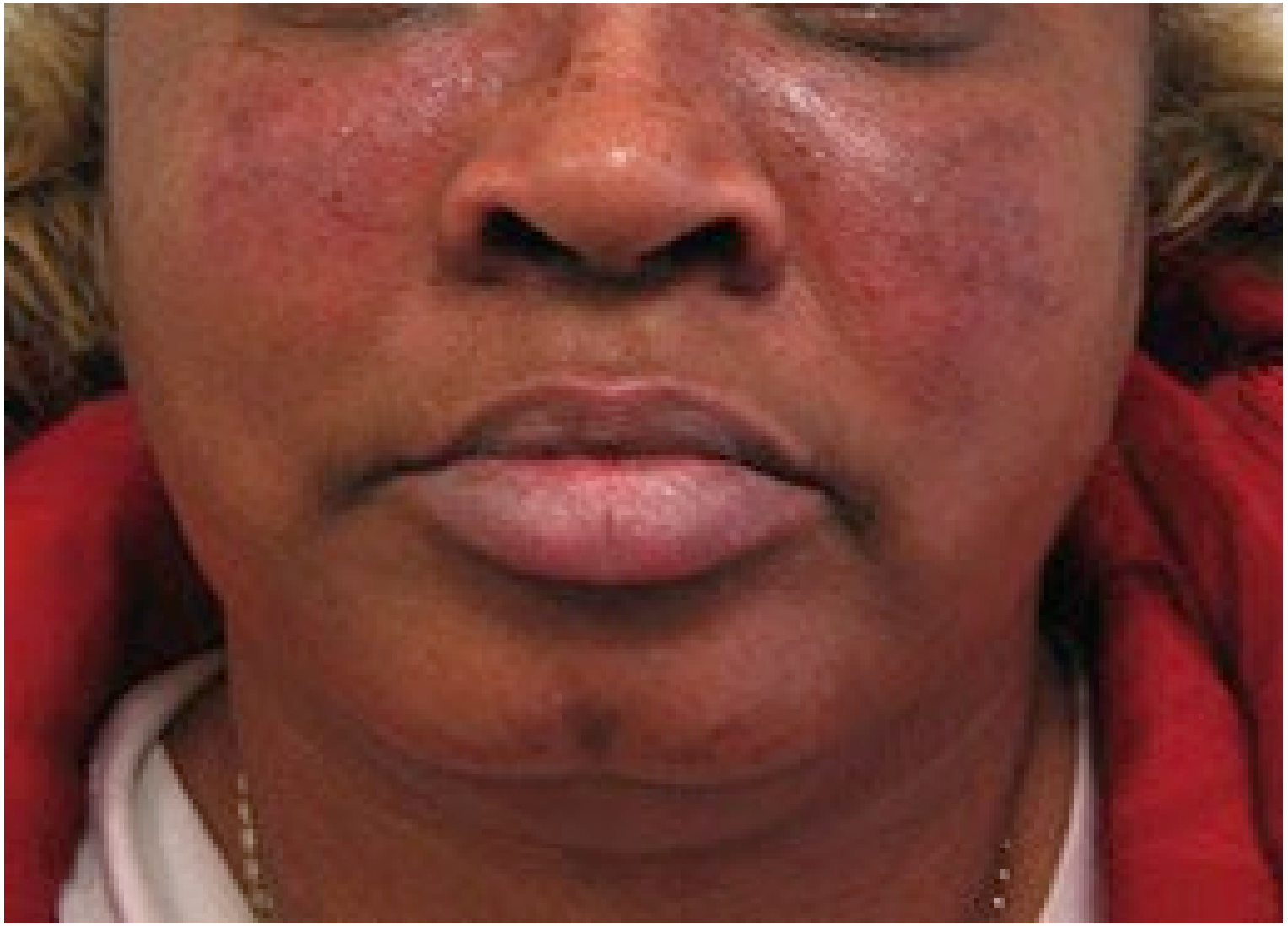
Rashes

- SLE specific: Malar Rash



Rashes

SLE specific: Malar Rash



Rashes

- Malar rash
- Photosensitivity
- Discoid
- Bullous
- Livedo
- Vasculitic
- Alopecia
- Oral/nasal ulcers.

} Typical SLE

Isolated cutaneous SLE

- Isolated cutaneous features:
  - Do full set of SLE labs
  - Refer for biopsy to confirm if necessary
  - If anything positive on labs – refer to rheumatology
  - if work-up negative, consider repeating annually or as needed and refer if becomes positive.

Investigations - Antibodies

- **ANA:** Highly sensitive, poorly specific. Excellent screening tool.
  - 99% of patients will be positive for ANA (usually at titer above 1:80, not always).
  - Up to 20% of healthy pediatric population positive for ANA at 1:40-1:80.
  - This means you only order an ANA if you suspect SLE

  - if it is negative there is almost NO reason to refer / work-up further, unless there is a manifestation so pathognomonically SLE that you suspect false negative (GN, APLS, etc…)

Investigations - Antibodies

- **dsDNA:** Highly sensitive and extremely specific. Excellent diagnostic tool.
  - Will be positive in > 90% of SLE (bit less than ANA though)
  - < 5% of SLE patients negative with active disease.
  - Can be used as a marker of activity in some patients.

- **ENA:** The types of ANA.
  - Each ENA is associated with certain manifestations of disease
  - Can be seen in other diseases as well.
  - Is notorious to have low titer false positives).*

Investigations - other

- CBC: Any/all cell lines can be down; can present as an isolated chronic ITP that later involves other cell lines.
- Creatinine, Urea, Urinalysis: **The most important test for SLE**
- Complements: Low C4 and C3 is common in SLE
- General chemistries: screening for end organ function, MAS, and differentials (malignancy, infection) depending on presentation.

CASE 1

- 15 year-old girl presented with
  - Increasing headaches
  - Malaise, overall feeling unwell
  - Bilateral 6^{th} nerve palsy

CASE 1 investigations

- ANA positive, ENA positive (chromatin, SS-A, SS-B, SM, SM/RNP, RNP)
- Anti-dsDNA negative
- Proteinuria with normal creat/urea/alb
- CT/MRI head: Cerebral sinus vein thrombosis (CSVT)
- Ophthalmology: papilledema sec to CSVT
- Kidney biopsy class V nephritis.
- APLS antibodies negative, including lupus anticoagulant (performed after stop rivaroxaban)

MANAGEMENT

- Management: Guided by the manifestations; ORGANS take priority.
  - Corticosteroids: IVMP (3-7days) followed by oral prednisone 2 mg/kg (max 60 mg).
  - Cytotoxic Agents: used primarily for renal disease (class II-V), end-organ disease, or refractory manifestations.
    - **Cyclophosphamide:** Eurolupus protocol or NIH protocol – predominantly given iv in jSLE.
    - **Mycophenolate Mofetil:** non-inferiority to IV cyclophosphamide, excluding NPSLE (because of low CNS penetrance). Given orally.

Management

- **Plaquenil:** The gold standard for maintenance therapy – used in almost every flavor and variety of SLE. Has been shown to decrease flare rates and severity of flares when they occur.
- **Sun Safety:** UV light can trigger DNA release and cause an SLE flare, even in those without cutaneous disease. All patients with SLE should be counselled on sun safety / clothing, and to use sunscreen liberally and regularly.
- **Rituximab:** used mostly in refractory SLE or in isolated / severe hematologic SLE.
- **Imuran:** used for milder disease, particularly class I/II GN, systemic disease, cutaneous disease, or vasculitic disease.
- **ASA:** sometimes used alongside other agents in the management of APLA.

CASE 1 treatment

- Hydroxychloroquine
- Rivaroxaban
- MMF 1000 mg BID
- Perindopril 2 mg OD

CASE 1 follow-up

- Bilateral 6th nerve palsy (ICP related) – resolved
- Papilledema - resolved
- Repeat MRI 3 months – CSVT resolved

Neonatal lupus

- Prototype of a vertically transmitted autoimmune disease
- Mainly due to the passage of maternal anti-Ro antibodies across the placenta and into the fetal circulation.
- Onset in utero – CARDIAC
- Onset first month of life – others (neutropenia, elevated liver enzymes, rash)
- Is **NOT** a permanent condition; lasts as long as antibodies do (~ 6 mos).

- Some mothers unaware they have antibodies – refer to rheumatology
- Plaquenil treatment mother can prevent many of the symptoms

- Children have a very low slightly increased risk for JIA and SLE – do not follow after 1 year of age – refer if develop new symptoms

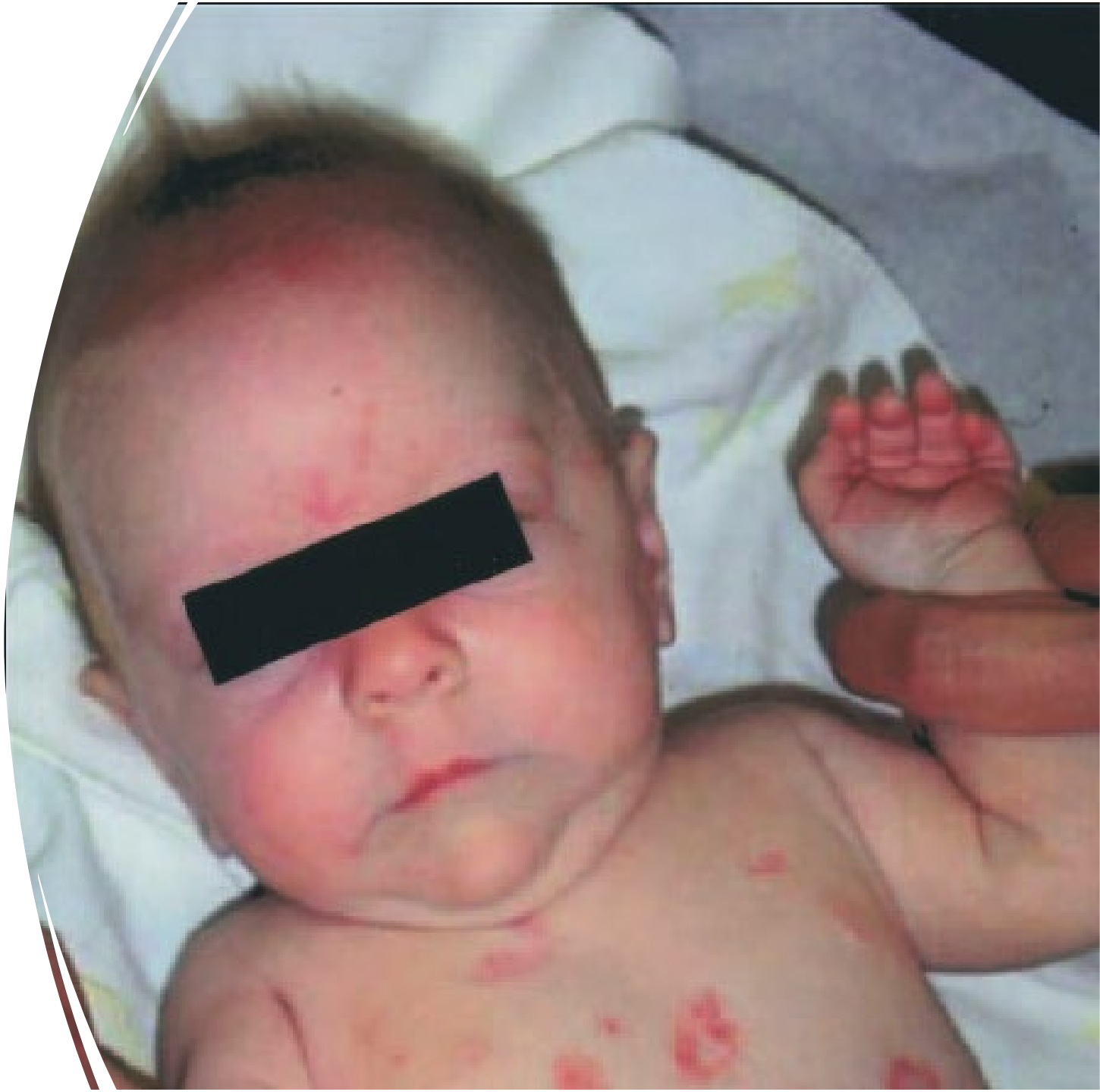
CARDIAC NLE

- Congenital heart block most common cardiac manifestation
- Mostly 3 degree heart block
- No good evidence in progresses through stages
- NLE cause > 90% of congenital heart block
- Risk of CHB in Anti-Ro positive mother is 1-2%; increases to 15% if previous baby CHB

- serial echocardiograms from weeks 18-30 for anti-Ro pos mothers
- Dexamethasone from diagnosis to delivery at first sign of CHB. IVIG and Beta agonist added if low fetal heart rate.

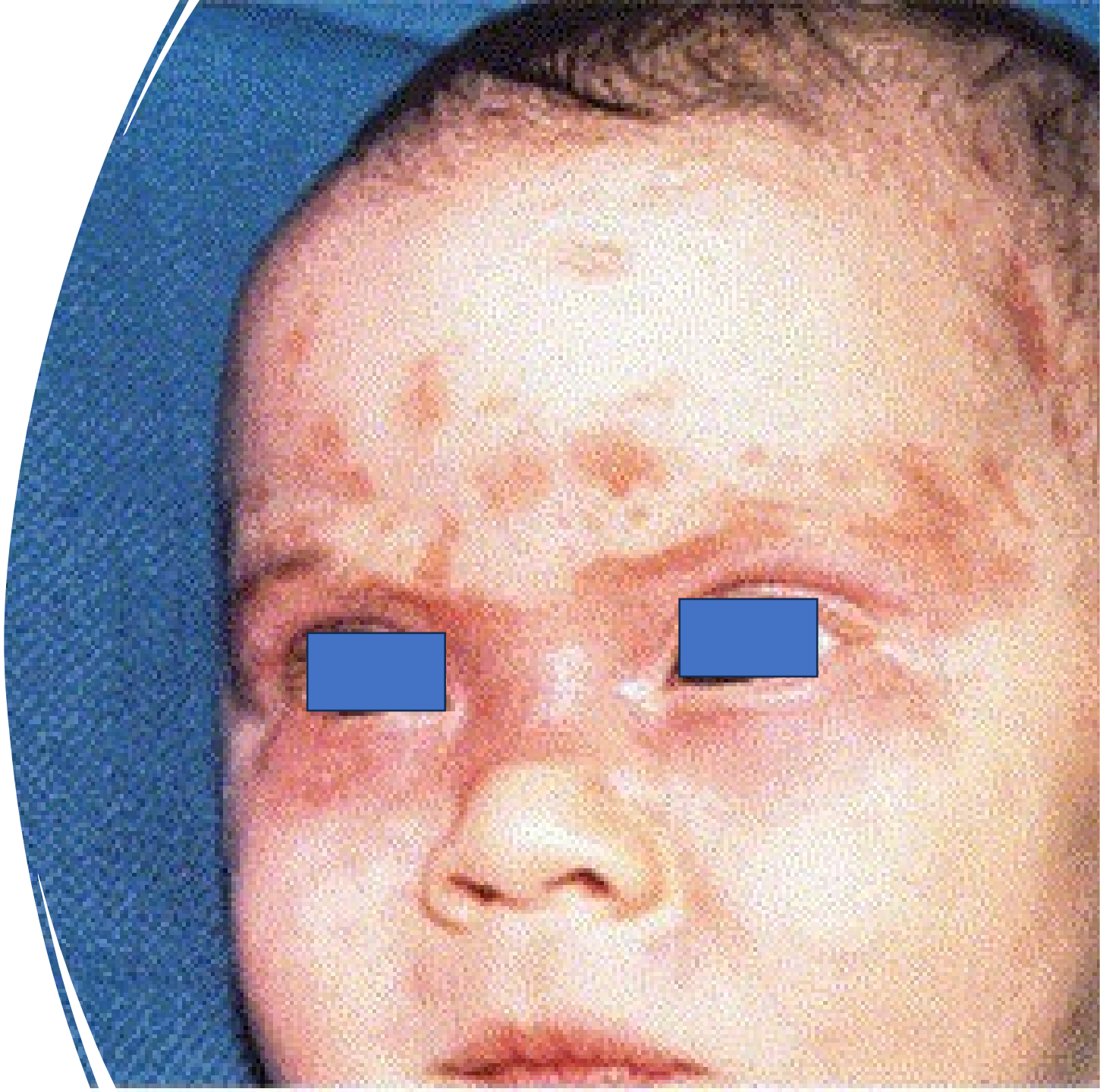
Cutaneous

- discrete, round papules with fine scale
- annular and usually on the face and upper chest



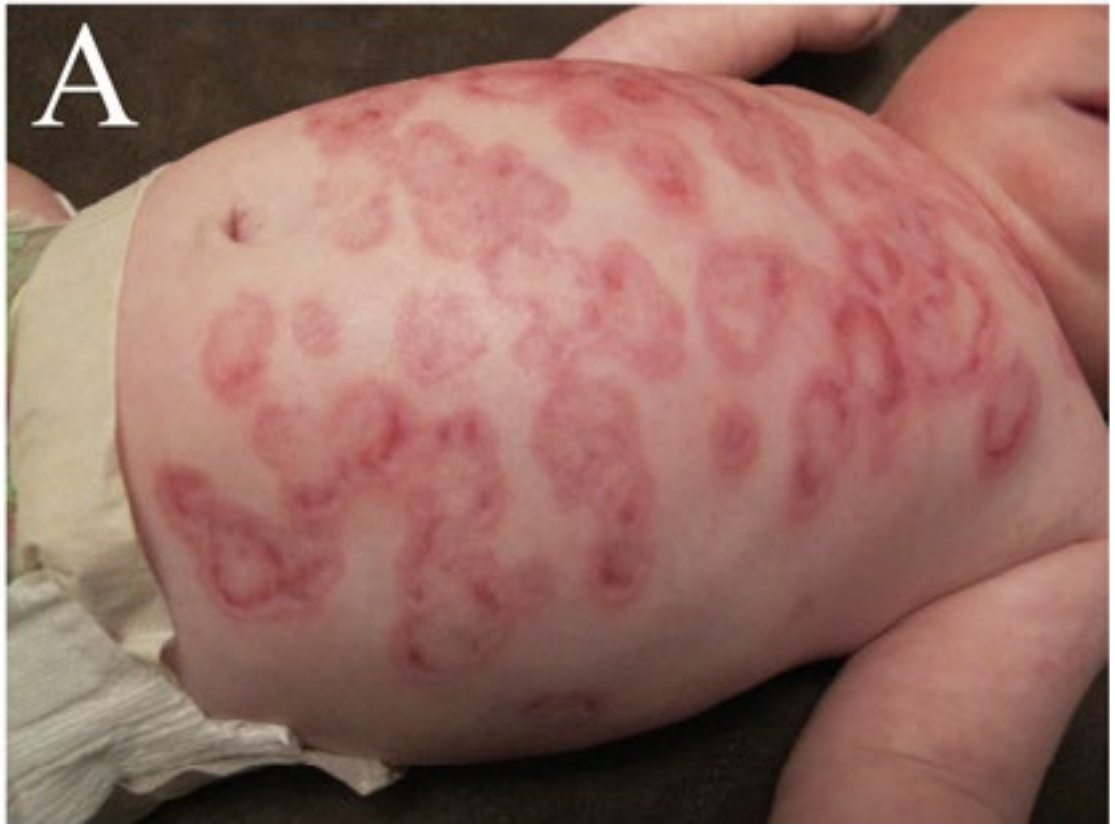
Cutaneous

- discrete, round papules with fine scale
- annular and usually on the face and upper chest
- More specific is the “racoon eyes”



Cutaneous

- discrete, round papules with fine scale
- annular and usually on the face and upper chest
- More specific is the “racoon eyes”
- bullous, targetoid, or other lesions
- **Rarely** present at birth; peak onset ~ 6 weeks, resolution by 6 months
- Does not require any treatment. Can use topical steroids but is purely cosmetic. Should not scar.



Other NLE features

- **Hematologic:** seen in up to 30%; most common is isolated thrombocytopenia (first week) or neutropenia (weeks 2-6), though aplastic anemia also seen.
  - Self-limited and requires no treatment; if symptomatic, may consider IVIG / steroids.
- **Liver:** transaminitis seen in up to 25%; case reports of fulminant liver failure.
- **Neurologic:** Case reports of hydrocephaly / macrocephaly and seizures.

Other CTD

Raynaud Phenomenon

- primary (most common) or secondary.
- likely Raynauds if it is (1) induced by cold, and (2) results in a well demarcated area of biphasic color change (usually white -> blue -> red).
- In general RP affects fingers (+/- toes, noes, ears) asymmetrically, is well demarcated, and causes paresthesias.
- Occurs with relative change in temperature and with emotional distress.
- Can take 10-40 minutes to revert to normal when rewarmed.

- *Risk factors for secondary RP:* male, young age, ANA, abnormal nailfolds.
- *Management:* avoid vasoconstrictors (i.e. ADHD meds, smoking), core temperature maintenance, extremity warmth, “windmilling”.
  Main DDx: Vasomotor instability / acrocyanosis, Erythromelalgia.

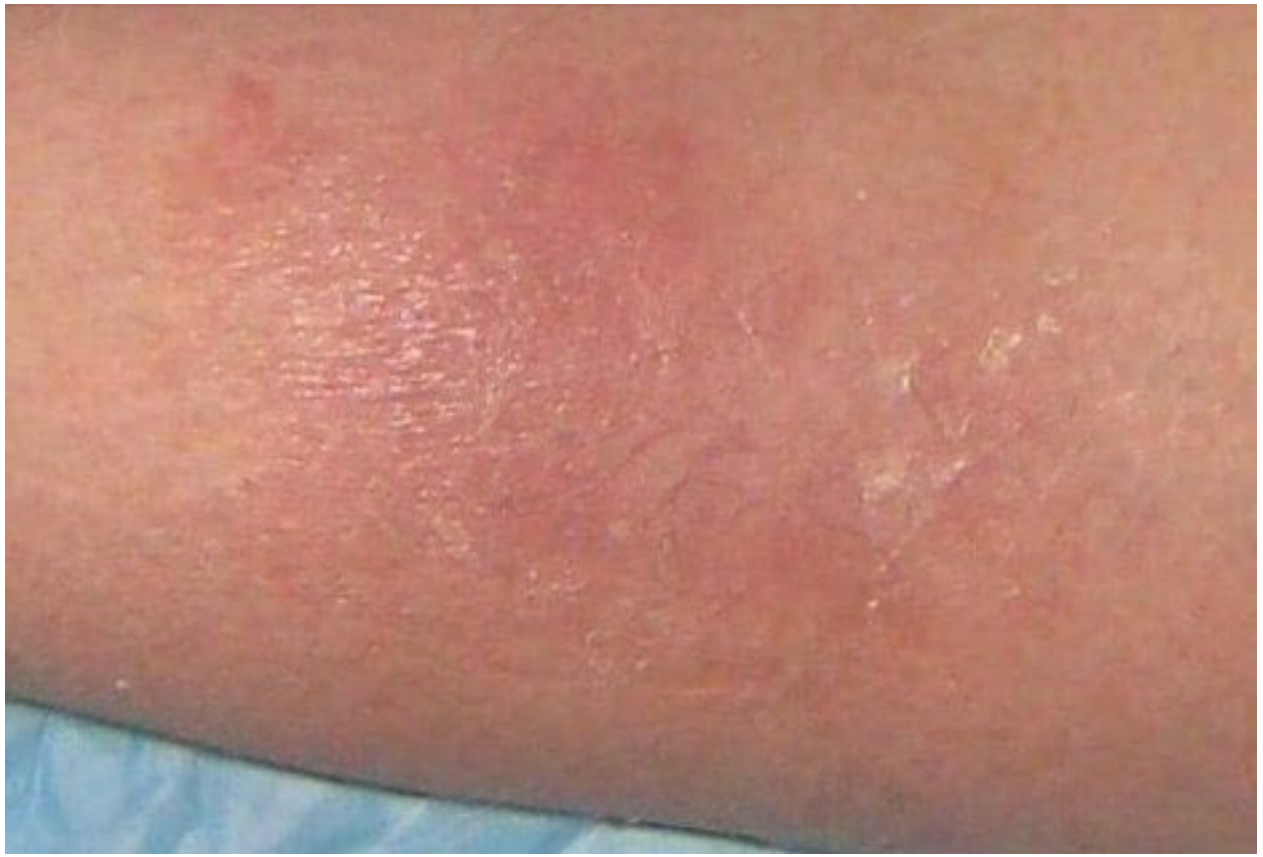
Scleroderma

- **Linear Scleroderma:** see photos;
- slowly growing patch of abnormal skin or subcutaneous tissue
- skin hypopigmentation
- over time will develop loss of fat / muscle, atrophy of site, hyperpigmentation, and change in skin to a hard, shiny appearance.
- ANA often positive. Clinical + pathologic diagnosis. Treated with topical therapy, prednisone, and methotrexate.

Linear scleroderma

En coup de sabre

Morphea



Scleroderma

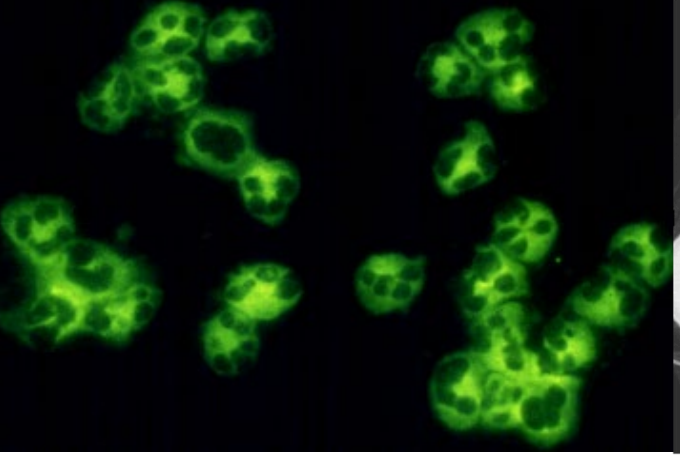
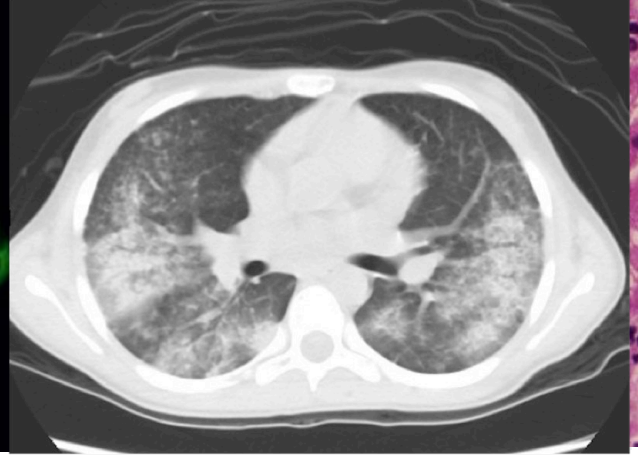
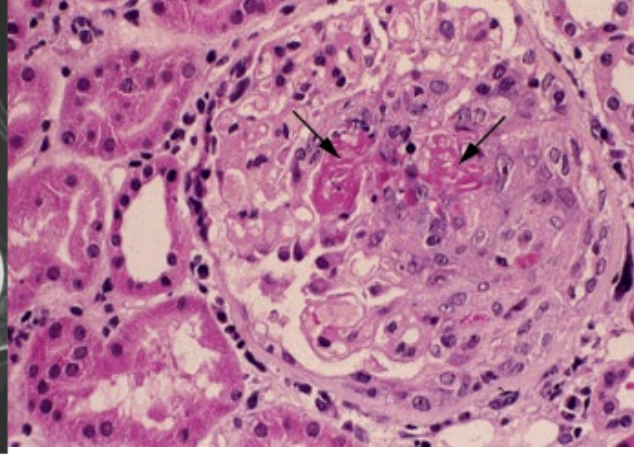
- **Systemic Sclerosis:**
- very rare; manifestations highly variable in childhood
- include sclerodactyly (tightening of skin around hands and mouth) and interstitial lung disease.
- Can also have arthritis as a common manifestation.
- Treatment depends on disease, but notably steroids are avoided, as it can cause renal disease (renal crises).

Other MCTDs

- **Mixed CTD:** essentially is a diagnosis given to patients who have some features of multiple CTDs (usually combination of SLE, JDM, and RP) but who have abnormally high anti-RNP levels. Treated same as SLE.
- **Undifferentiated CTD:** essentially MCTD without high levels of RNP.
- **Overlap Syndrome:** when patient meets diagnostic criteria for more than one connective tissue disease.

Wrap-up

- SLE can have many faces – severity depending on organ involvement
- NLE due to maternal anti-Ro antibodies
- Many other mixed connective tissue diseases with overlap of SLE features.

Clinical, diagnostic aspects and treatment of systemic vasculitis in children

Marinka Twilt, MD, MsCE, PhD
Section of Rheumatology
Alberta Children's Hospital

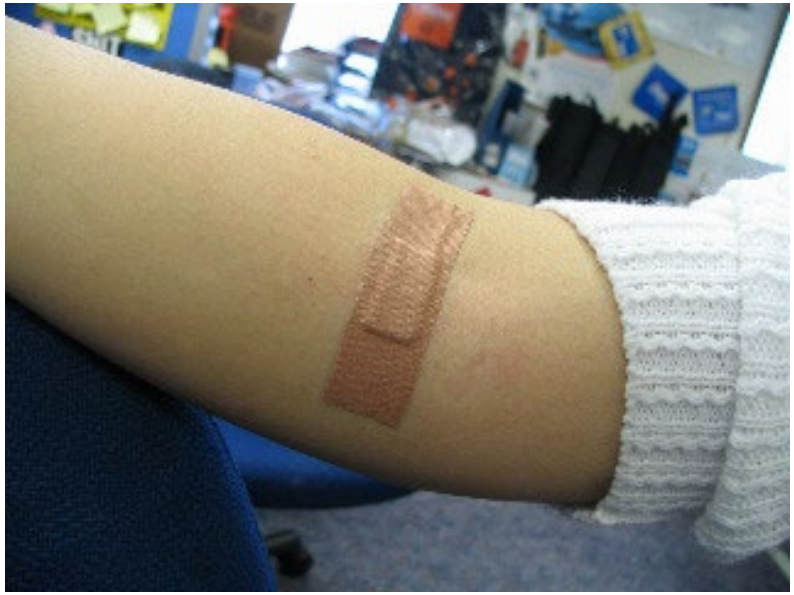
- patients…

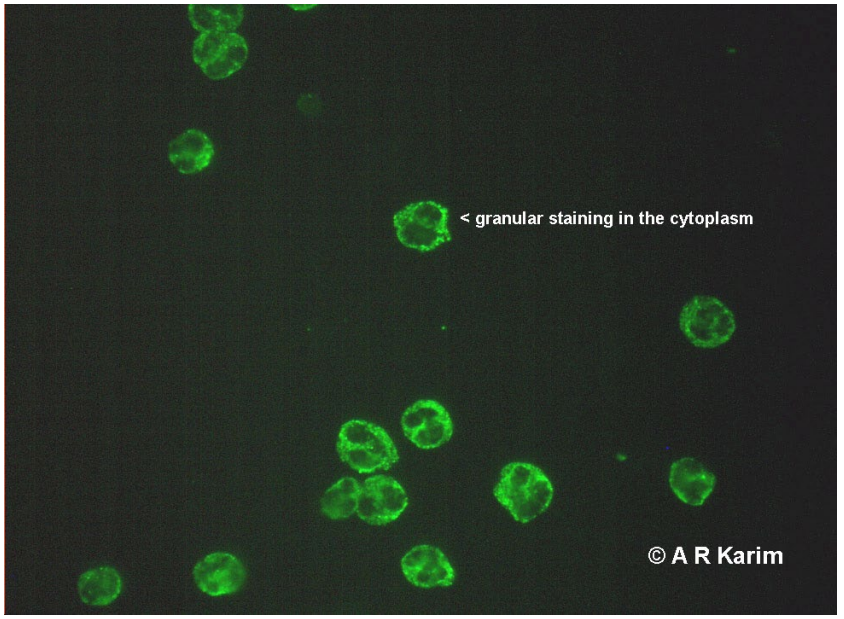
Patient 1, 9 year old girl

- ER: presented with weeks of fever on and off, fatigue, congestion, swollen glands, nosebleeds and cough
- Previously perfectly healthy

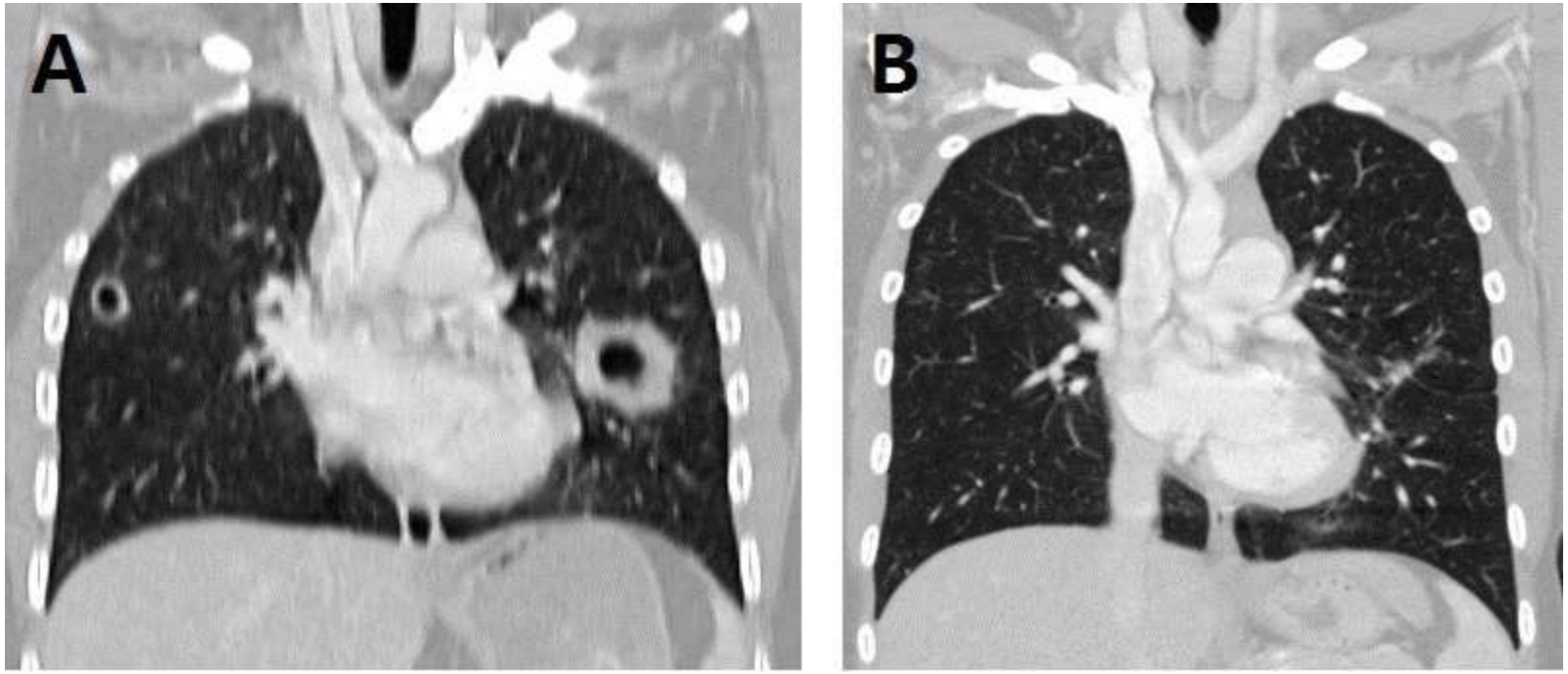
Laboratory test results

- High levels of inflammatory markers
- No evidence of infection
- Positive ANCA (cANCA PR3 positive)



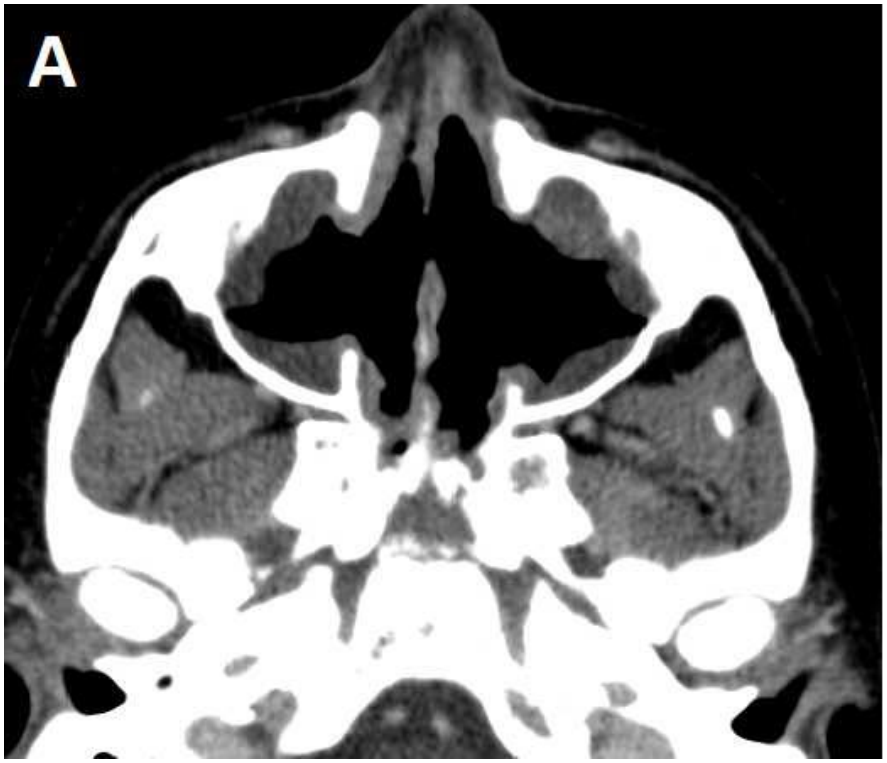


Chest imaging



Cavitating lung lesions and nodules

Sinus disease



Destroyed sinus walls and saddle nose deformity

Diagnosis:

Childhood Vasculitis

ANCA Vasculitis, Granulomatosis with Polyangiitis

Diagnosis of GPA in children

EULAR/PRINTO/PReS

A patient is said to have GPA when 3 of the following 6 criteria are present:

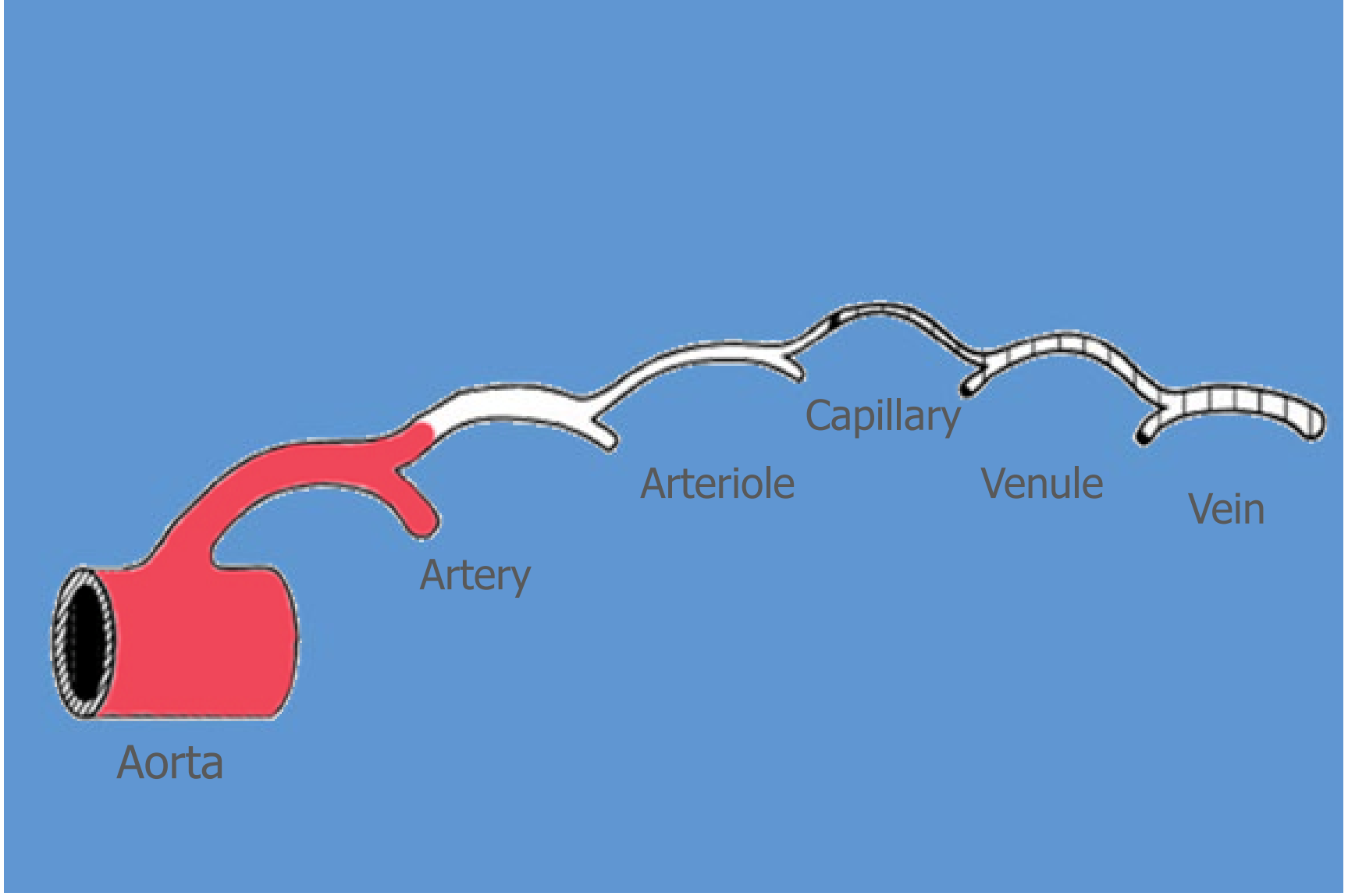
1. Upper airway involvement: nasal, oral inflammation; recurrent epistaxis; nasal septal perforation; or sinus inflammation
2. Pulmonary involvement: abnormal chest radiograph or chest CT scan
3. Renal involvement: abnormal urinalysis (proteinuria, hematuria, or red blood cell casts) or necrotizing pauciimmune glomerular nephritis
4. Granulomatous inflammation: within an artery or in perivascular or extravascular areas
5. Laryngo-tracheo-bronchial involvement: with stenosis
6. ANCA positivity: by immunofluorescence or by ELISA (MPO/p or PR3/cANCA)

Ozen et al, Ann Rheum Dis 2010

Treatment

- 24 months of immunosuppressive therapy:
  - Cyclophosphamid infusions 6 months, high-dose steroids
- Relapse after 36 months:
  - Rituximab therapy
  - Complication: fungus infection (PCP) of the lungs
- Relapse after 52months:
  - Re-treatment with Rituximab
  - Severe hearing loss

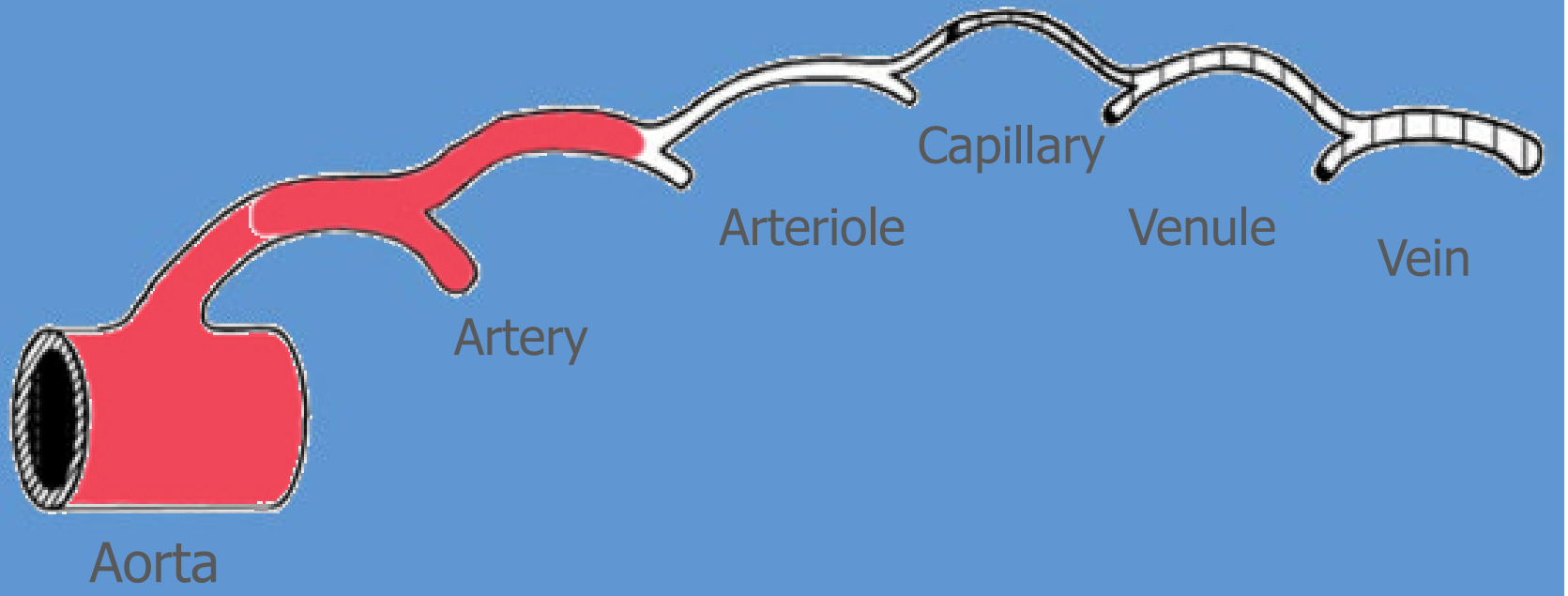

SIGH



Predominantly <u>Large</u> Vessel Vasculitis

Takayasu arteritis

Classification

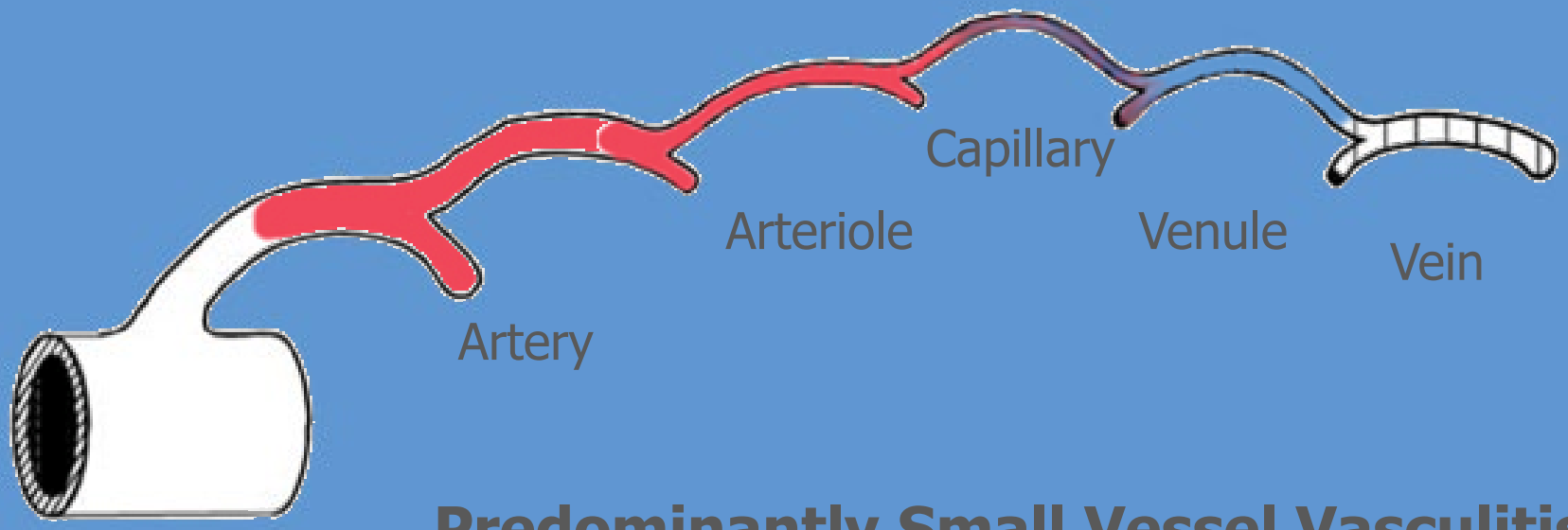


Predominantly Medium Vessel Vasculitis

Predominantly Large Vessel Vasculitis

Takayasu arteritis

Polyarteritis Nodosa (PAN)



Predominantly Small Vessel Vasculitis

- IgA vasculitis (Henoch-Schönlein Purpura)

Predominantly Medium Vessel Vasculitis

Non-granulomatous

- Isolated Cutaneous Leukocytoclastic Vasculitis
- Kawasaki disease
- Microscopic Polyangiitis
- Polyarteritis Nodosa (PAN)

Granulomatous

- Granulomatosis with Polyangiitis (Wegener Granulomatosi
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)

Nomenclature

American College of Rheumatology (ACR); American Society of Nephrology (ASN);European League Against Rheumatism (EULAR)

ANCA-associated vasculitis (AAV) includes:

- Granolumatosis with polyangiitis **(GPA)**
  previously known as Wegener's granulomatosis (WG)

- Microscopic polyangiitis **(MPA)**

- Eosinophilic granulomatosis with polyangitis **(EGPA**)
previously known as Church Strauss (CSS)

Falk et al, Arthritis Rheum 2011

Clinical presentation

- **Upper and lower respiratory tract:**
  - Granulomatous inflammation of lungs and upper airways causing erosive sinusitis and nodular / cavitating lung lesions
  - Alveolar hemorrhage

- **Kidneys:**
  - Pauci-immune necrotizing crescentic glomerulonephritis

- **Other organ systems:**
  - Involvement of other organs possible (e.g. musculosceletal; gastrointestinal; eyes; skin; CNS)

Twilt et al, Curr Opinion Rheum 2013

Patient 2, 12 year old girl

- ER: Fever, chest pain, anuric, requiring oxygen
- Previously perfectly healthy

Patient 2

- 10d ago: presented to ER with persistent bilateral conjunctivitis → eyedrops
- 3d later: presented at family MD; Sinusitis (X-ray confirmed). Biaxin started
- Developed;
  - rash
  - vomiting
  - diarrhea
  - fever on and of,
  - weight loss of 10 pounds in 4 weeks,
  - right sided pleuritic chest pain

Patient 2

- Vaccinations
  - Including varicella
- No exposure to animals
- No known exposure to TB

Past medical history

- Until first presentation unremarkable
- Traveled to Mexico in December before symptoms started

Exam

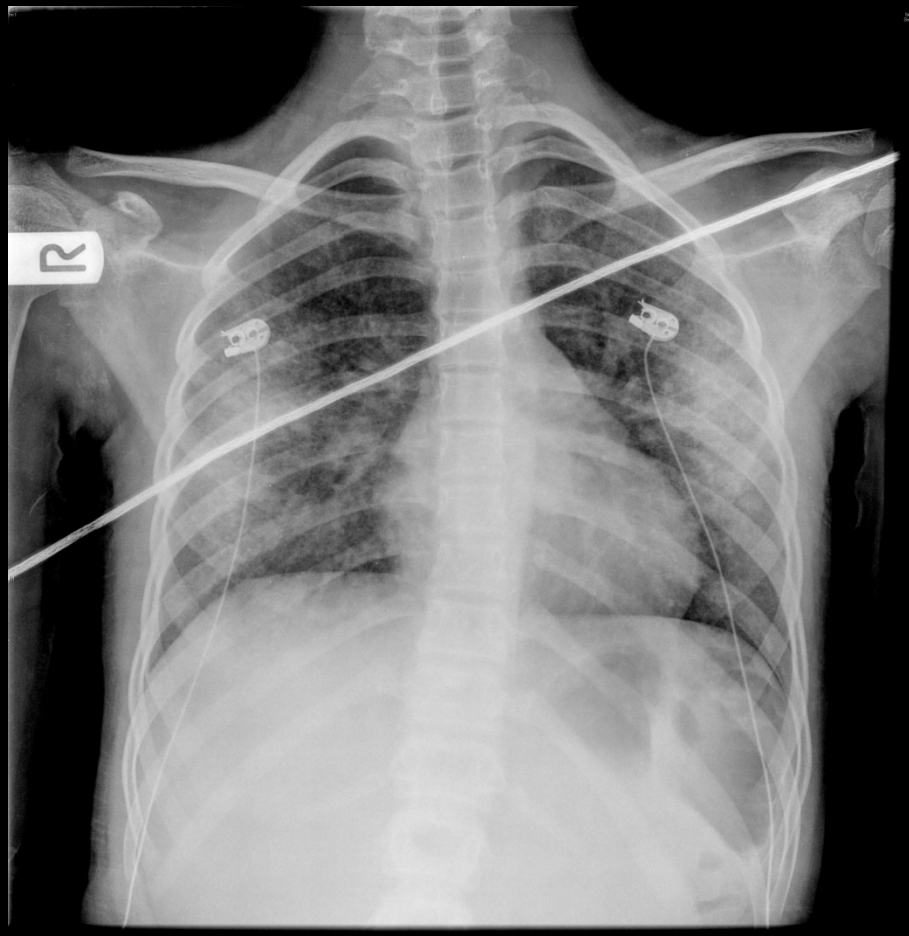
- T 38.5, HR 138, BP 102/60
- RR 28, sat 93%
- Pale, panting, ill
- H+N:
  - no nasal or oral ulcerations/crusts
  - no sinus tenderness
  - small cervical LN
- Resp: ↓ air entry R lower lobe, no crackles, no retractions, increased work of breathing

Exam

- CVS: normal
- Abdo: normal
- Skin: no purpura
- MSK: small bilateral knee effusions with normal range of motion
- Neuro: normal

Investigations

- CBC:
  - Hgb 47
  - WBC 29.2 (PMN 23.37, lymph 1.75)
  - Plt 563
- ESR 145, CRP 241.9
- Creatinine 861, urea 47.8
- Complements normal
- Urinalysis RBC casts



RES ROOM 740HRS

UPRIGHT

Pulmonary Renal syndrome

Definition

- Specific pulmonary-renal syndromes:
  - Disorders associating pulmonary (hemoptysis; lung hemorrhage; infiltrates or nodules) and glomerular manifestations
- Non-specific pulmonary-renal syndromes:
  - Either pulmonary disease complicating glomerular disease, or glomerular diseases following pulmonary disease

Pulmonary Renal Syndrome in Childhood: A Report of Twenty-One Cases and a Review of the Literature

Rodo O. von Vigier, MD,[1] Stefan A. Trummler, MD,[1] Regula Laux-End, MD,[1]
Marie J. Sauvain, MD,[1,2] Anita C. Truttmann, MD,[1] and Mario G. Bianchetti, MD[1]*

- 21 children, 1991-1998
- Specific pulmonary-renal syndrome: n=5
  - 3 vasculitis (2 WG, 1 MPA)
  - 2 SLE

Pediatric Pulmonology 2000;29:382

Pulmonary Renal Syndrome in Childhood: A Report of Twenty-One Cases and a Review of the Literature

Rodo O. von Vigier, MD,[1] Stefan A. Trummler, MD,[1] Regula Laux-End, MD,[1]
Marie J. Sauvain, MD,[1,2] Anita C. Truttmann, MD,[1] and Mario G. Bianchetti, MD[1]*

- Non-specific pulmonary-renal syndrome: n=16
  - 12 with pulmonary disease complicating GN
    - 9 pulmonary edema
    - 2 PE
    - 1 pulmonary infection
  - 4 with GN complicating pulmonary disease

Pediatric Pulmonology 2000;29:382

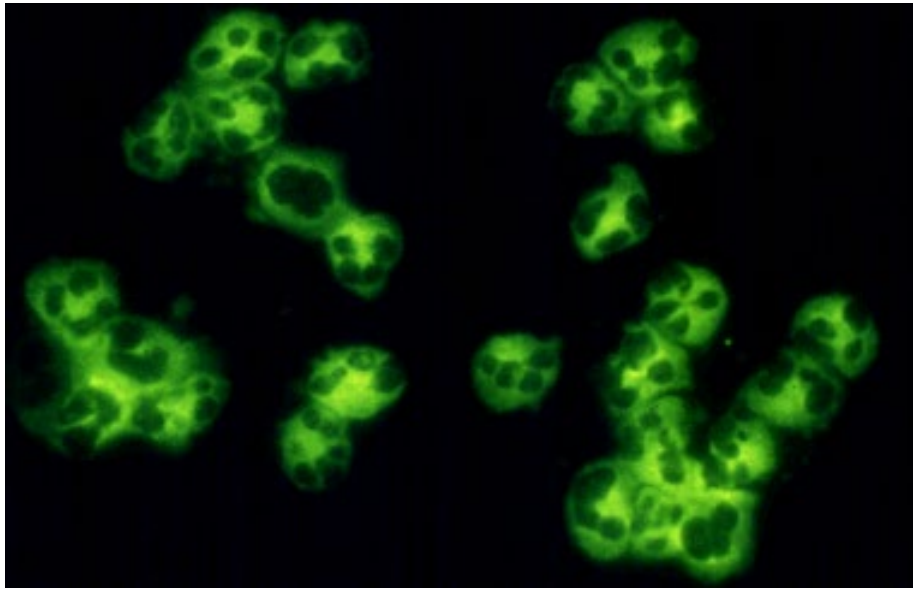
Specific pulmonary-renal syndrome

- ANCA-associated vasculitis
- SLE
- Goodpasture's syndrome
- Henoch-Schonlein purpura

Pediatric Pulmonology 2000;29:382

ANCA-associated vasculitis

- Granulomatosis with polyangiitis GPA (Wegener's granulomatosis)
  - C-ANCA, proteinase-3 positive



Clinical feature	At presentation (n = 25)	At any time (n = 25)
Constitutional symptoms	24 (96.0)	24 (96.0)
Fever	18 (72.0)	19 (76.0)
Arthralgias	16 (64.0)	19 (76.0)
Weight loss	14 (56.0)	15 (60.0)
Renal involvement	22 (88.0)	22 (88.0)
Glomerulonephritis	22 (88.0)	22 (88.0)
Elevated serum creatinine	7 (28.0)	11 (44.0)
Requirement for dialysis	5 (20.0)	6 (24.0)
Ear, nose, throat involvement	21 (84.0)	24 (96.0)
Sinusitis	11 (44.0)	14 (56.0)
Epistaxis	10 (40.0)	15 (60.0)
Oral ulcers	7 (28.0)	8 (32.0)
Otitis media	6 (24.0)	6 (24.0)
Nasal ulcers	6 (24.0)	11 (44.0)
Conductive/sensorineural deafness	4 (16.0)	4 (16.0)
Saddle nose	2 (8.0)	2 (8.0)
Subglottic stenosis	1 (4.0)	1 (4.0)
Nasal septal perforation	0 (0.0)	2 (8.0)
Pulmonary involvement	20 (80.0)	21 (84.0)
Alveolar hemorrhage	11 (44.0)	12 (48.0)
Nodules	11 (44.0)	13 (52.0)
Airspace disease (nonhemorrhagic)	4 (16.0)	6 (24.0)
Required ventilation	4 (16.0)	5 (20.0)
Pleuritis	2 (8.0)	2 (8.0)
Eye involvement	13 (52.0)	15 (60.0)
Conjunctivitis	11 (44.0)	14 (56.0)
Scleritis/episcleritis	3 (12.0)	3 (12.0)
Proptosis	2 (8.0)	2 (8.0)
Skin involvement	8 (32.0)	12 (48.0)
Petechiae/palpable purpura	8 (32.0)	10 (40.0)
Urticaria	0 (0.0)	2 (8.0)
Panniculitis/erythematous nodules	0 (0.0)	2 (8.0)
Arthritis	8 (32.0)	11 (44.0)
Hypertension	6 (24.0)	13 (52.0)
Gastrointestinal involvement	3 (12.0)	4 (16.0)
Venous thrombotic event	3 (12.0)	4 (16.0)
Deep vein thrombosis	3 (12.0)	4 (16.0)
Pulmonary embolus	2 (8.0)	3 (12.0)
Nervous system involvement	2 (8.0)	3 (12.0)

Table 2. Comparison of clinical features of granulomatosis with polyangiitis in the four largest paediatric series

	Belostotsky *et al.* [14]	Akikusa *et al.* [11]	Cabral *et al.* [13]	Siomou *et al.*[a] [15▪]
Number of patients	17	25	65	13
Male (%)	24%	20%	37%	23%
GPA/MPA	17/0	25/0	65/0	7/6
Median age at onset (years)	6	14.5	14.2	13.2[b]
Clinical features (%)				
Constitutional	29%	96%	89%	85%
Ophthalmology	53%	52%	37%	23%
ENT	100%	84%	80%	15%
Renal	53%	68%	75%	100%
Pulmonary	82%	80%	80%	54%
Gastrointestinal	41%	12%	42%	8%
Musculoskeletal	53%	64%	57%	31%
Mucocutaneous	53%	32%	35%	15%
Nervous system	12%	8%	25%	8%

GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.
[a]Patients collected through renal clinic all diagnosed with ANCA-associated glomerulonephritis. All other cohorts are retrieved through rheumatology clinics.
[b]Mean instead of median.

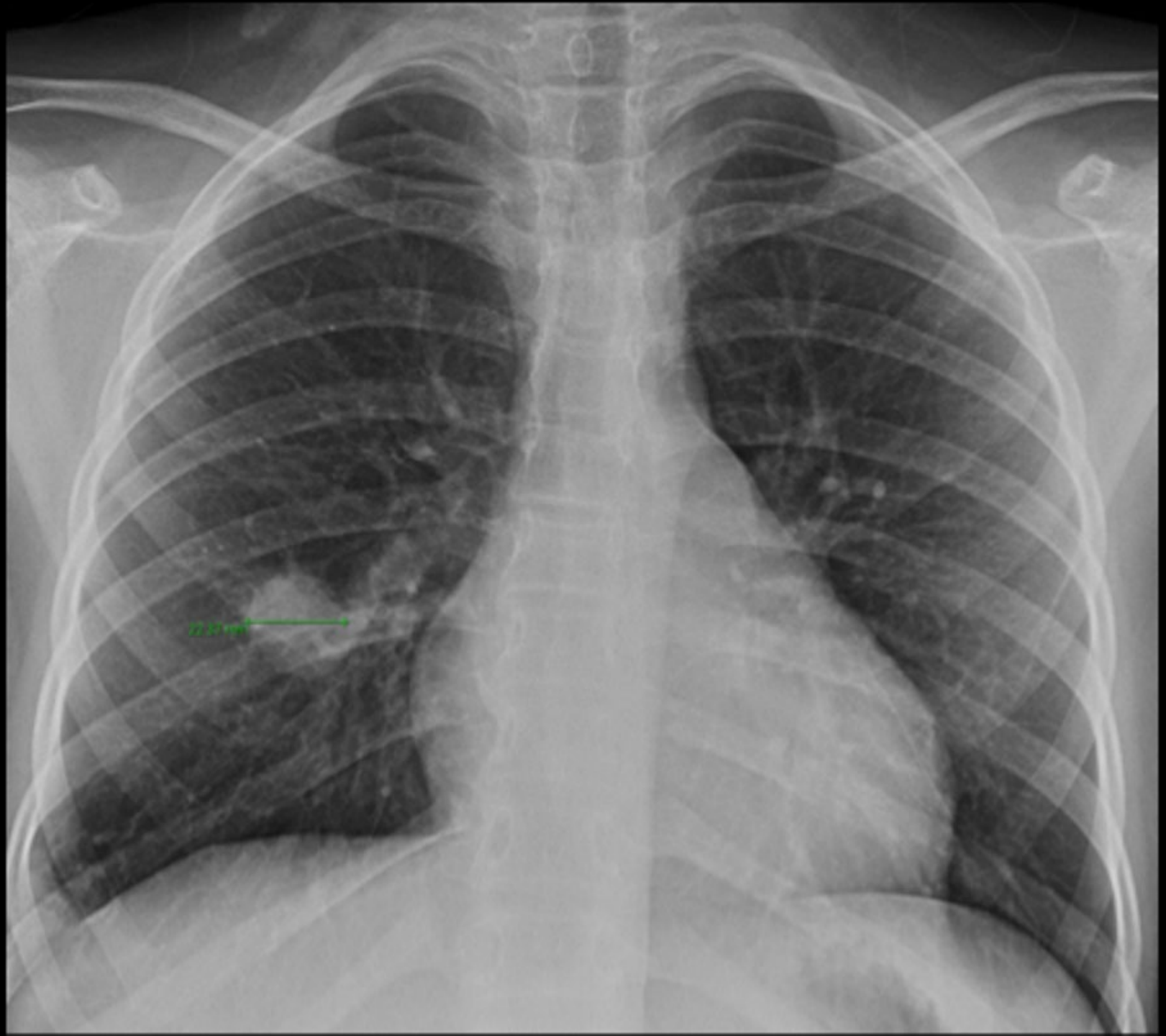
Twilt et al, Curr Opinion Rheum 2013

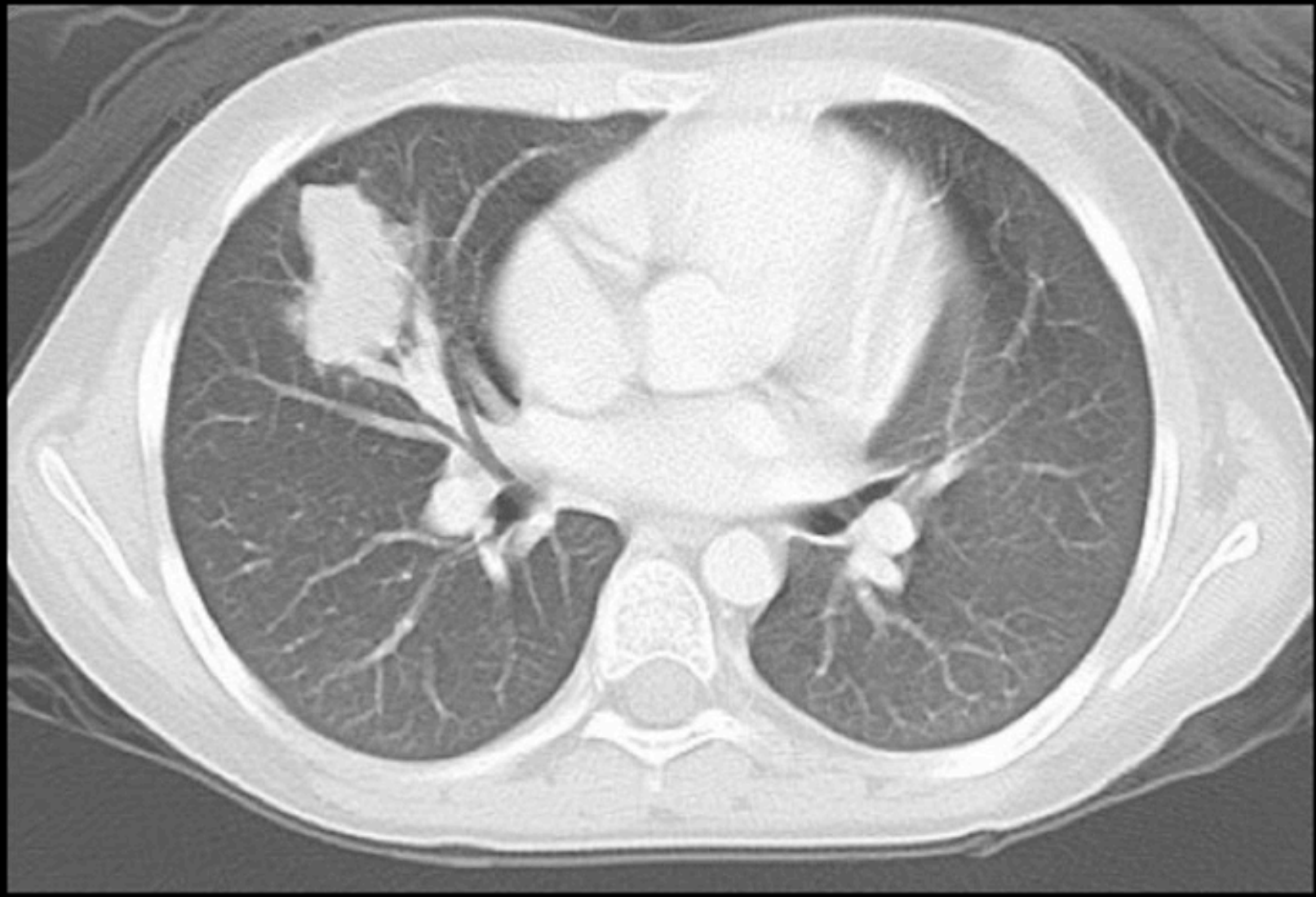
Patient 2

- Dx: GPA (c-ANCA, PR-3 +)
- Plasmapheresis
- Methylprednisolone
- Cyclophosphamide
  - CT chest; pulmonary haemorrhage with ground glass appearance
  - CT sinus: clear

3 months later

- Developed cough
- No other systemic features
- Repeat imaging
  - Previous abnormalities resolved
  - New lesion


22.37 mm



Flare?

Investigations

- Needle biopsy

- Culture positive: Blastomycoses
- Treatment started
- No changes immunosuppressive treatment

Current treatment practice and evidence

Treatment rationales

- **AAV (GPA / MPA) is a severe disease**
  - Acutely life- and/or organ-threatening
  - Chronically active with the potential to flare
- **Successful treatment requires:**
  - Both *Induction* and *Maintenance* therapy
  - Balance between treatment benefit and side effects
- **Current treatment:**
  - **Inflammation:** Immunosuppressants / Anti-inflammatory agents
  - **Antibodies:** Plasmapheresis B-cell suppression

Translation into clinical care

Clinical Syndrome	Autoantibody	Renal biopsy	Treatment
VASCULITIS 1.GPA 2.MPA	c-ANCA (PR-3) p-ANCA (MPO)	"pauci-immune" focal segmental necrotizing and crescentic GN	plasmapheresis Prednisone Cyclophosphamide IVIG Rituximab
SLE	ANA Anti-ds DNA Sm, RNP, Ro, La	+++ Immune deposits "lumpy-bumpy"	Prednisone Azathioprine MMF Cyclophosphamide
Goodpasture's	GBM	"linear deposits" of GBM antibodies	Plasmapheresis Prednisone

Childhood Systemic Vasculitis Protocols
ANCA associated systemic vasculitis

ACH Childhood Systemic Vasculitis Protocols (EUVAS)

ANCA-Associated Systemic Vasculitis

Induction , option 1

Severe disease with pulmonary hemorrhage /renal failure

Alberta Children's Hospital
Childhood Vasculitis Program

Prednisone pulses
30mg/kg/day, max 1g X ___ days (3-7)
then 2 mg/kg max 60 mg/day with monthly taper

Start date __/__/__
Dose _____

Start date __/__/__
Dose _____

Start date __/__/__
Dose _____

Plasmapheresis
x 7 in 14 days

Cyclophos-phamide 15mg/kg @ 0-2-4 weeks then @ 7-10-13 weeks. (dosage adjustment for renal impairment)

Every 2 weeks x 3 doses

Every 3 weeks x 3-6 doses

Date __/__/__
Dose _____

Date __/__/__
Dose _____

Date __/__/__
Dose _____

Date __/__/__
Dose _____

Date __/__/__
Dose _____

Date __/__/__
Dose _____

Date __/__/__
Dose _____

Date __/__/__
Dose _____

☐ **Septra/Co-Trim**
2.5-5 mg/kg/day

Cyclophosphamide dose 7-9 optional (every 3 weeks)
Check if PVAS=0 after third three weekly dose

☐ **Calcium**
1000 mg/day

☐ **Vitamin D**
1000 units/day

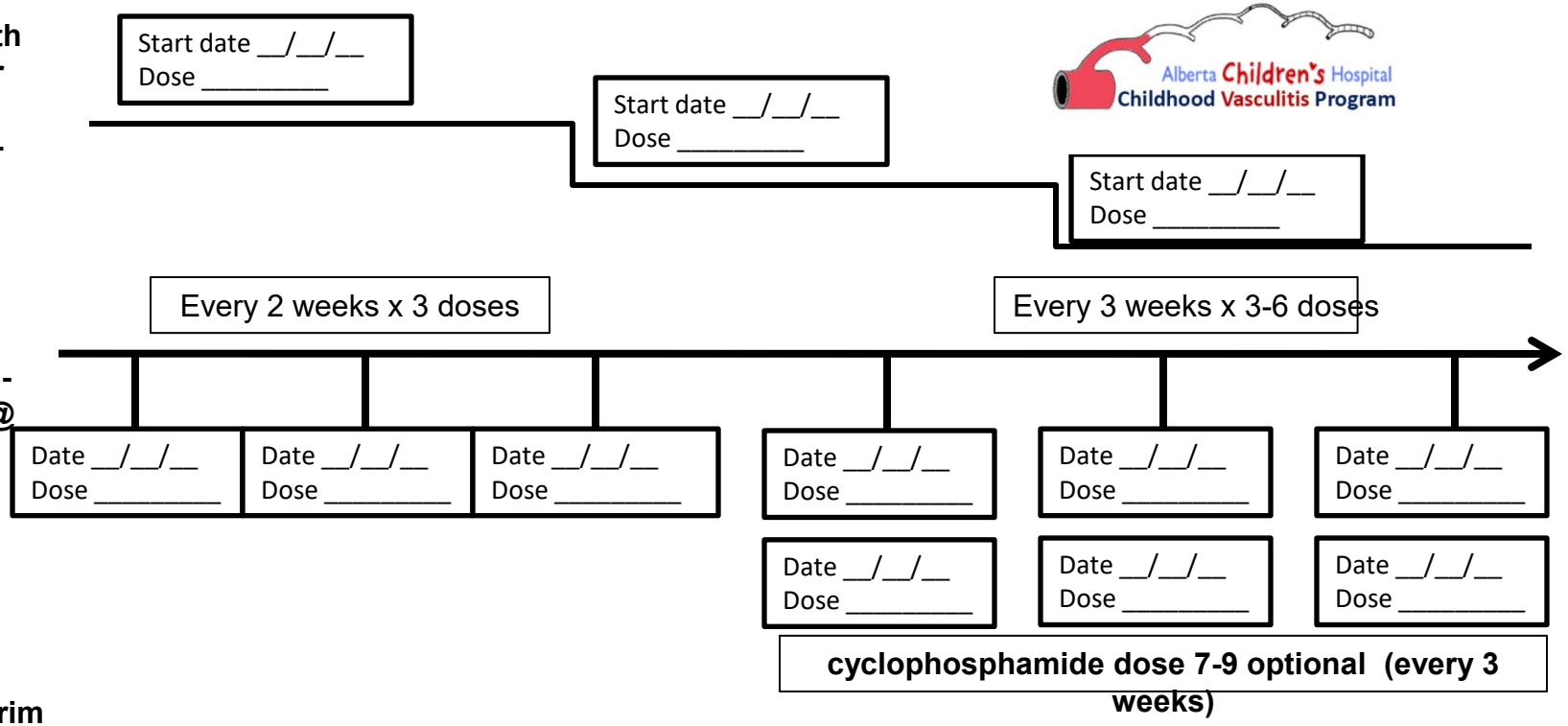
Version May 2015

ACH Childhood Systemic Vasculitis Protocols (EUVAS)

ANCA-Associated Systemic Vasculitis

Induction , option 2

Severe disease other than pulmonary hemorrhage /renal failure



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ACH Childhood Systemic Vasculitis Protocols (EUVAS)

ANCA-Associated Systemic Vasculitis Maintenance

Severe disease

Alberta Children's Hospital
Childhood Vasculitis Program

Prednisone once daily with monthly taper (60-50-40-30-25-20-17.5-15-12.5-10-7.5-5-2.5-0)

Start date __/__/__
Target dose _____

Stop date __/__/__

Options:

☐ **Azathioprine**
2-3mg/kg/day
(vasculitis)

Start date __/__/__
Target dose _____

Stop date __/__/__

☐ **Methotrexate**
15mg/m2/week
(granuloma)

Start date __/__/__
Target dose _____

Stop date __/__/__

☐ _____
_____

Start date __/__/__
Target dose _____

Stop date __/__/__

☐ **Septra/Co-Trim**
2.5-5 mg/kg/day

☐ **Calcium**
1000 mg/day

☐ **Vitamin D**
1000 units/day

Version May 2015

ACH Childhood Systemic Vasculitis Protocols ANCA-Associated Systemic Vasculitis

Limited new dis[illegible]se flare

Start date __/__/__
Target dose _____

Prednisone once daily with monthly taper (60-50-40-30-25-20-17.5-15-12.5-10-7.5-5-2.5-0)

Stop date __/__/__

Options:

☐ **Azathioprine** 2-3mg/kg/day (vasculitis)

Start date __/__/__
Target dose _____

Stop date __/__/__

☐ **Methotrexate** 15mg/m2/week (granuloma)

Start date __/__/__
Target dose _____

Stop date __/__/__

☐ _____

Start date __/__/__
Target dose _____

Stop date __/__/__

☐ **Calcium** 1000 mg/day

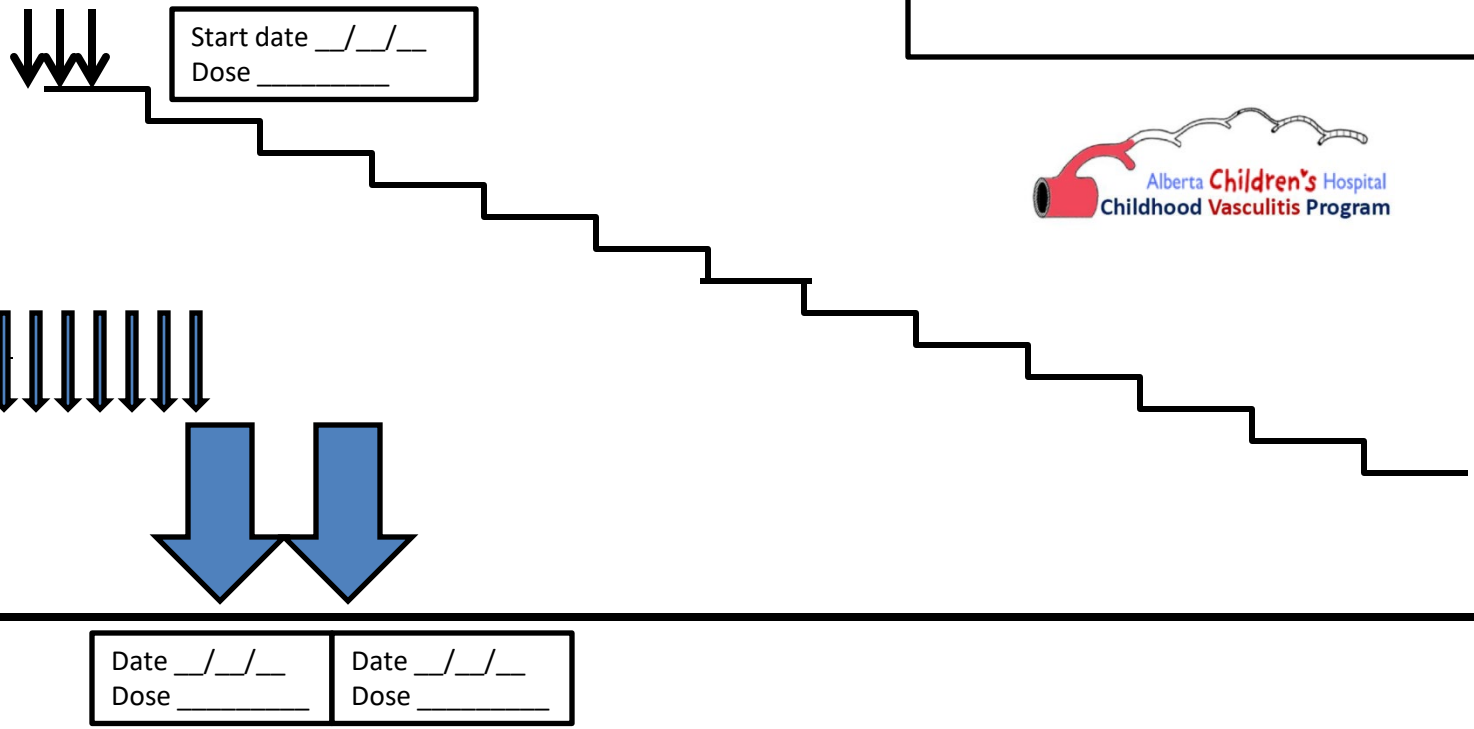
☐ **Vitamin D** 1000 units/day

Version May 2015

ACH Childhood Systemic Vasculitis Protocols (RAVE)

ANCA-Associated Systemic Vasculitis

Severe disease flare with pulmonary hemorrhage /renal failure



Alberta Children's Hospital
Childhood Vasculitis Program

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ACH Childhood Systemic Vasculitis Protocols

ANCA-Associated Systemic Vasculitis

Severe disease flare other than pulmonary hemorrhage /renal failure

☐ **Prednisone pulses**
30mg/kg/day, max 1g X ___ days (3-7)
then 2 mg/kg max 60 mg/day with 2 weekly taper

Start date __/__/__
Dose _____

Alberta Children's Hospital
Childhood Vasculitis Program

☐ **Rituximab**
500mg/m2
2 doses 2 weeks apart

Date __/__/__
Dose _____

Date __/__/__
Dose _____

☐ **Septra/Co-Trim**
2.5-5 mg/kg/day

☐ **Calcium**
1000 mg/day

☐ **Vitamin D**
1000 units/day

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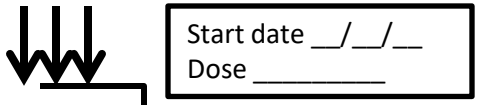
ACH Childhood Systemic Vasculitis Protocols

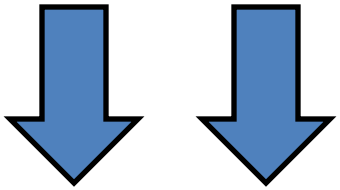
ANCA-Associated Systemic Vasculitis

Rituximab maintenance therapy

Induction



☐ **Prednisone pulses**
30mg/kg/day, max 1g X ___ days (3-7, optional)
then 2 mg/kg max 60 mg/day with 2 weekly taper



☐ **Rituximab 500mg/m2 2 doses 2 weeks apart**

Date __/__/__
Dose _____

Date __/__/__
Dose _____

☐ **Septra/Co-Trim**
2.5-5 mg/kg/day

☐ **Calcium**
1000 mg/day

☐ **Vitamin D**
1000 units/day

Alberta Children's Hospital
Childhood Vasculitis Program

Version May 2015

ACH Childhood Systemic Vasculitis Protocols ANCA-Associated Systemic Vasculitis

Rituximab maintenance therapy

Maintenance

Alberta Children's Hospital
Childhood Vasculitis Program

☐ **Rituximab**
500mg/m2 ,
Max 1000mg

Rituximab (single dose)
re-treatment every 6 months

Date __/__/__
Dose _____

☐ **Septra/Co-Trim**
2.5-5 mg/kg/day

☐ **Calcium**
1000 mg/day

☐ **Vitamin D**
1000 units/day

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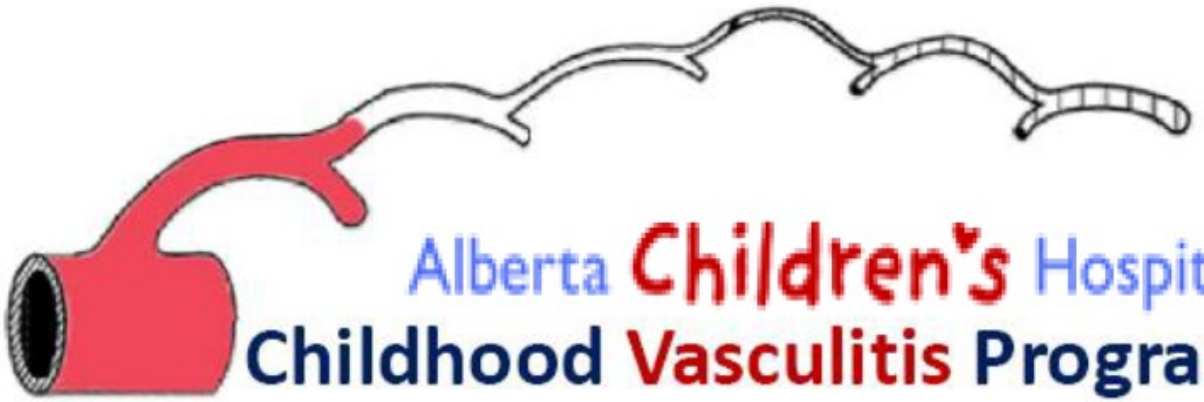
Summary and perspectives

- Childhood Vasculitis is life threatening
- Pulmonary-renal syndrome is a severe presentation and needs immediate treatment
- Adaptation (childhood protocols)
- New future treatment options

Thank you


Alberta Children's Hospital
Childhood Vasculitis Program

Renal Biopsy in Children

Dr A.D Ademola

Outline

- Introduction
- Historical Perspective
- Indications
- Contraindications
- Patient Preparation
- Procedure
- Complications
- Renal Pathology in Children in Nigeria and Africa
- Take Home Message and Concluding Remarks

Introduction

- Renal biopsy is the process of obtaining tissue from the kidney in an individual for the purpose of histopathological evaluation.

- Types
  - Percutaneous
  - Transvenous or transjugular
  - Laparascopic
  - Open surgical approach

- The percutaneous approach is preferred by the paediatric nephrologist.

Historical Perspective

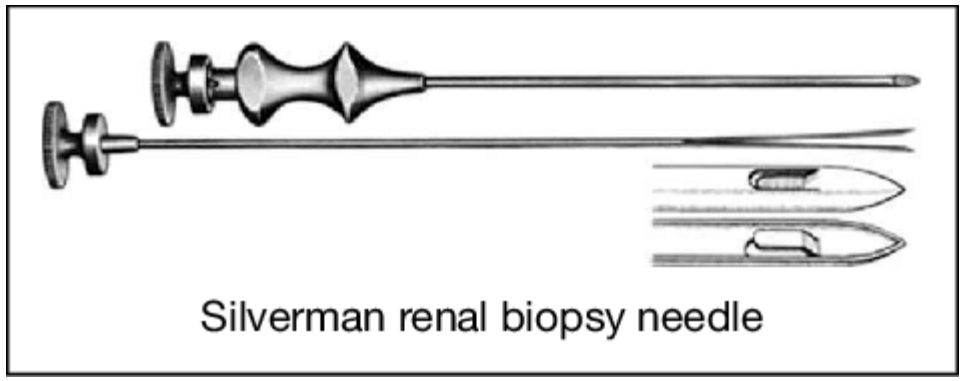
- **Nils Alwall,** Sweden 1944- first systematic aspiration needle biopsies of the kidney but results not published his results & technique abandoned b/c of an early death.
- **Iversen & Brun**, Copenhagen published in 1951, cutting as well as aspiration biopsies. Success inconsistent and operator dependent
- **Robert Kark & Muehrcke** in 1954- New Technique including use of Vim-silverman needle & improved anatomic description led to establishment as routine medical procedure.
  - Immunofluorescence & electron microscopy became available about the same time
- Use in children- first reported in 1957
- The performance and interpretation of renal biopsies one of the agents that led to the establishment of nephrology as subspecialty 1960

Historical Perspective- Localization of the Kidneys

- Initially done ‘blind’- radiological renal outlines were limited to surface landmarks
- Followed by direct fluoroscopic needle guidance- enhanced the precision
- USS Guided renal biopsy
- CT guided renal biopsy

Renal biopsy needles

Vim- Silverman Needle

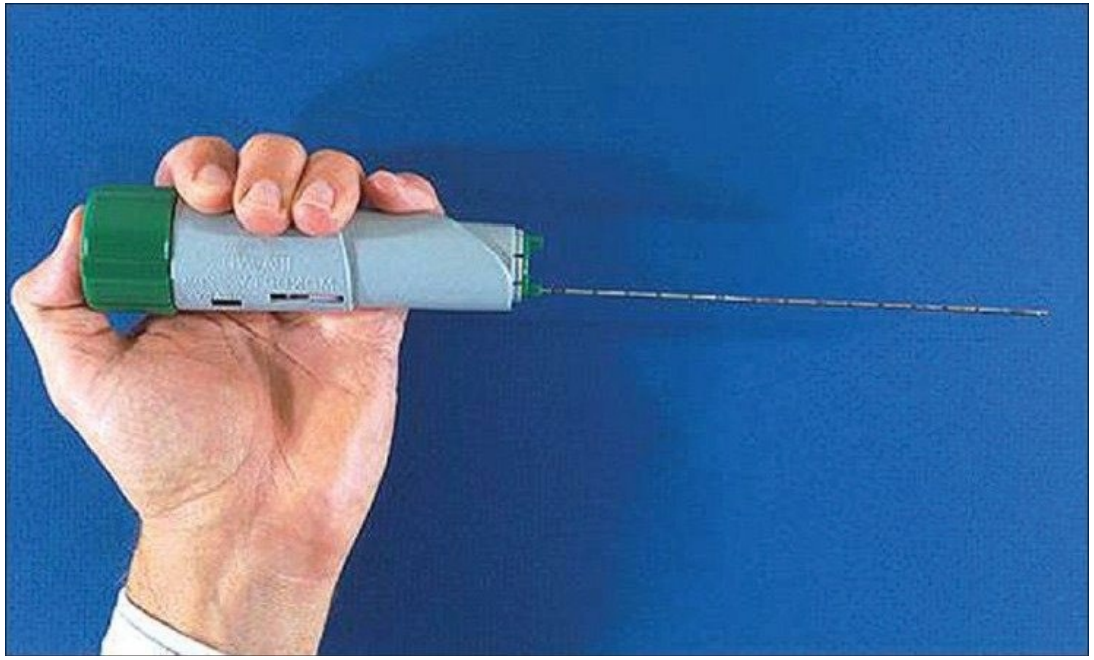


https://www.researchgate.net/publication/6721699_Proximal_Tubular_Injury_in_Myeloma/figures?lo=1

Manual Tru-cut Biopsy Needle

Renal Biopsy Needles

Tru-cut spring-loaded automatic biopsy system



Tru-cut spring-loaded automatic biopsy system

Indications for Renal Biopsy

- Establishment of the exact diagnosis
- As an aid to determine the nature of recommended therapy
- To help decide when treatment is futile
  - To ascertain the degree of active (potentially reversible) and chronic changes (irreversible)
- Follow up of treatment or disease
- Research
- Prognostication based on kidney pathology alone may be affected by sample size especially focal lesions (biopsies with glomeruli < 5 may not be accurate

Indications for Renal Biopsy

- Nephrotic syndrome
  - Age < 1 or > 7 years
  - SRNS
  - Those with evidence of nephritis (HTN, hematuria, low C3, or decreased renal function persisting in spite of volume correction.
- Acute Glomerulonephritis
  - Course not typical of PSAGN
  - HSP or SLE
    - Assessment of severity of injury, To guide therapy, & prognosis
  - Differentiation of specific types of proliferative lesions e.g MPGN, C3Glomerulopathies including dense deposit disease & C3- dominant GN
- Recurrent persistent Haematuria, proteinuria

Indications for Renal Biopsy

- Unexplained AKI- when pre- and post-renal causes are excluded
  - AKI associated with nephritis, nephrotic syndrome, evidence of vasculitis or sytstemic disease- biopsy usually performed
  - Persisting ATN when the cause remains uncertain after complete evaluation
- Suspected RPGN
  - Determination of cause, activity and chronicity
  - Serology- Anti GBM antibody, ANCA- screening test for necrotizing vasculitides
  - Imunoflouresence- p-ANCA, c-ANCA, MPO or PR3

Indications for Renal Biopsy

- CKD
  - When Kidneys are not shrunken
  - Diagnosis of Primary Disease
    - Assessment of severity of morphologic lesions
    - Determination of risk of recurrence in eventual renal Transplant
    - Suitability of deceased versus living-related donor transplantation.
- Systemic Diseases
  - To assess severity of renal disease e.g SLE, Atypical HUS
  - Patients with Diabetes with clinical course atypical of Diabetic nephropathy

Indications for Renal Biopsy

- Follow up of disease and Treatment e.g CNI
- Renal Transplant
  - Acute rejection
  - Recurrence of kidney disease
  - Calcineurin toxicity
  - Some infections
  - Chronic allograft rejection

Analysis

- Samples analysis and specimen transport medium
  - Light microscopy: 10% buffered formalin
  - Immunoflourescence: Michel's Transport Media
  - Electron microscopy: Glutaraldehyde

Contraindications

- Uncorrectable bleeding diathesis (absolute contraindication)
- Uncontrolled hypertension
- Active renal or peri-renal infection
- Hydronephrosis
- Obesity
- Hydronephrosis, ascites,
- Small shrunken kidneys
- Tumors, large cysts, abscesses, or pyelonephritis
- Solitary, ectopic, or horseshoe kidney
- Uncooperative patient
- Skin infection over the biopsy site
- When a skilled operator or appropriate pathology support is not available

Patient Preparation

- Patient should be admitted at least the day before procedure.
- History
  - Bleeding disorders
  - Ensure patient is not on warfarin, any anticoagulant or antithrombotic agent, and has had no aspirin or other NSAID for at least 7 days.
- Check Blood Pressure: Hypertesion should be cotrolled before biopsy
- Patient/Parents to be informed of procedure, risks explained and obtain consent.

Investigations

- PCV > 24-30%
- FBC platelet count at least 100 000/mm3
- Coagulation profile.
  - PT
  - INR < 1.2
  - APTT < 2ce control or < 40 secs
- E&U and Creatinine
- Abdominal USS KUB to assess if patient has two kidneys, kidney sizes etc
- Urinalysis
- Urine mcs
- Group and Crossmatch 1 unit of blood

Patient Preparation Continued

- If the child is on hemodialysis, the procedure should be done after at least 24 hours of last dialysis session.
- For patients with prolonged BT (>8-10 minutes, e.g., in SLE, azotemia), IV desmopressin 0.3 µg/kg 30 min prior, or intranasal DDAVP 2-4 µg/kg 2 hours before the procedure may be considered.

Premedication

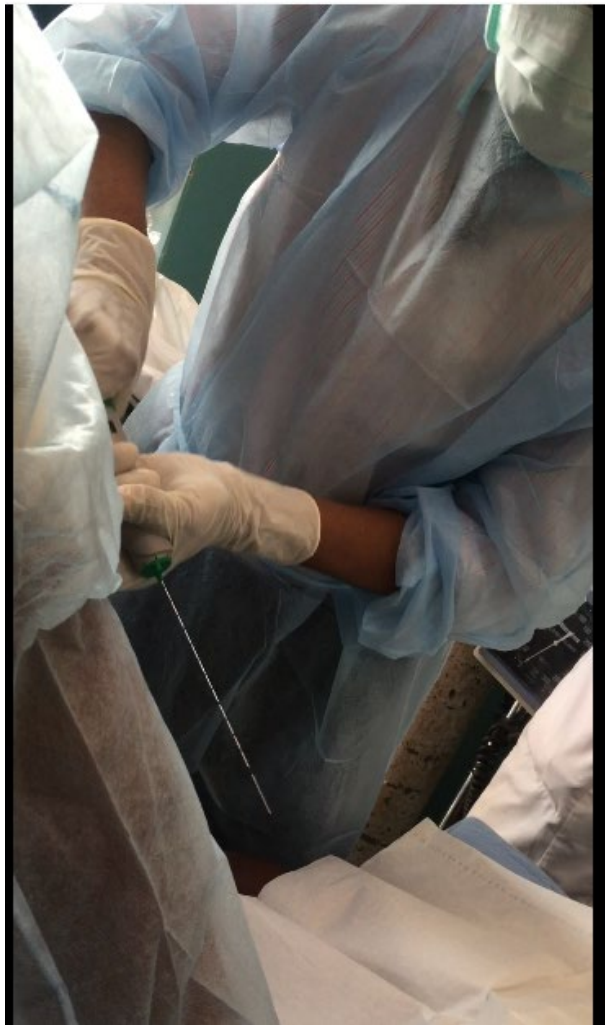
- NPO 4 hrs before procedure and commence 5% D/W at maintenance
- Local Anaesthesia and sedation
- Sedation:
  - Most widely used: 1-2 doses of midazolam (0.1mg/kg) & ketamine 0.5-1.0 mg/kg. (+ Anaesthetist)
  - +/- Intravenous atropine 0.01 mg/kg 1-2 minutes after midazolam
- In UCH Ibadan
  - i.m pentazocine 1mg/kg 30 minutes before procedure.
  - i.m phenergan 0.25mg/kg 30 minutes before procedure.
  - Just before the percutaenous biopsy titrate i.v diazepam 0.3mg/kg to sedate patient

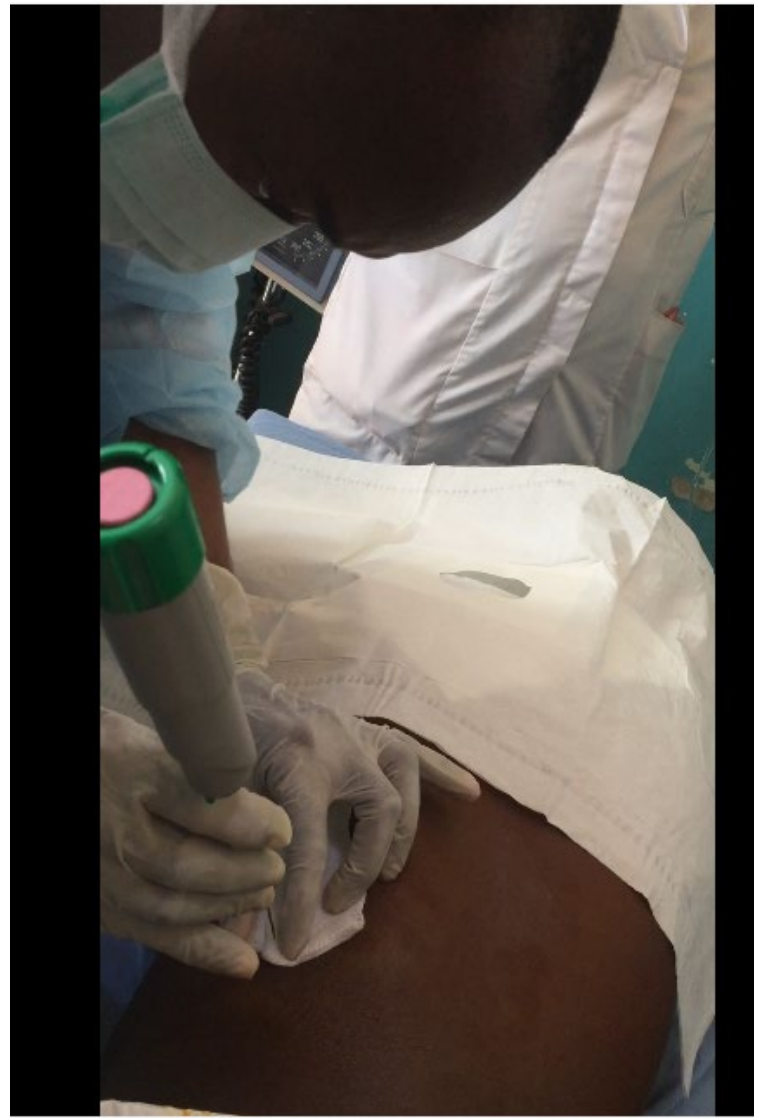
Procedure

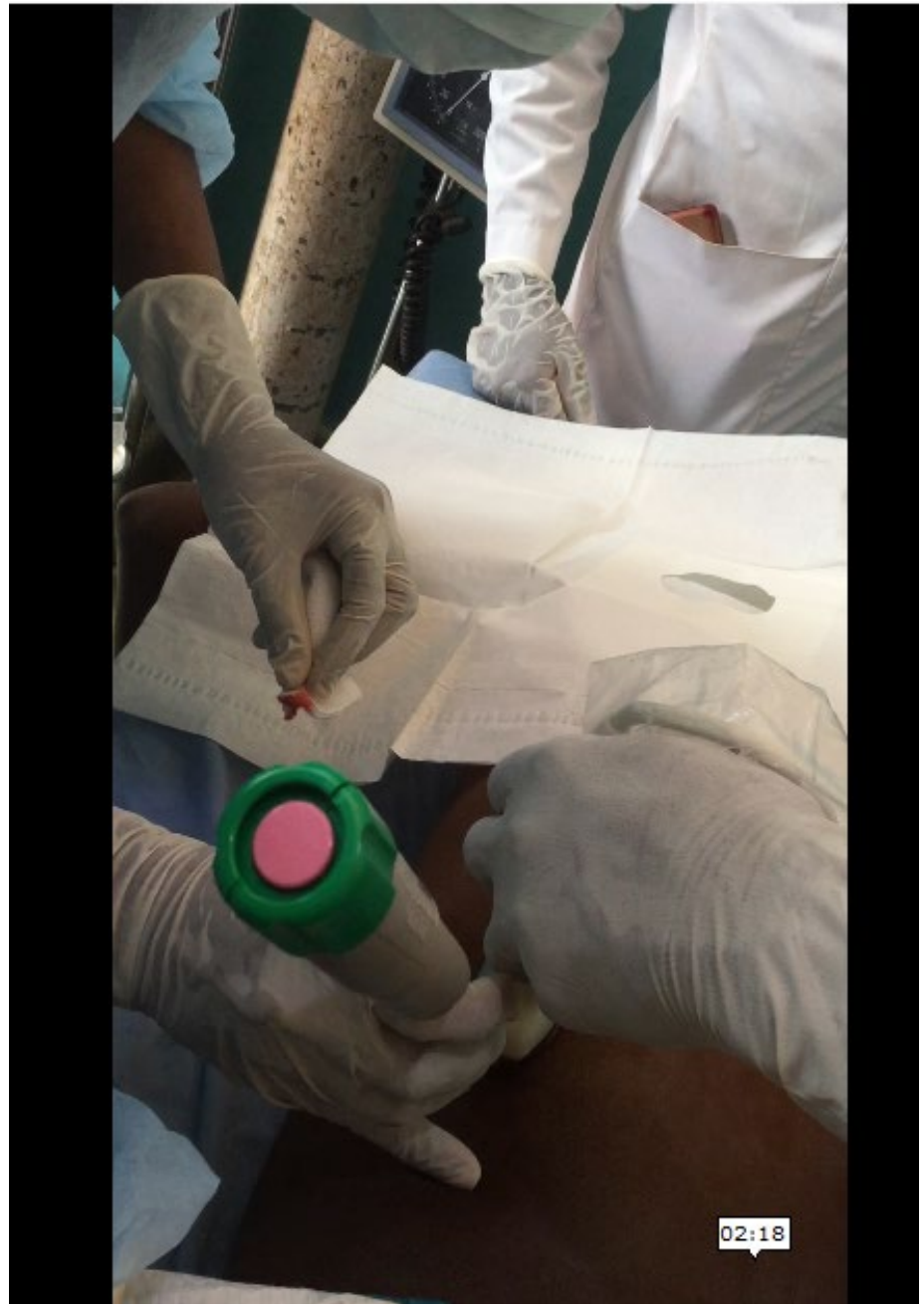
- Persons in attendance: Paediatric nephrologist, Radiologist, Pathologist (Presence of Radiologist or Pathologist may vary across centers)
- Prone position for biopsy of native kidney
- Supine position for graft kidney
- In conditions like abdominal distension and ascites the biopsy can be done in lateral decubitus position
- Oxygen saturation, heart rate, blood pressure monitoring during the procedure
- Left kidney usually biopsied
- Identify the lower pole of the kidney under real time USS, and determine the skin entry point for the biopsy needle.

Procedure

- Clean skin with methylated spirit ad povidone iodine
- Give local anesthesia with 1% Lignocaine (under USS guidance)
- Make a nick on the skin at the site of entry of the biopsy needle
- Advance the biopsy needle under real time ultrasound guidance ito the cortex of the kidney
  - 16G versus 18G needle
- Sample is obtained from the renal cortex
- 2-3 passess
- The core can be examined for the presence of glomeruli



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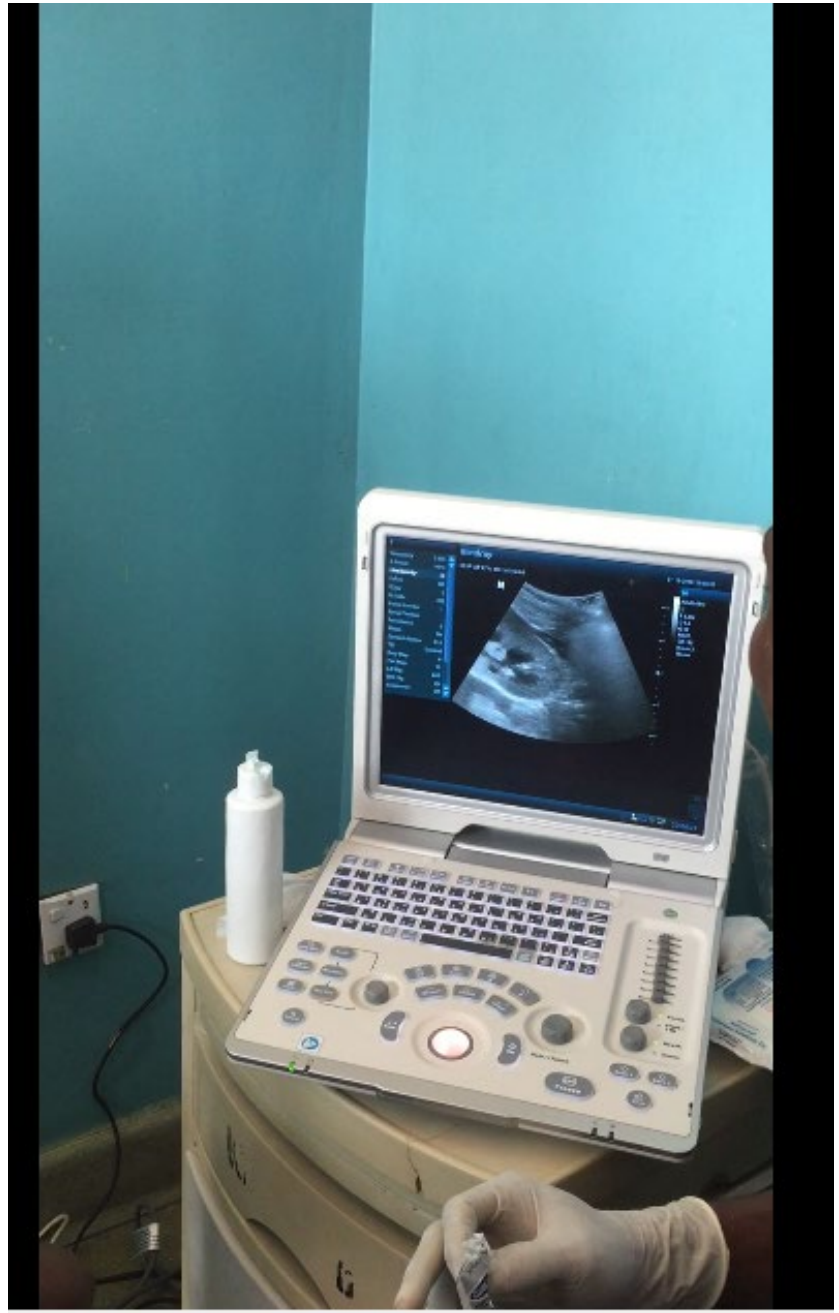

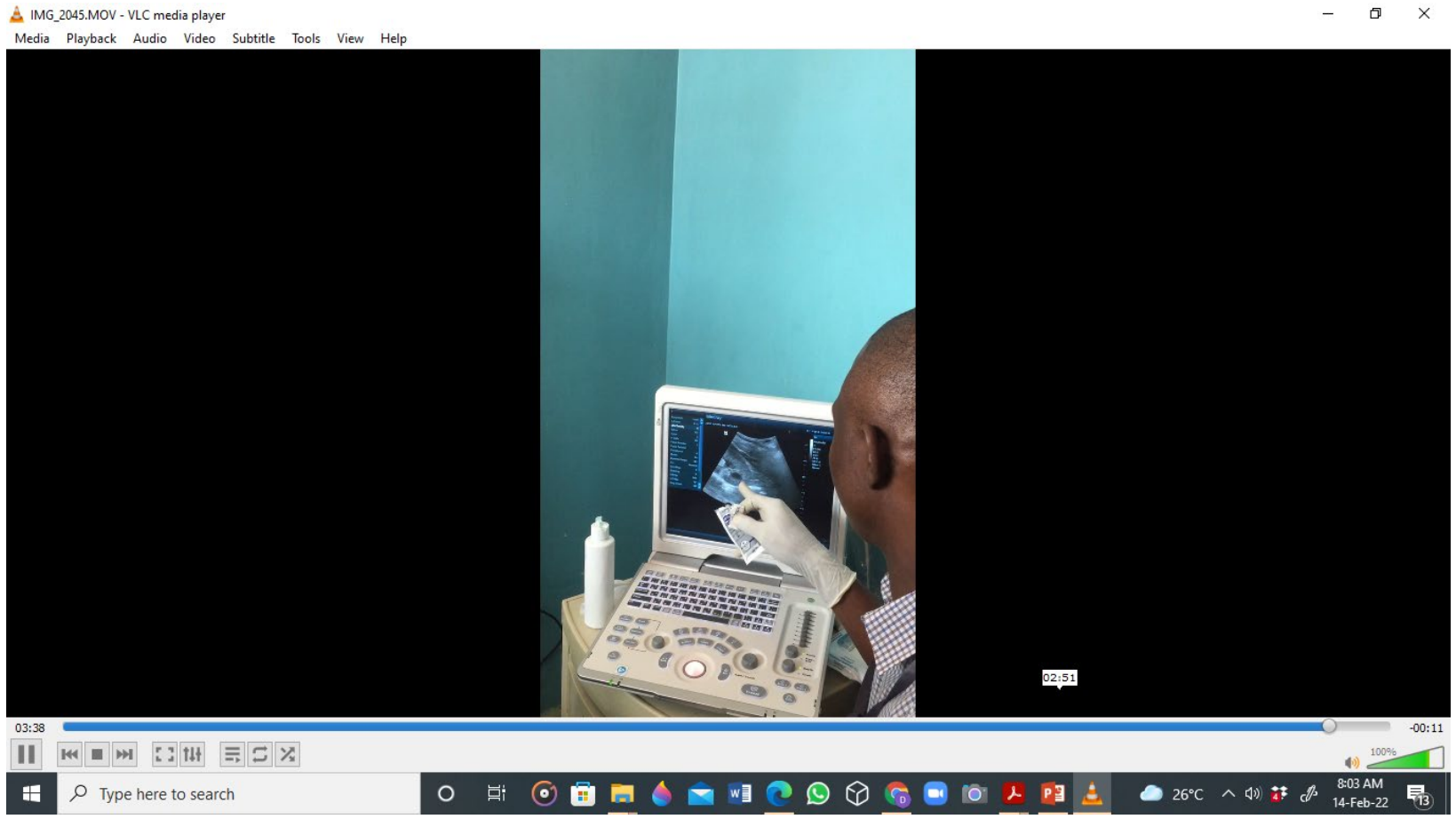
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Post-Biopsy instructions

- Do a post renal biopsy clinical evaluation of patient.
- Monitor Vital signs BP, Heart rate, Respiratory rate, temperature ¼ hrly for 1 hour, half hourly for 2 hours, hourly for 4 hours then 4 hrly for 24 hours.
- Keep urine rack.
- i.v fluids 10% dextrose to run at maintenance fluid requirements.
- Fluid input and output monitoring.
- Patient can eat as soon as he/she is fully conscious
- Watch out for gross haematuria, abdominal pains, or flank pains.

Complications

- Significant haematuria.
- Anaemia and Hypotension
- Bowel or solid organ perforation/ laceration
- Loss of a Kidney
- Death
- AV malformation
- Hypertension
- Persistent loin pain

Studies in Ibadan

Asinobi *et al. BMC Nephrology* (2015) 16:213
DOI 10.1186/s12882-015-0208-0

BMC Nephrology

RESEARCH ARTICLE Open Access

Trends in the histopathology of childhood nephrotic syndrome in Ibadan Nigeria: preponderance of idiopathic focal segmental glomerulosclerosis

Adanze O. Asinobi[1,2*], Adebowale D. Ademola[1,2], Clement A. Okolo[3,4] and Joseph O. Yaria[5]

- In Ibadan (n=78) children undergoing renal biopsy
- Compared children who had renal Bx 1997-2001 & 2006-2013
- FSGS most common among children with Idiopathic NS followed by MPGN
- MCD was more common among children with Secondary NS

Renal Histology among children with nephrotic syndrome in Africa

- Review of all paed African studies from 1946-July 1st 2020 (Wine 2021) MCD, FSGS, and other histologic types 38%, 24% and 38% respectively

Histologic Type	Before 1990	After 1990
MCD	24%	30%
FSGS	13%	41%
Others	54%	29%

Paediatric Kidney Biopsies In Africa 1946-2021 *(Wine 2021)*

Country	No of studies	No of Biopsies	MCD	FSGS	Others
South Africa	7	1280	411	296	402
Egypt	7	1020	521	196	303
Nigeria	25	683	91	122	445
Sudan	4	308	138	64	106

Paediatric Kidney Biopsy in Nigeria

- Historically Paediatric Kidney biopsy took place in Nigeria with Light Microscopy, Immunofluorescence (IF) and Electron Microscopy (EM)
- Currently a number of centres still carry out native kidney biopsies but limited to light microscopy
- At a number of sites renal biopsy is supported by Multicentre Research
- Transplant biopsies are few
- Sustained training of both paediatric nephrologists, pathologists, provision of facilities for IF and EC, and registry of renal pathology may further improve renal histology in our country.

Take Home Messages

- Renal Bx including in children has undergone much improvement in terms of kidney localization and tissue procurement
- It can be safely carried out in children by trained personnelle with meticulous attention paid to the safety precautions
- The number of paediatric renal biopsies done in our country may have increased in recent times due to support from collaborative research project specifically H3Africa KDRN
- There is need to further develop local capacity through training, development of immunoflouresence and electron microscopy and renal registry.

POINT OF CARE ULTRASOUND(POCUS) IN PEDIATRIC NEPHROLOGY

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IBADAN

OBJECTIVES OF THE LECTURE

- What is POCUS?
- What is the objective?
- Understanding the basic principles of ultrasound
- Understand the use of some basic knobs on the ultrasound machine
- POCUS in pediatric nephrology
- Basic sonographic anatomy of the kidney
- Basic principles of ultrasound scanning

INTRODUCTION

- **Point-of-care ultrasound (POCUS) is the use of ultrasound scans at the point of care of patients**
  - **Bed side**
  - **Clinic**
- **It has now become an adjunct to clinical examination in critical care units.**
- **Studies have shown that clinician-performed ultrasound frequently changes the diagnosis**
- **It also leads to appropriate management compared to conventional physical examination in various clinical settings**
- **In addition, POCUS has the potential to reduce further diagnostic workup and unnecessary radiation exposure**
  e.g. plain radiography, IVU, MCUG

INTRODUCTION (CONTD)

- POCUS is a limited ultrasound examination
- Aimed at answering focused/immediate clinical questions
- Therefore, it must not be viewed as an alternative to radiologist-performed comprehensive ultrasound
- NOTE :This session is not intended to make us radiologists

What is ultrasound

- Ultrasound is defined as any sound wave frequency greater than the upper limit of human hearing ability
  - Frequency >20KHz
- Diagnostic range-1MHz to 20 MHz

IMPORTANT PROPERTIES OF ULTRASOUND

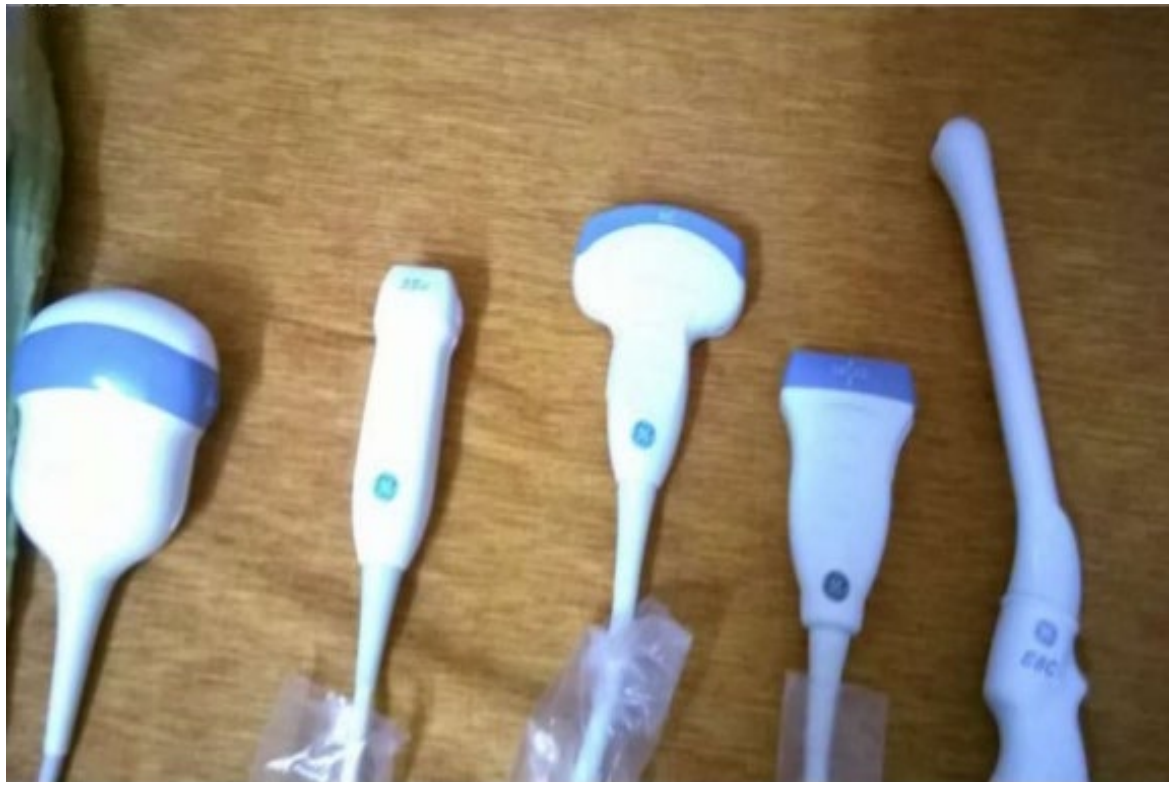
- FREQUENCY
- WAVELENGTH
- INTERACTIONS WITH TISSUES
- RESOLUTION

PENETRATION VS FREQUENCY AND RESOLUTION

10-20 cm	=	3.5 MHz
5-10 cm	=	5.0 MHz
2-5 cm	=	7.5 MHz
1-4 cm	=	10.0 MHz

- Penetration depth is better at a low frequency (between 2.5 and 7.5MHz) but a disadvantage of the low frequency is a lower image quality
- The higher the frequency (above 7.5Mhz), the lower is the depth of penetration, however, you get better quality images close to the surface (7.5MHz = 20 cm).

TRANSDUCERS/PROBES



It is the hand-held part of the ultrasound machine that is responsible for

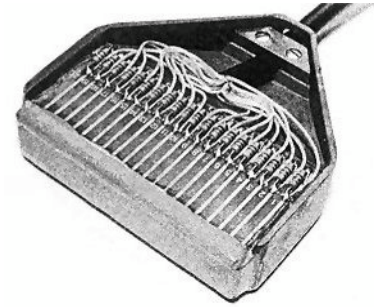
production	and detection of ultrasound waves.

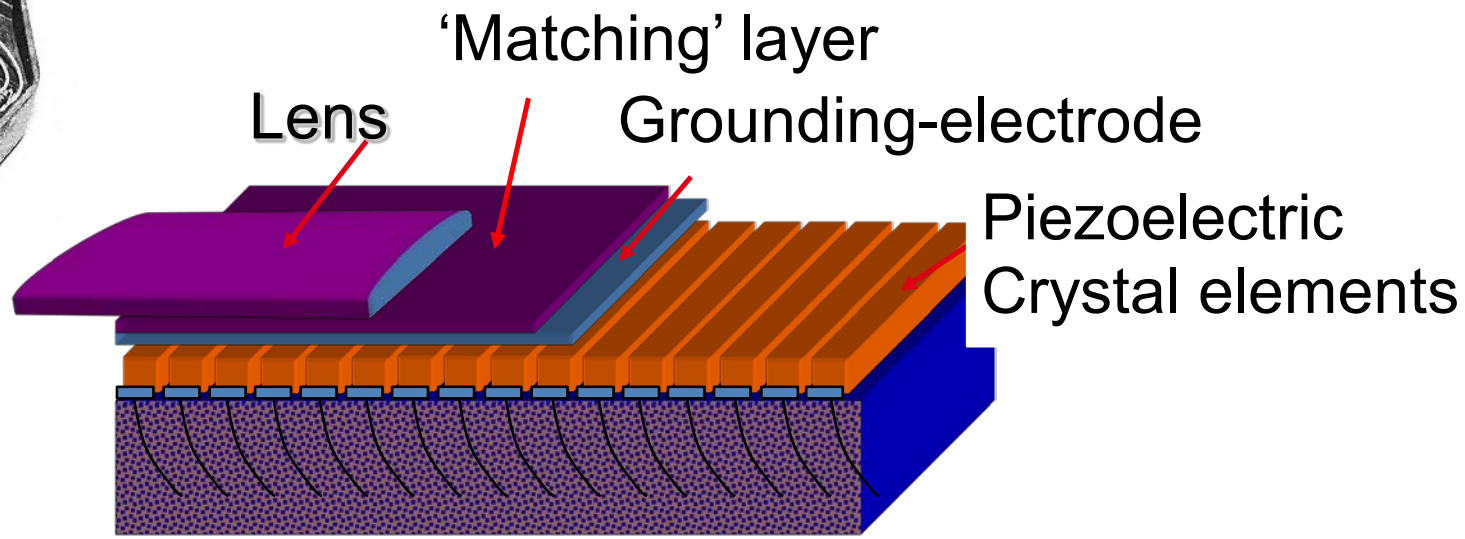
The main components are piezoelectric crystals

There are various types- depend on:

Frequency- high or low	Piezoelectric crystal arrangement	Application	Route- external or internal

Ultrasound transducer (probe)



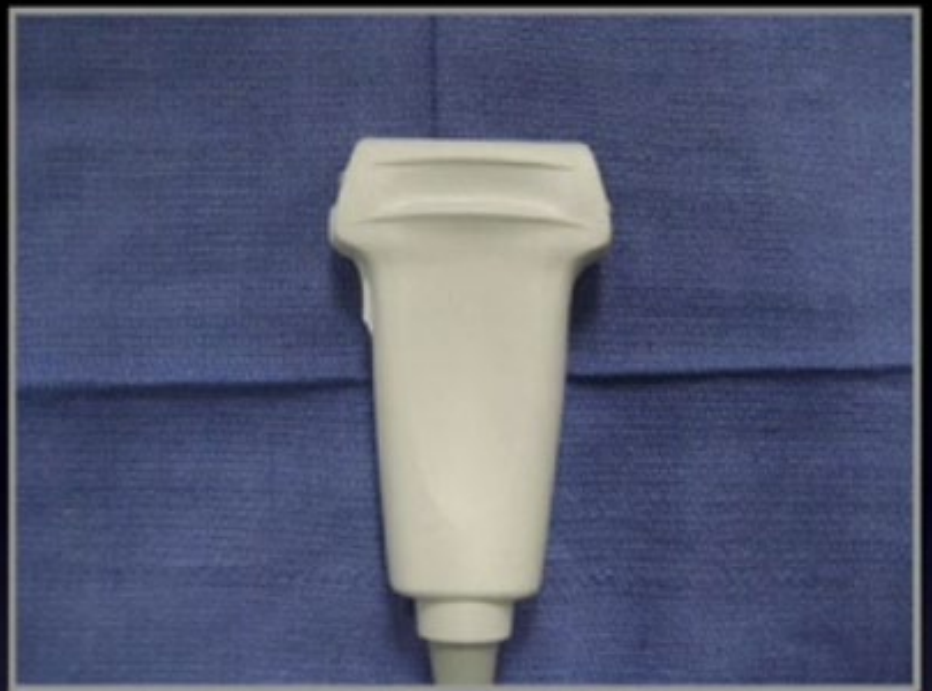


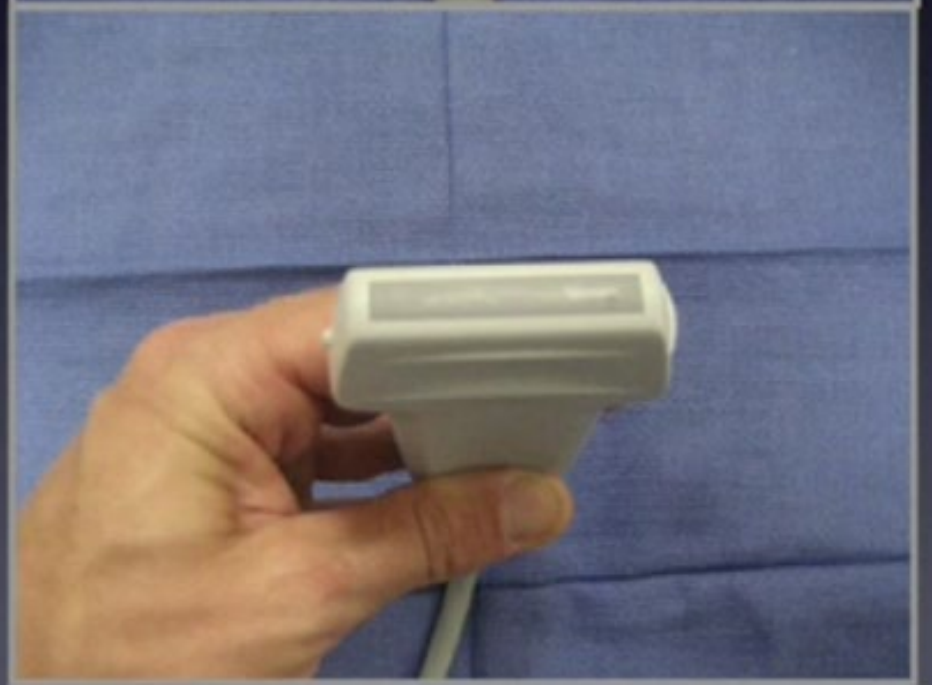
Curved array probe

- Large scanning area
- Lose resolution with depth
- Better penetration
- Abdominal applications, vascular application in the morbidly obese, OB, FAST, etc.

Linear array probe

- "Rays" are parallel
- Less loss of resolution with depth
- To scan superficial structures with high frequency
- *Probe of choice for vascular access*



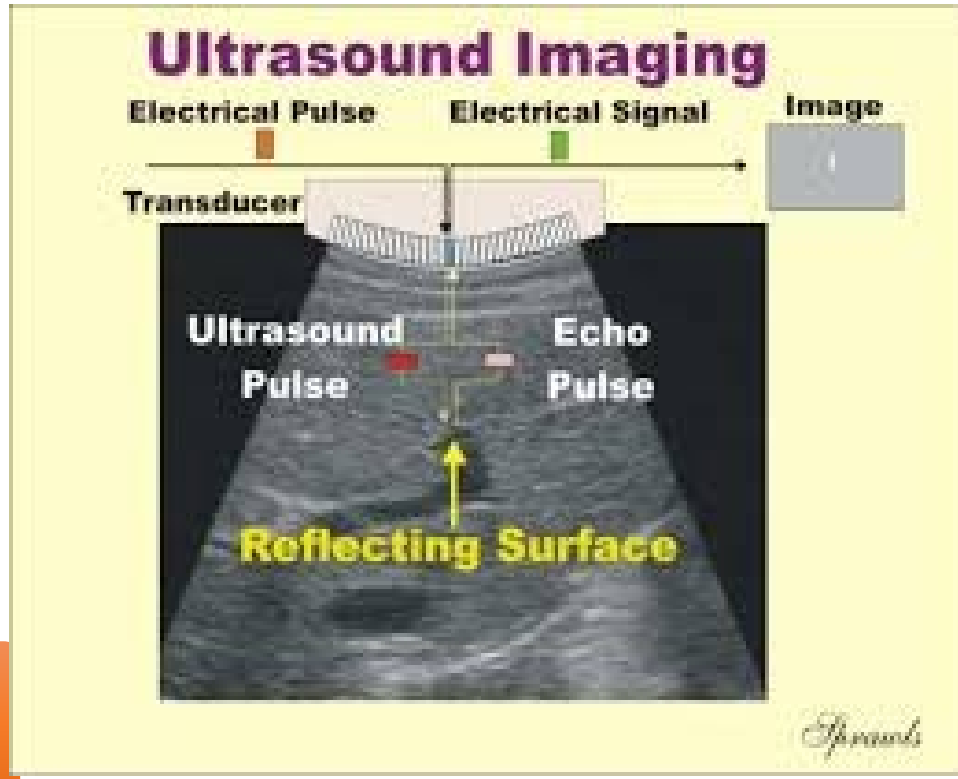


Phased array probe (Cardiac)

- Good scanning area, narrow footprint for rib spaces
- Same loss of resolution with depth
- Cardiac applications and FAST exam

How ultrasound images are produced

- The transducer converts electrical energy to ultrasound wave which is sent into tissues
- As the sound travels through the body, it is reflected by the tissue interfaces
- reflected echoes are picked up by the same transducer
- converted to electrical signal
- Machine processes the data and form a grey scale image



MODES OF ULTRASOUND

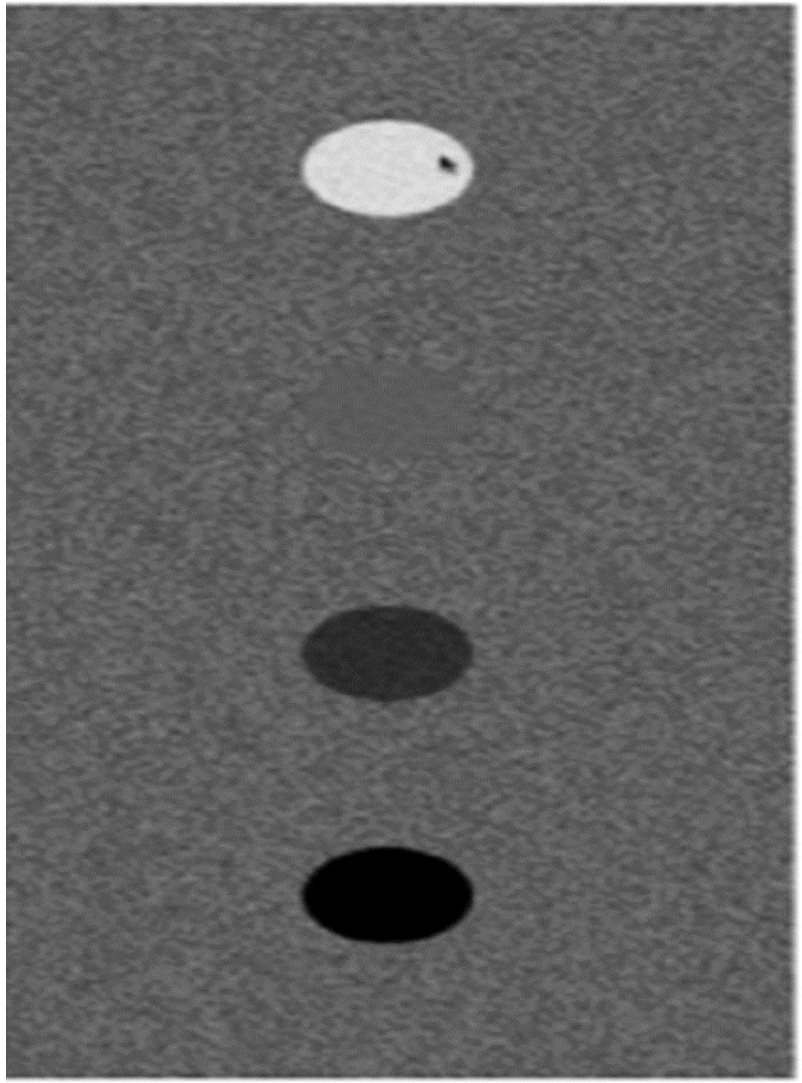
SCALE MODES

- A-Mode
- B-Mode
- M-Mode

DOPPLER MODES

- Continuous wave Doppler
- Power Doppler
- Color Doppler
- Duplex Doppler
- Pulsed wave Doppler

TERMINOLOGY- ECHOGENICITY



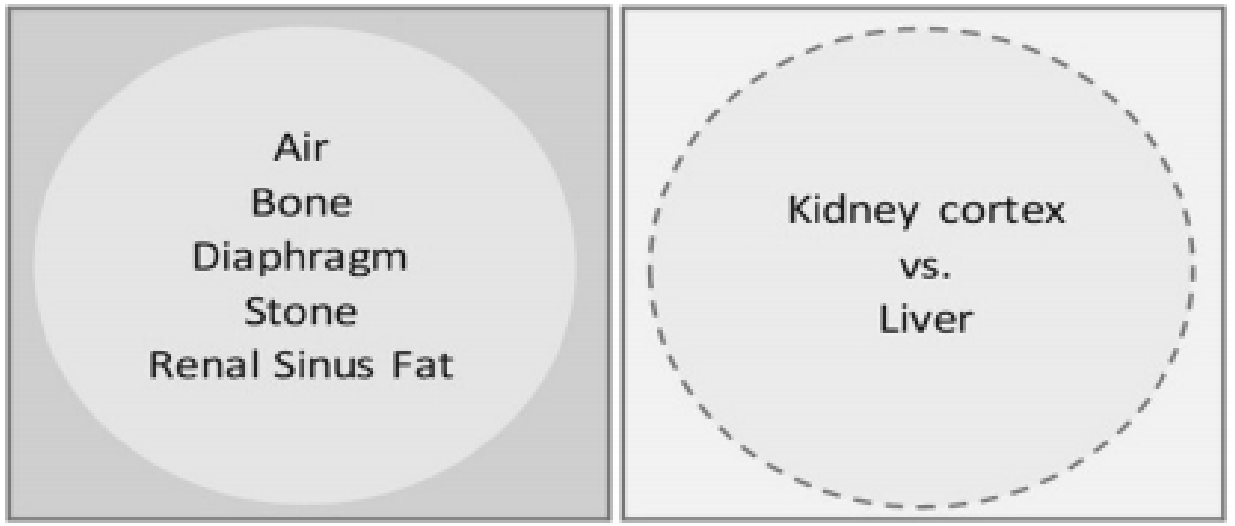
-Hyperechoic --High intensity echoes

-Isoechoic - Same intensity echoes

-Hypoechoic- Low intensity echoes

-Anechoic- No internal echoes

TERMINOLOGIES



A. Hyperechoic

B. Isoechoic

C. Hypoechoic

C. Anechoic

ULTRASOUND ARTIFACTS

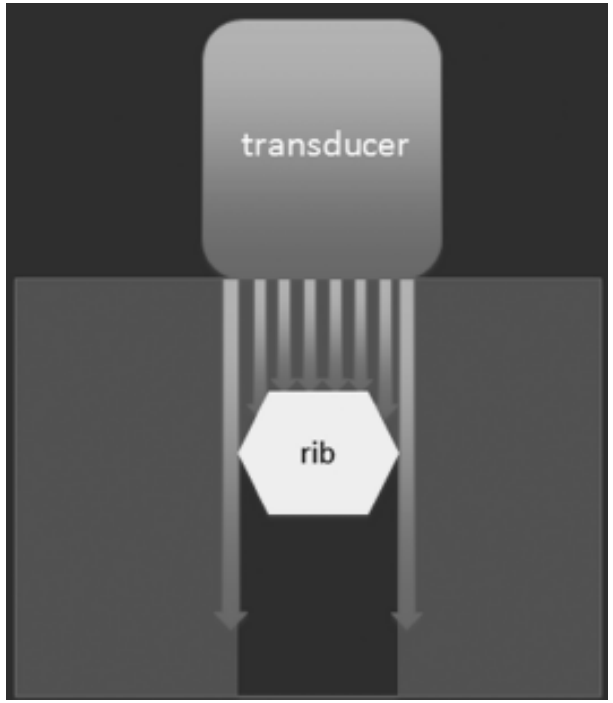
- Images produced that do not accurately reflect the anatomy of the scan plane
- May be seen in normal tissues
- Pathologic conditions

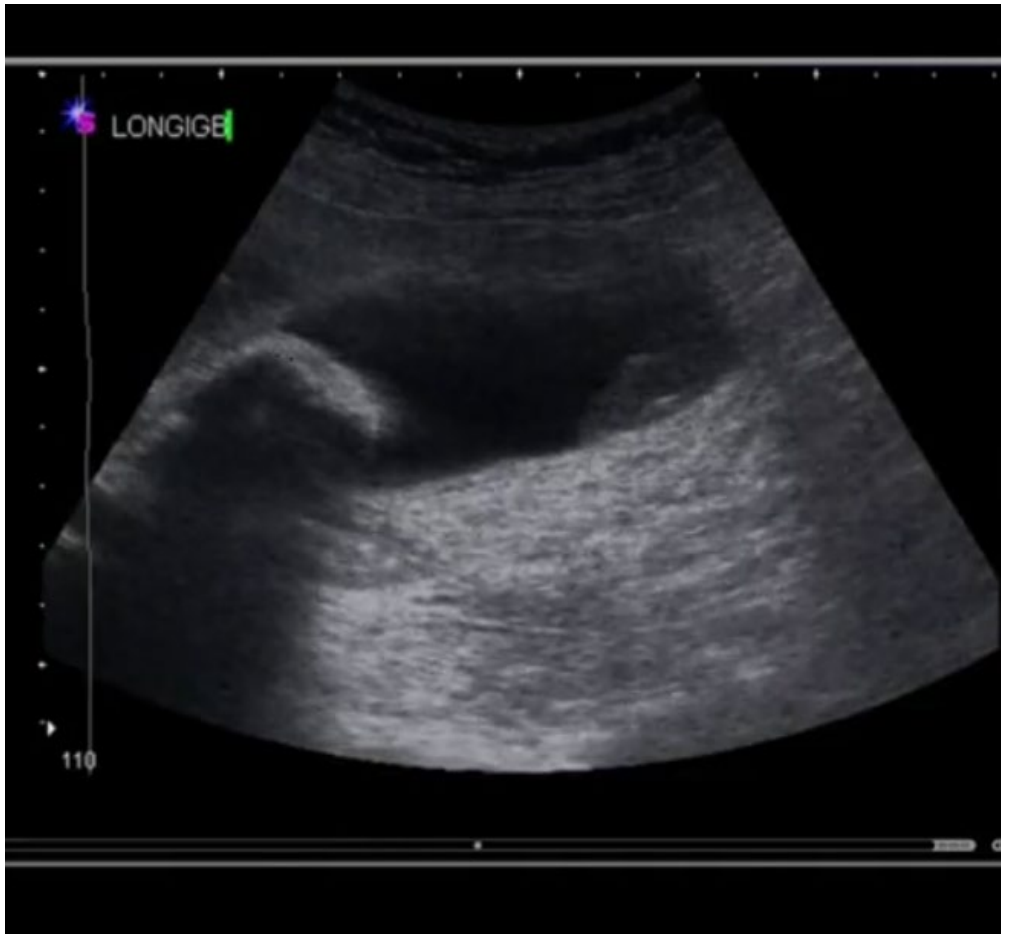
Ultrasound Artifacts

- Seen in both normal and pathologic situations (you interpret!)
  - Acoustic shadowing
  - Mirror artifact
  - Reverberation artifact
  - Gain artifact
  - Posterior acoustic enhancement
  - Lateral cystic shadowing (edge artifact)

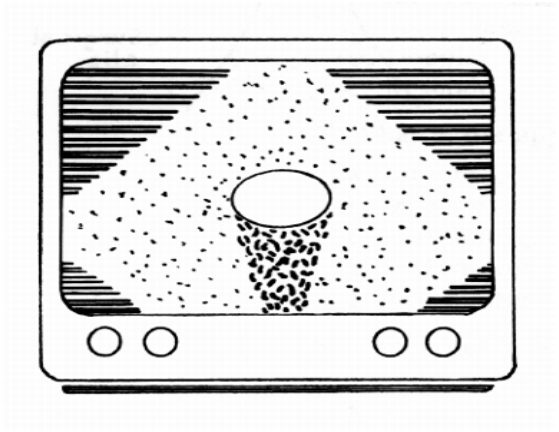
ACOUSTIC SHADOWING

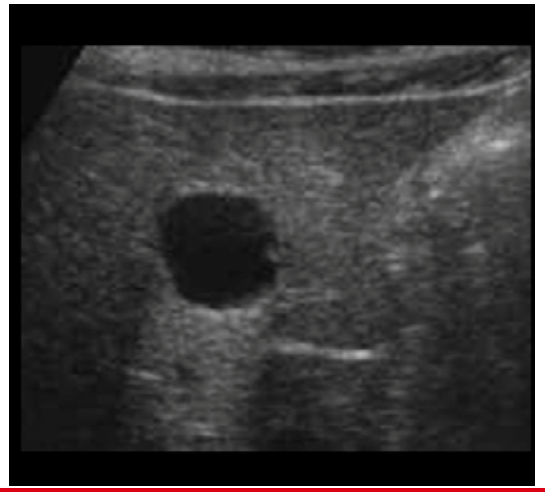
- due to the mechanism of total reflection of **ultrasound waves**
- Dark area posterior to the reflector
- Structures behind the reflector are obscured by the shadow
- Seen in Bones, calculi, stones





Posterior acoustic enhancement





- Area of increased brightness immediately posterior to a cystic structure
- Caused by lack in sound attenuation through a structure with few interfaces
- Occurs in fluid-filled structures

IMPORTANT MACHINE KNOBS/FUNCTIONS

Gain (= brightness)

- The overall brightness of the image can be adjusted.
- Either too bright or too dark ----→ it is difficult to see subtle differences in texture.
- This is the most important adjustment to become accustomed to making.

TGC (Time Gain Compensation)

- This knob allows adjustment of image brightness (gain) selectively at different depths
- In some machines, the TGC knob is replaced by the near gain or far gain control knobs.
- Up to 10 separate depth adjustments on platform based machines.
- This is used to compensate for strong attenuation or enhancement by superficial tissue.

Depth – changes the field of view or depth of view of the structure being imaged

- With this knob, you can adjust the field screen to be - **shallower** (increase the knob) or
  - **deeper** (increasing this knob)
- This can be repeated several times until you achieve the depth you need.

Zoom

- This takes a portion of the screen and magnifies it.
- This can be done while scanning
- For superficial structures it is normally easier to magnify by just to reducing the depth of the image.
- For deep structures it is necessary to use the zoom

Freeze Button

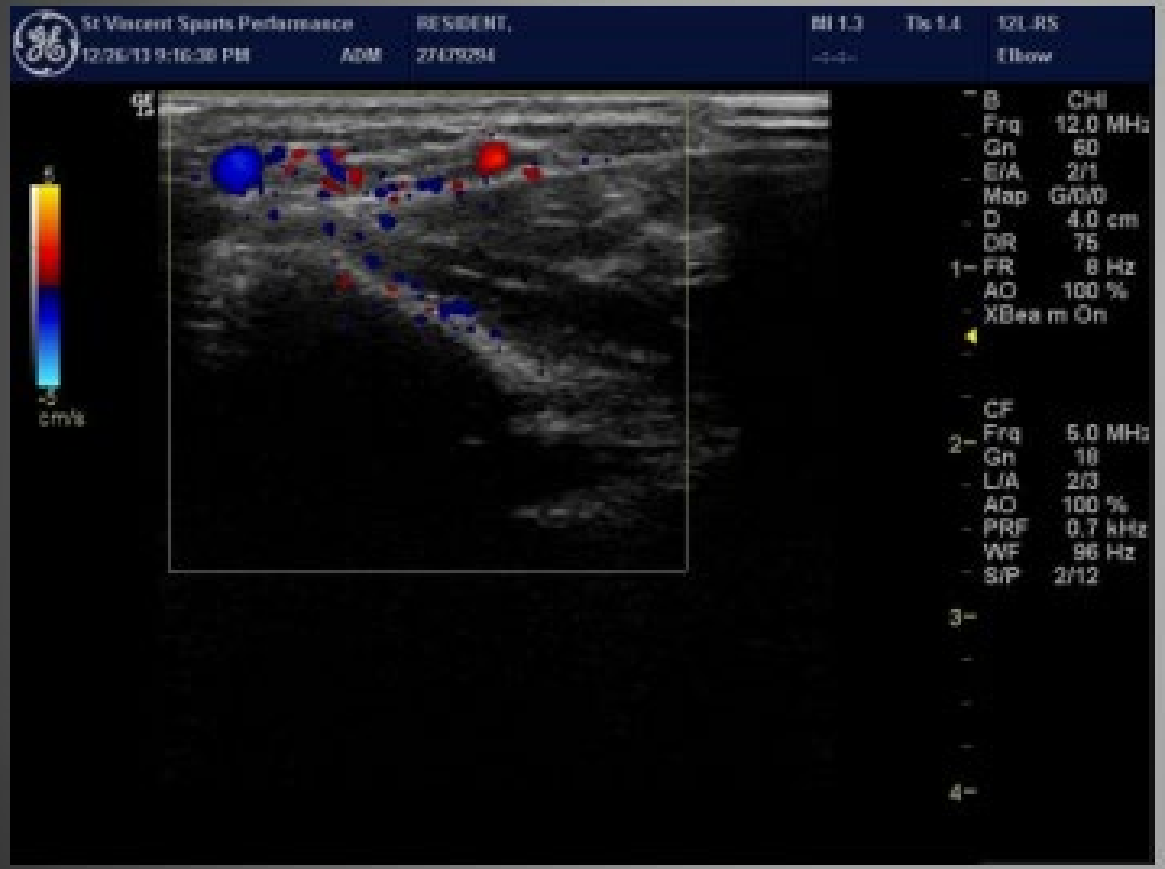
When you press the freeze button the image displayed at that moment is captured on the screen so that :

- Measurements can be taken
- A print can be made .
- Images can be stored.
- With experience, the operator always has a finger within instant striking distance of the freeze button
- Most modern machines will also have a **Cine Loop** function that allows you to scroll back through the preceding several seconds of the scan, frame by frame.
- 'Freeze' when not scanning

CALIPERS

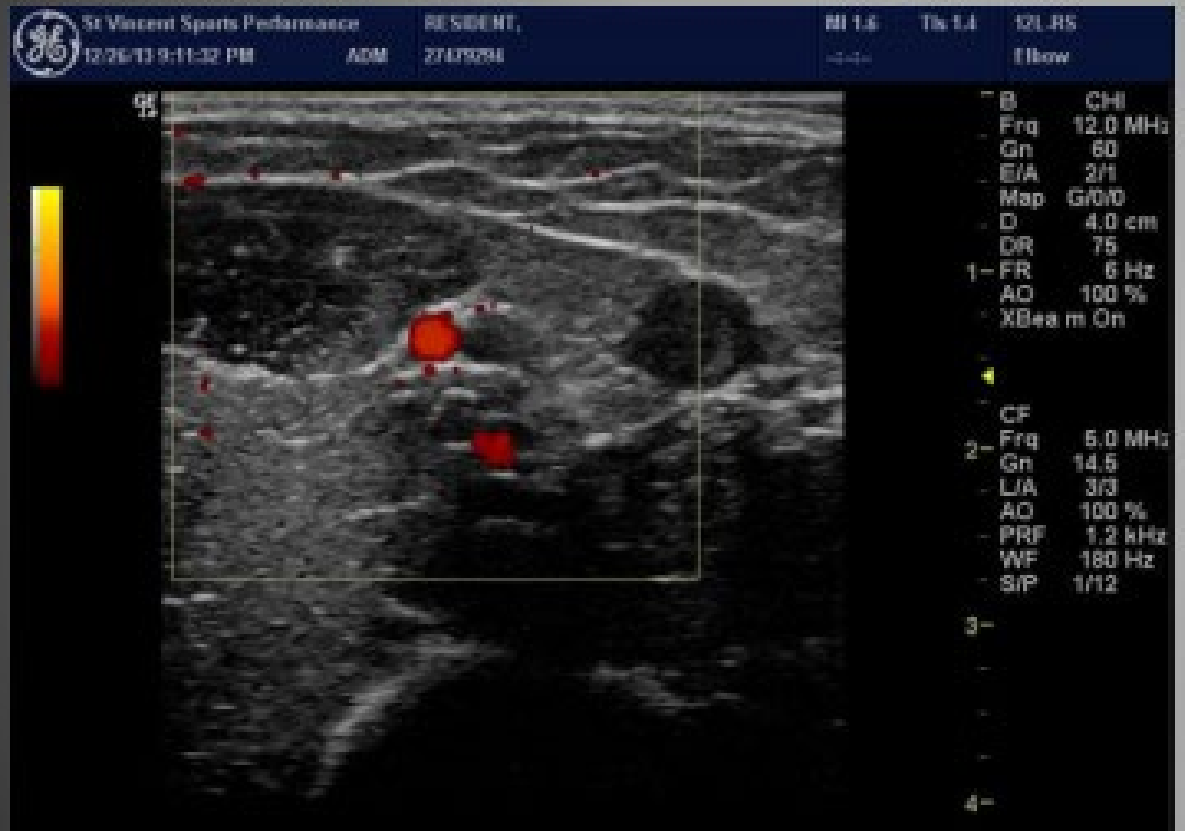
- Calipers are available on all modern machines and are calibrated so that reasonably accurate measurements can be made.
- Caliper markers are available to measure distances.
- The ellipsoid measurement is an added feature in most units. A dotted line can be created around the outline of structure to calculate either the circumference or the area.

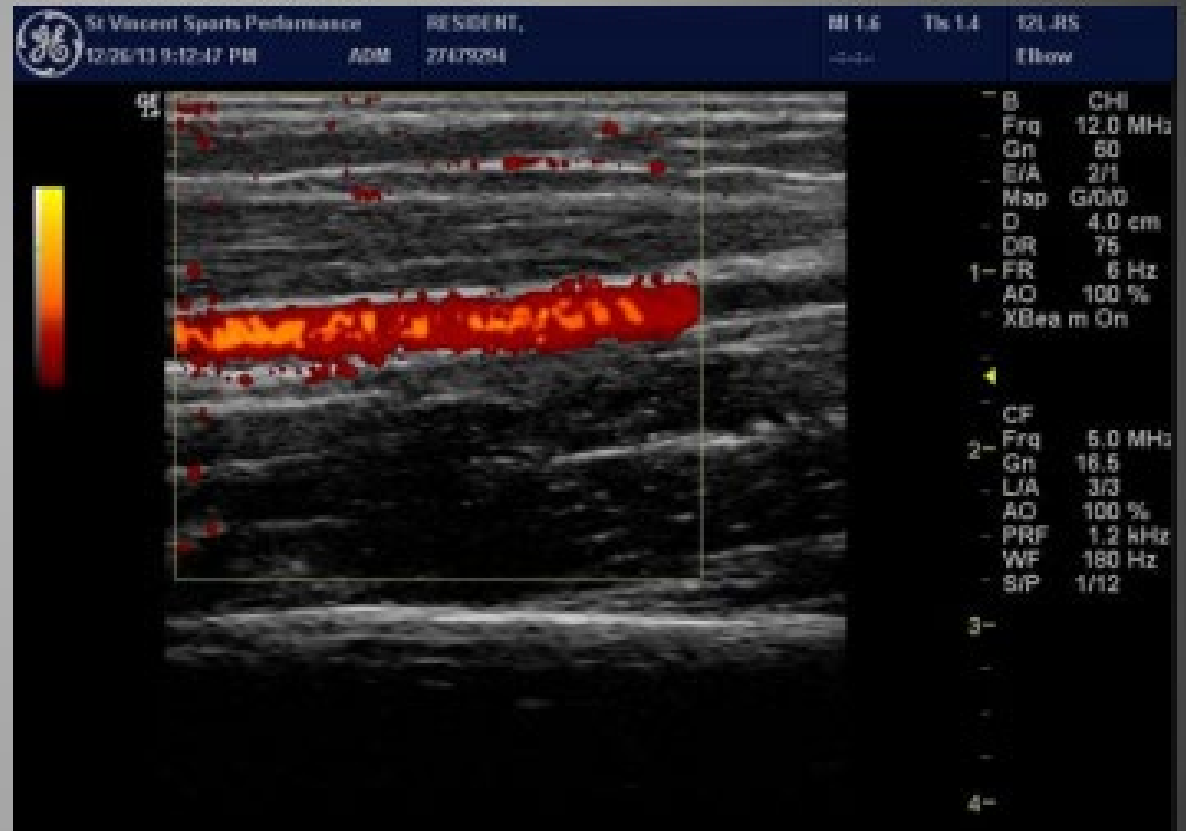
COLOUR DOPPLER



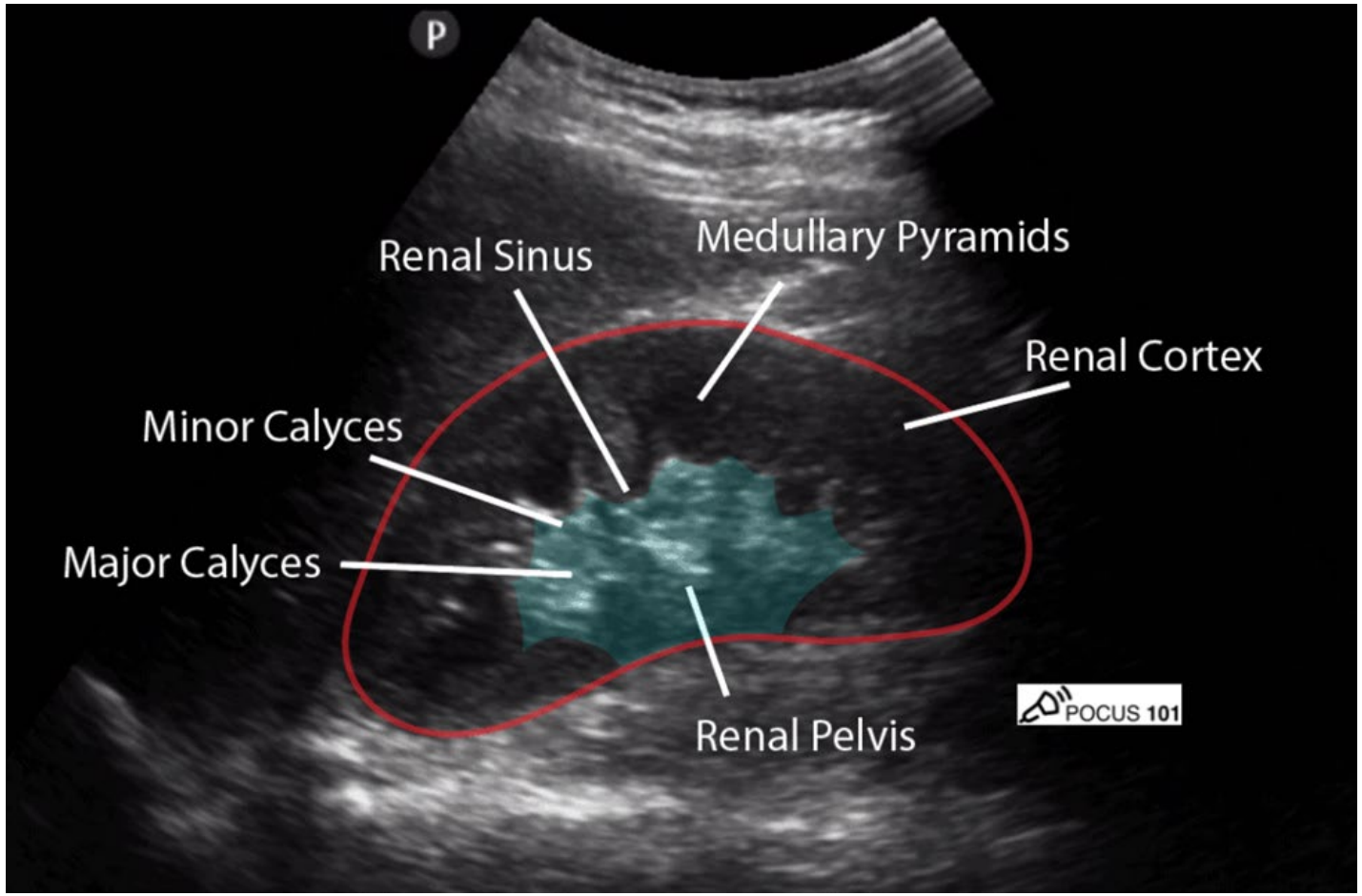
- detects presence of flow (Bidirectional flow)
- Blue –Flow away from the probe
- Red – Flow towards the probe

POWER DOPPLER- detects flow only, not direction of flow

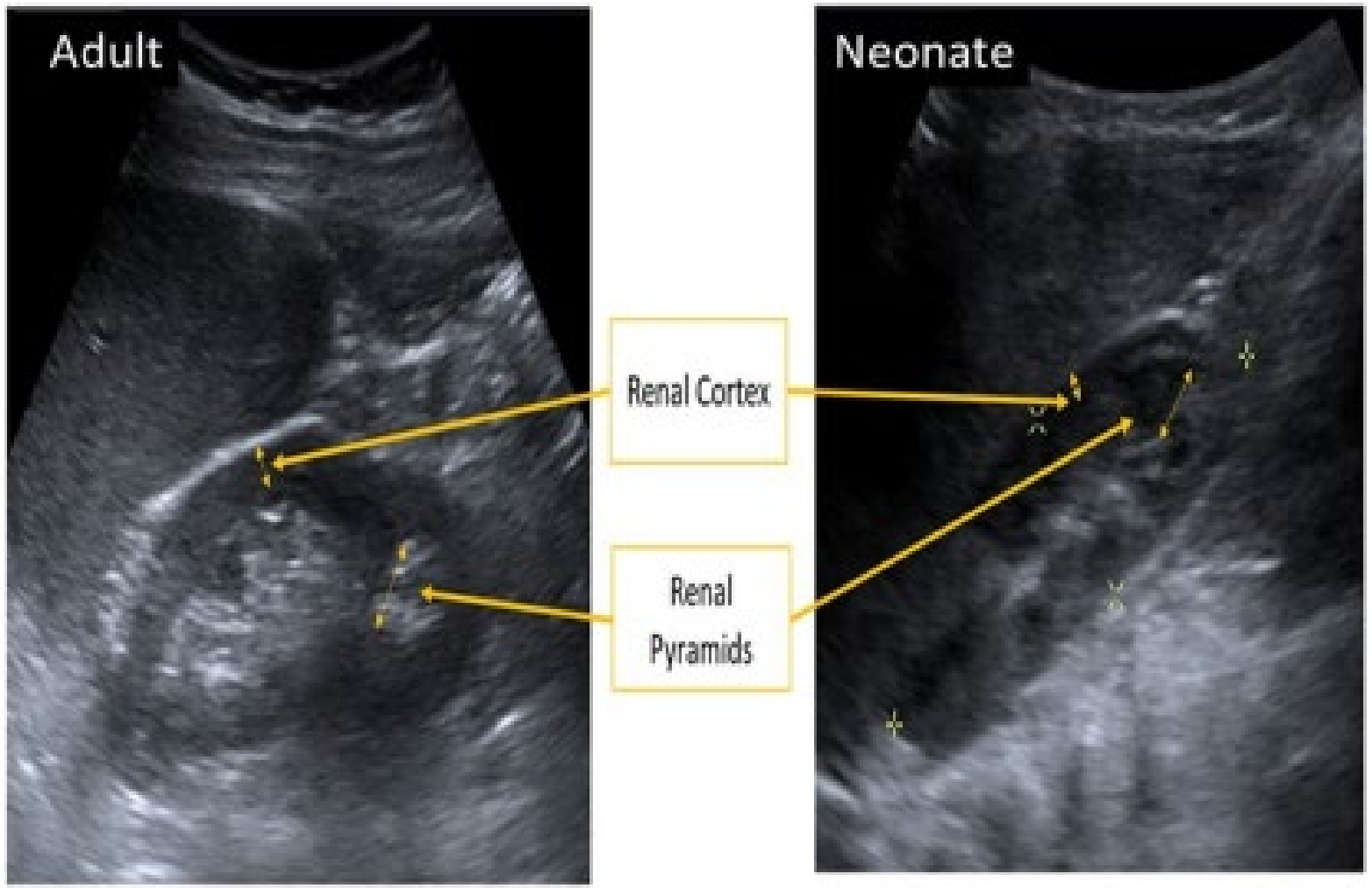




SONOGRAPHIC ANATOMY OF THE GUS-KIDNEY

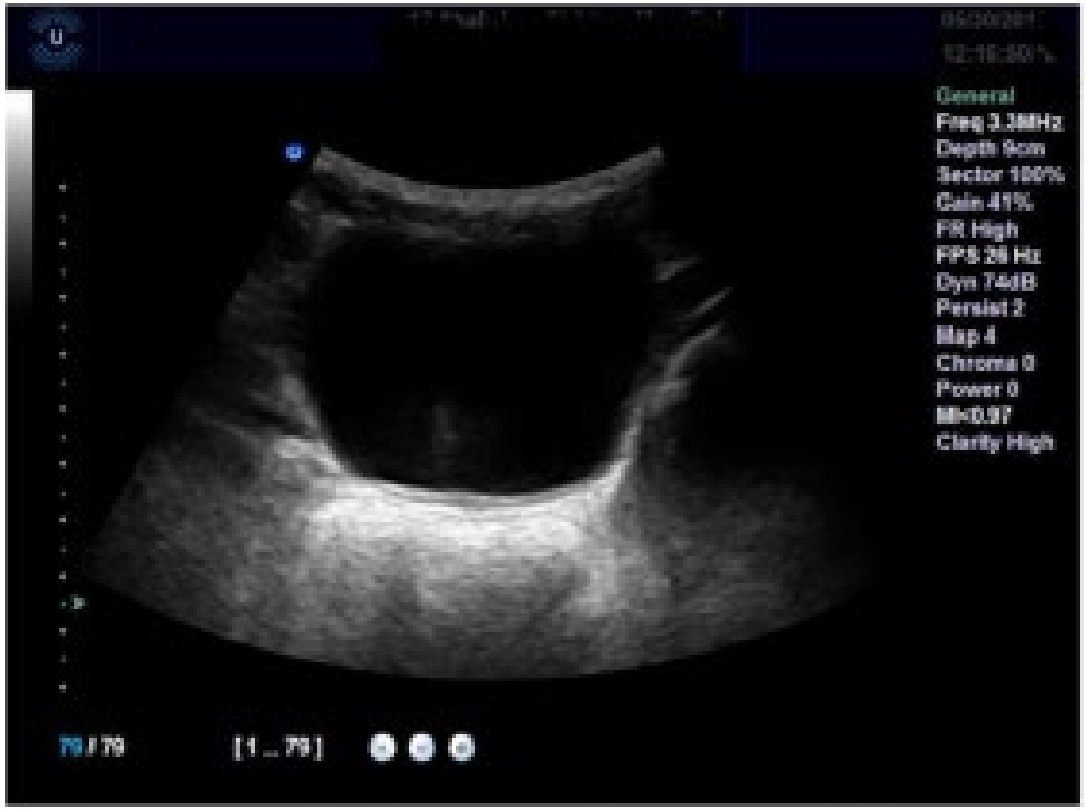


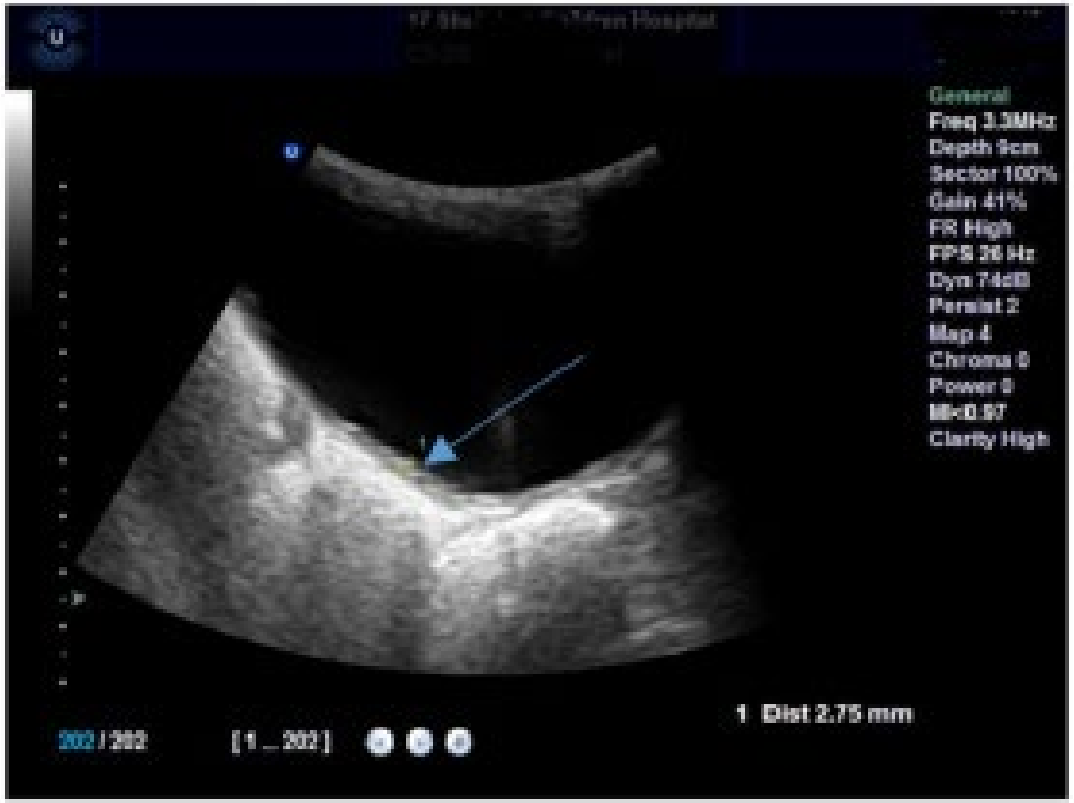
SONOGRAPHIC ANATOMY OF THE GUS-KIDNEY



[redacted] Ultrasound images highlighting differences in echogenicity in adults [left image] as compared to neonates [right image]. In neonates, the renal cortex is much thinner, therefore it makes the pyramids larger as compared to those visualized in the older children

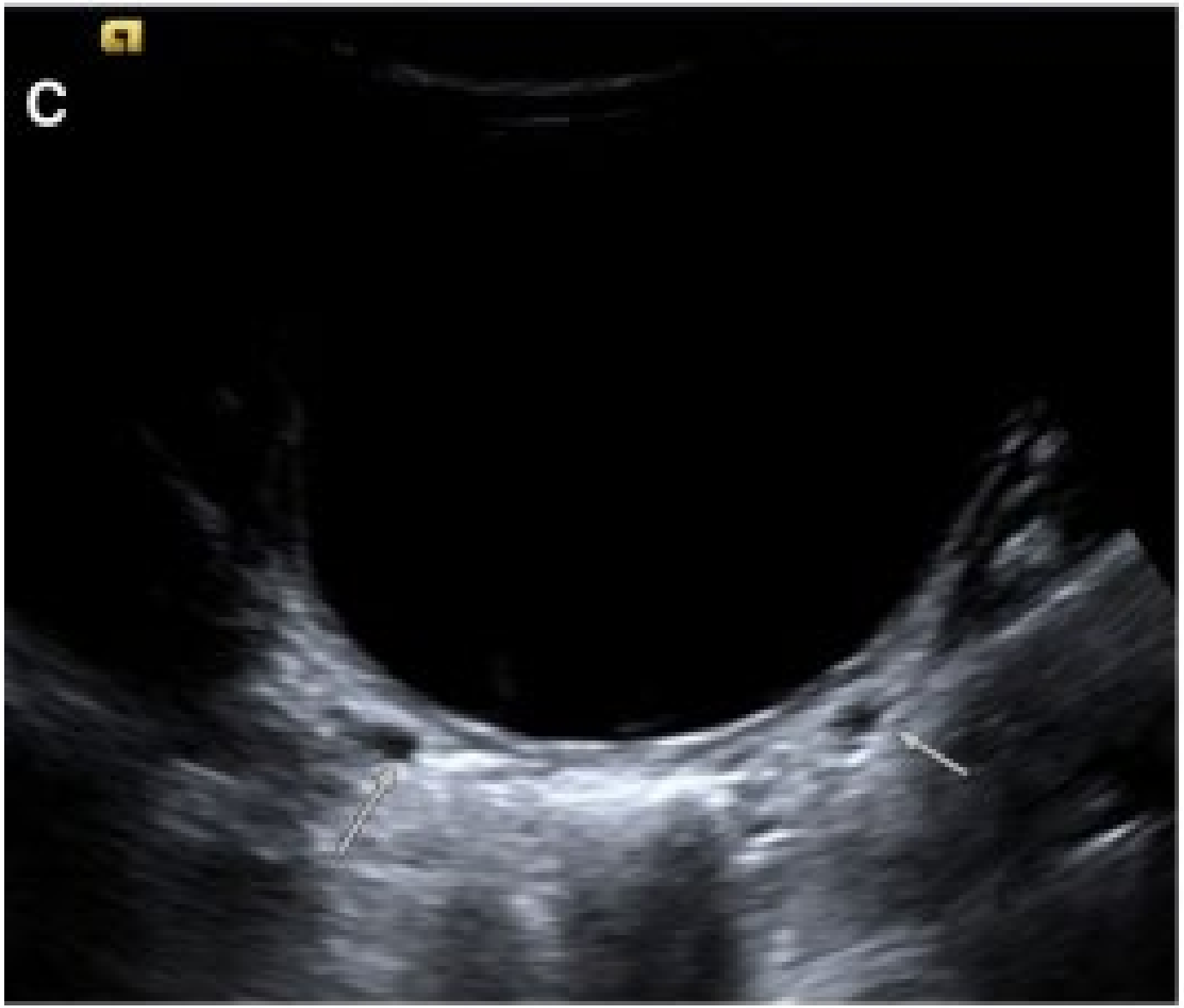
SONOGRAPHIC ANATOMY OF THE GUS-URINARY BLADDER



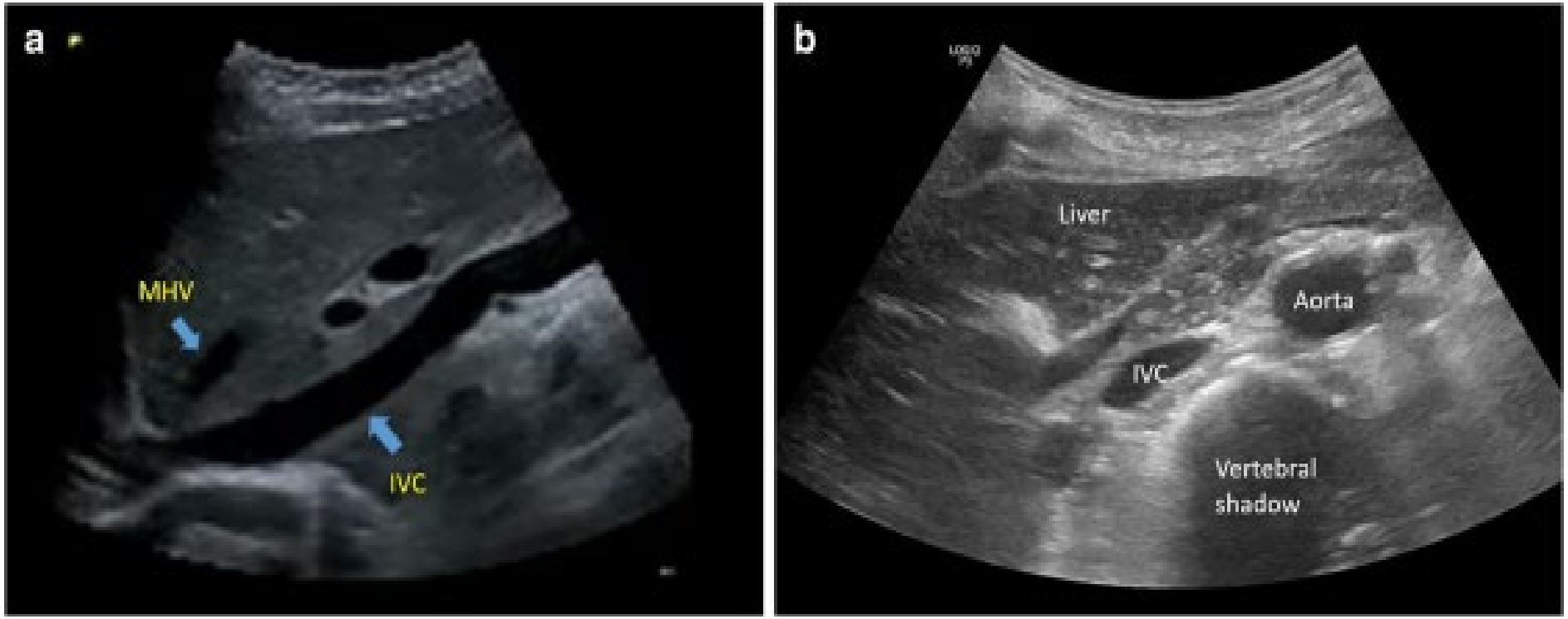


Bladder: left transverse, right sagittal view (arrow, bladder thickness)

URETERS AT THE POINTS OF THEIR INSERTION INTO THE BASE OF THE BLADDER

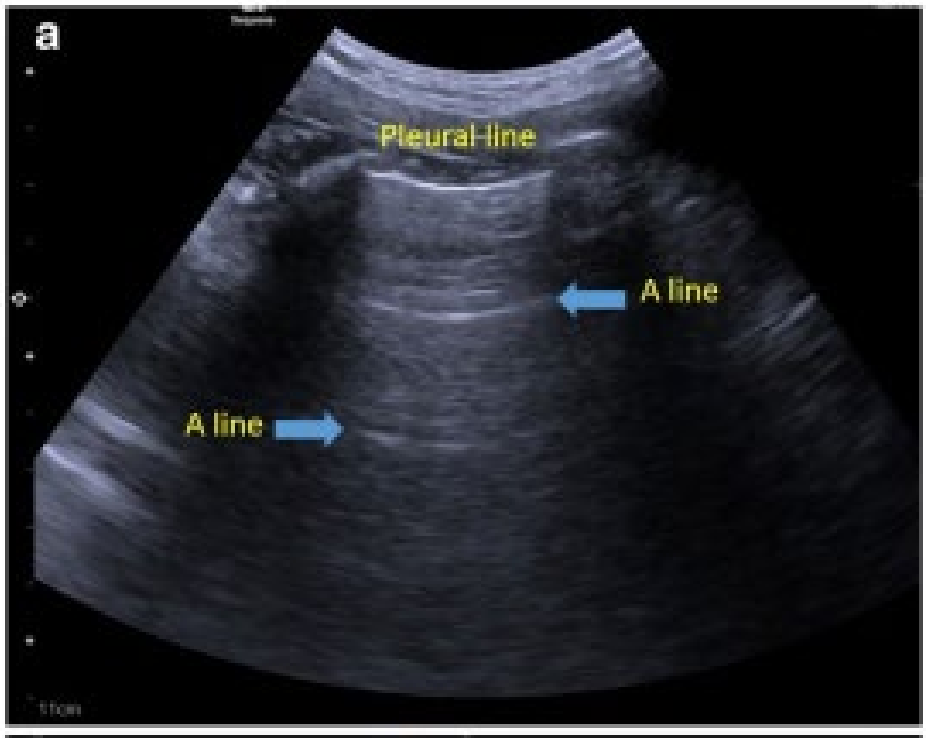


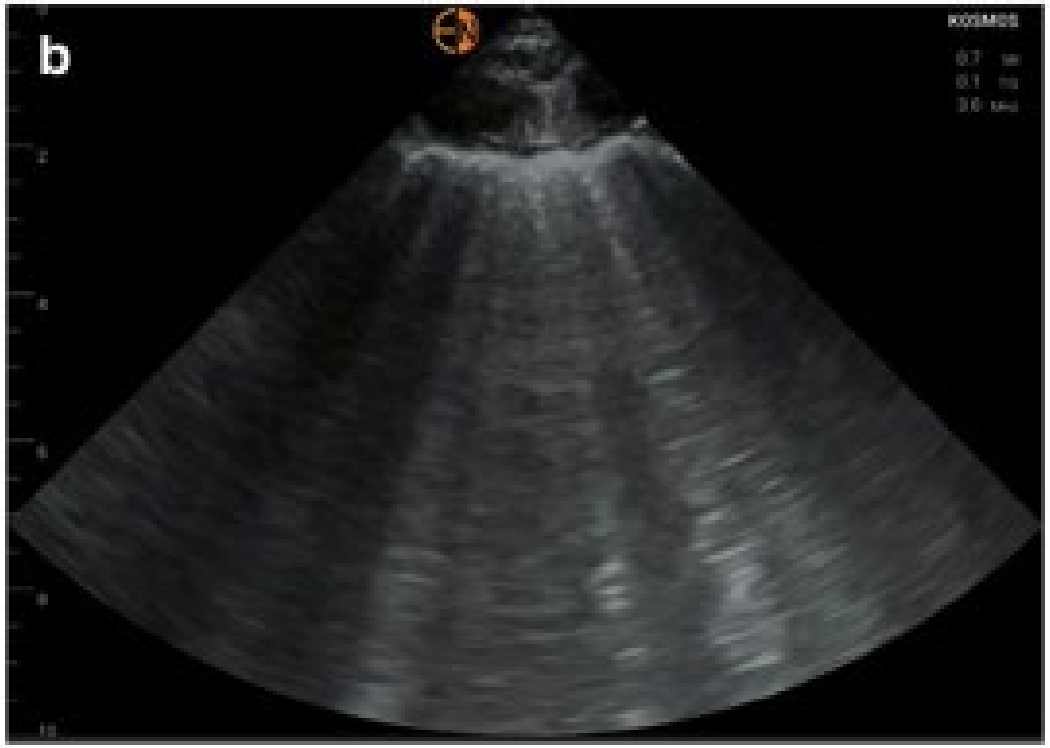
SONOGRAPHIC ANATOMY OF -INFERIOR VENA CAVA



[redacted] Inferior vena cava. a Long axis view of the inferior vena cava (IVC) obtained from the subxiphoid window. MHV denotes the middle hepatic vein draining into the IVC. b Short axis view of inferior vena cava (IVC)

SONOGRAPHIC ANATOMY OF THE LUNGS





[redacted] Lung ultrasound. a Lung ultrasound showing A-lines. b Lung ultrasound showing multiple B lines

SOME APPLICATIONS OF POCUS IN PEDIATRIC NEPHROLOGY

- **1. Clinical uses**
  - Assessment of congenital anatomical variants of the kidney and urinary tract,
  - urolithiasis
  - nephrocalcinosis
  - renal fusion
  - bladder outlet obstruction
  - cystic kidney disease
  - hydronephrosis
  - vascular anomalies

[redacted] Renal pathologies in relation to their generalized ultrasound findings

Pathology		Generalized Ultrasound Imaging
Congenital anatomical variants	Horseshoe kidney	The upper portion of each kidney in the low paraspinal location
	Ureteropelvic junction obstruction	Abnormal dilatation of the pelvicalyceal system
Bladder outlet obstruction		Bilateral hydroureteronephrosis and bladder wall thickening
Cystic kidney disease	Multicystic dysplastic kidney	Multiple cysts of various sizes that do not communicate
	Autosomal dominant polycystic kidney disease	Small bilateral simple renal cysts with or without kidney enlargement
	Autosomal recessive polycystic kidney disease	A sponge-like kidney appearance with small uniform cysts
	Nephronophthisis	Small kidneys with increased echogenicity and loss of corticomedullary differentiation
Kidney stone disease		Radiopaque and nonopaque urinary tract stones with acoustic shadowing
Nephrocalcinosis	Medullary	Loss of normal papillary hypoechogenicity and increased medullary echogenicity
	Cortical	Hyper-echogenic cortex
Hydronephrosis	Antenatal	Urinary tract dilation
	Postnatal	Collecting system dilation
Vascular anomalies	Renovascular hypertension	Turbulent flow and aliasing, slow systolic acceleration, and diminished peak systolic velocity
	Renal vein thrombosis	Elevation of the arterial resistive index
	Arteriovenous malformation and fistula	Turbulent flow and arterial velocity in the draining veins
	Nutcracker syndrome	Elevated velocity of the narrowed left renal vein or retro-aortic left renal vein

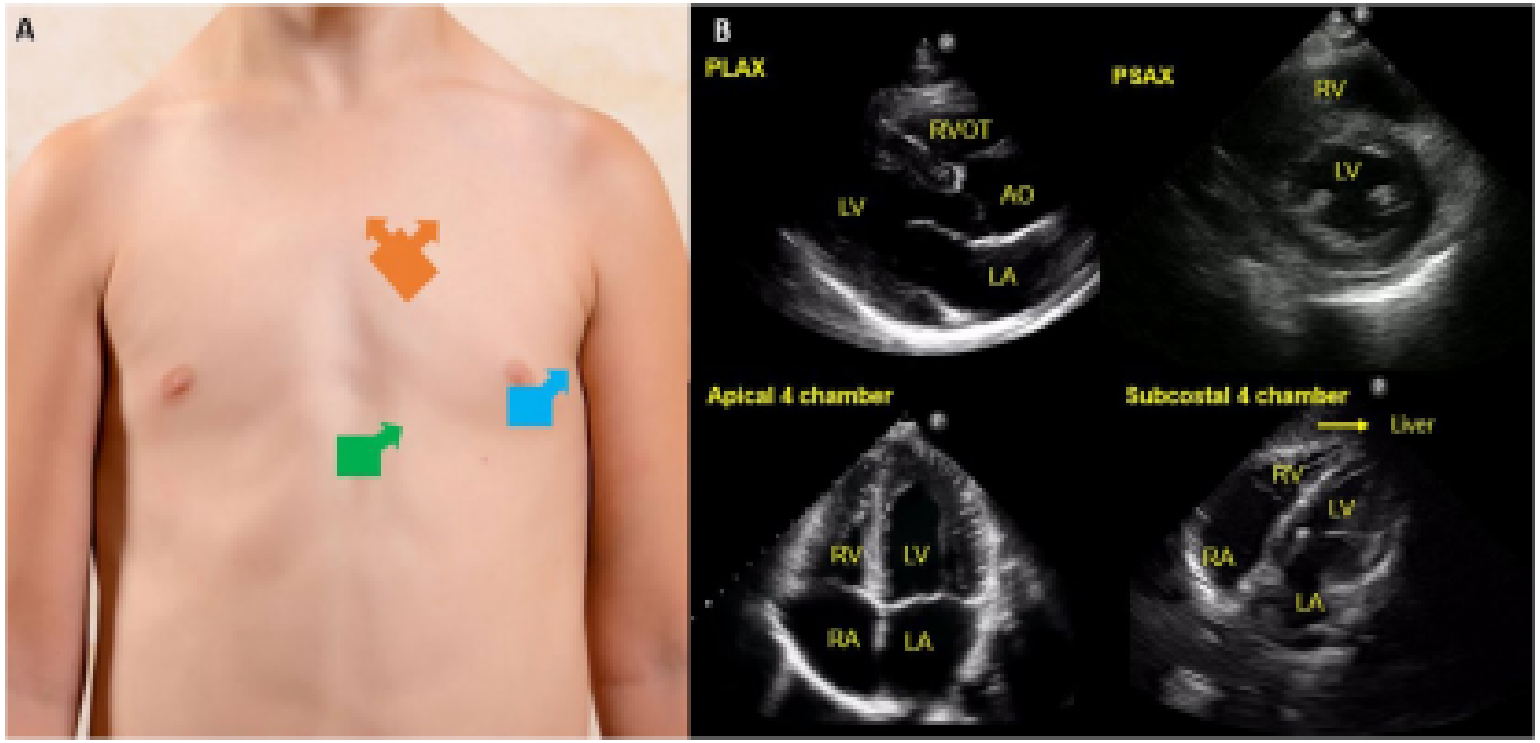
2. Evaluation of hemodynamic status in critical illnesses- lung ultrasound

.

Table 3 Typical sonographic findings in different types of shock

Sepsis	Focused cardiac ultrasound imaging	Lung ultrasound imaging
Hypovolemic	Hyperdynamic LV ↓ Cardiac output* Small collapsible IVC	A-lines
Cardiogenic	↓ LV function ↓ Cardiac output Dilated IVC	B-lines Pleural effusions
Obstructive	Pericardial effusion Dilated right ventricle with interventricular septal flattening (in pulmonary embolism) ↓Cardiac output Dilated IVC	A-lines Focal B-lines may be seen with large lung infarcts
Distributive	Varying LV function (usually hyperdynamic) ↑ Cardiac output Variable IVC	A-lines Focal B-lines/hepatization in case of pneumonia

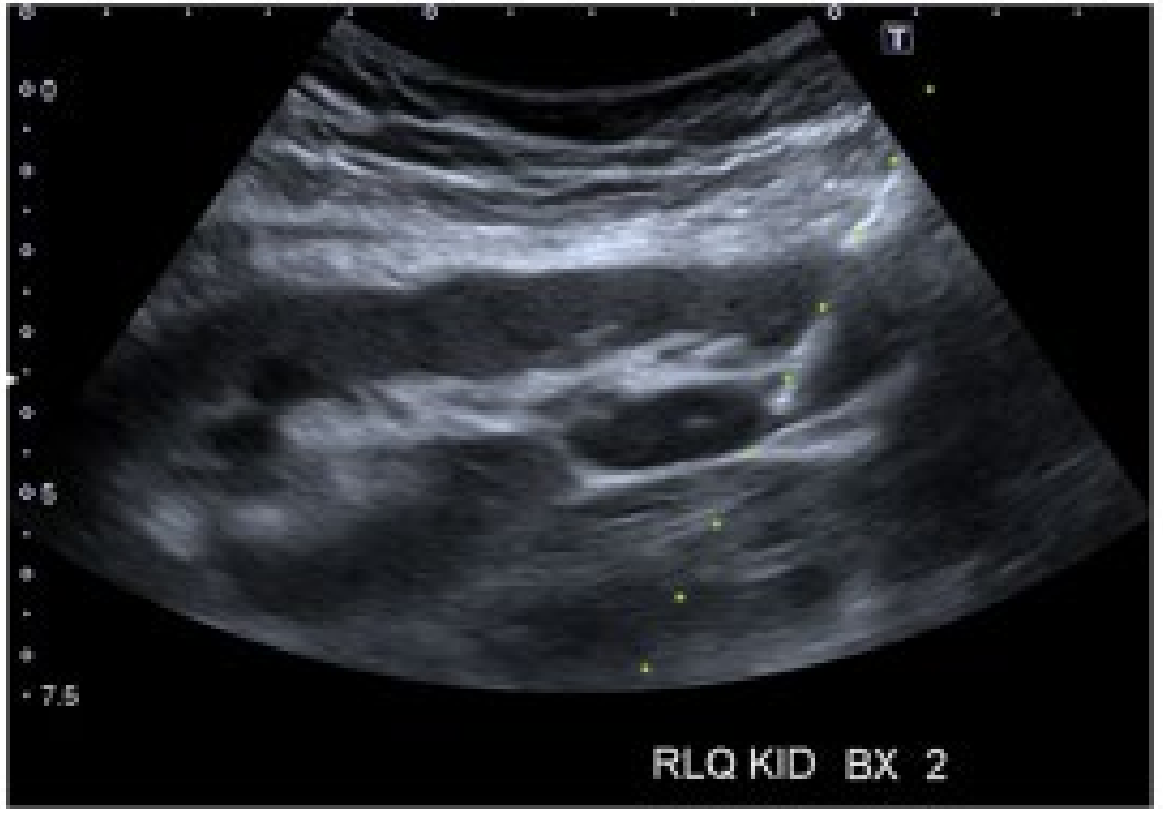
3. **Focus cardiac ultrasound**



[redacted] The figure illustrates four standard views of focused cardiac ultrasound (FoCUS). **A** Illustration of transducer positions (orange-parasternal window, blue-apical and green-subcostal) and orientation of probe indicator (direction of the arrow). **B** Corresponding sonographic images. PLAX, parasternal long axis, PSAX parasternal short axis, LA, left atrium, RA, right atrium, LV, left ventricle, RV, right ventricle, RVOT, right ventricle outflow tract, AO, aorta. Chest photograph is licensed from Shutterstock

4. INTERVENTIONAL NEPHROLOGY

- Ultrasound-guided procedures in the PICU

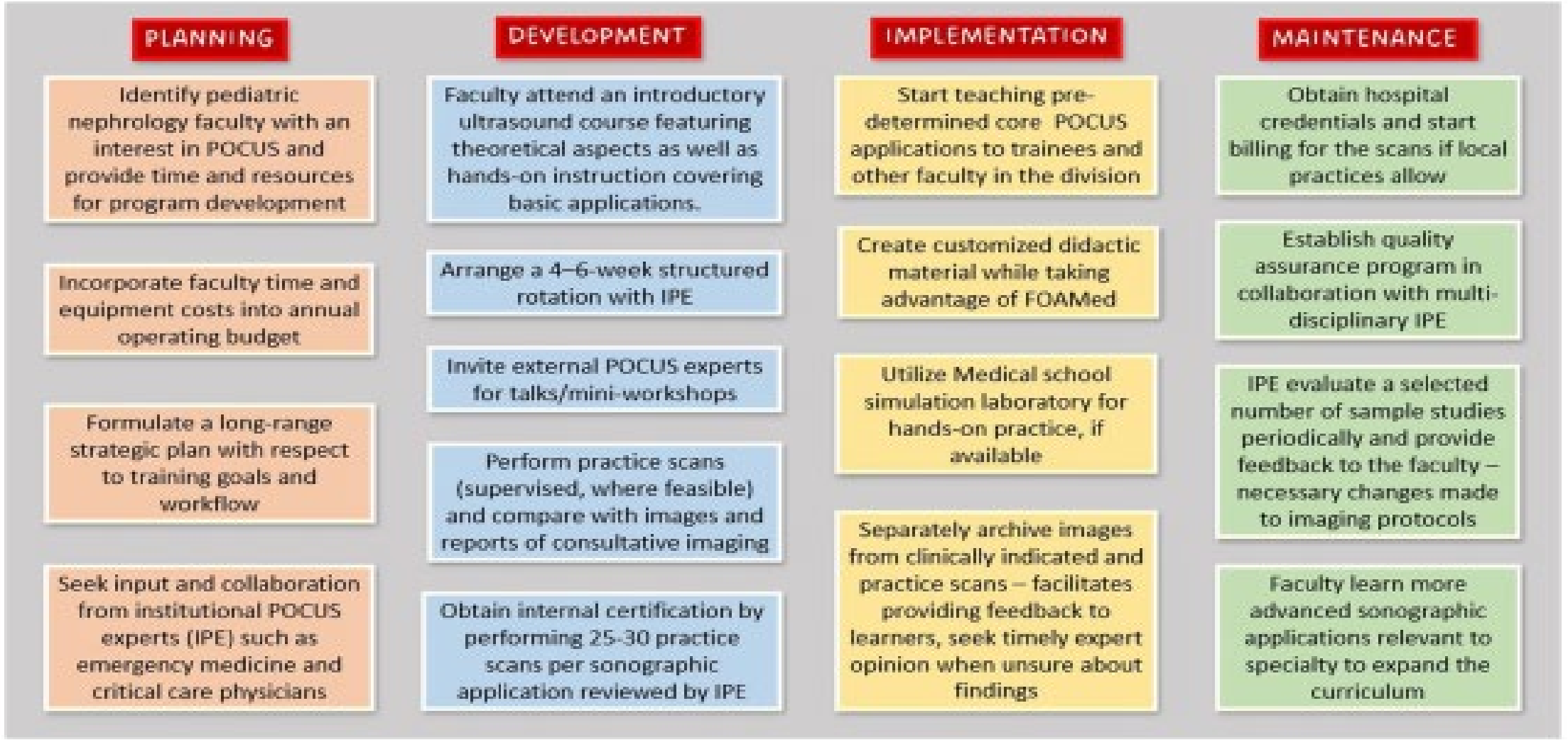


[redacted] Ultrasound-guided real-time visualization of needle track during kidney biopsy

5. **POCUS in dialysis access**

- Hemodialysis vascular access
- Arteriovenous access
- Peritoneal dialysis catheter placement

TRAINING AND COMPETENCY- VERY IMPORTANT



[redacted] Key elements of developing a point-of-care ultrasound (POCUS) program at the departmental level. Figure adapted from NephroPOCUS.com, with kind permission of the author

DEMONSTRATION

PRACTICAL SESSION

BASIC PRINCIPLES OF ULTRASOUND SCANNING

- Knowledge of probe handling
  - Orientation marker
- Basic Probe movements
  - SLIDING
  - ROTATION
  - ANGLING
  - DIPPING/PRESSURE

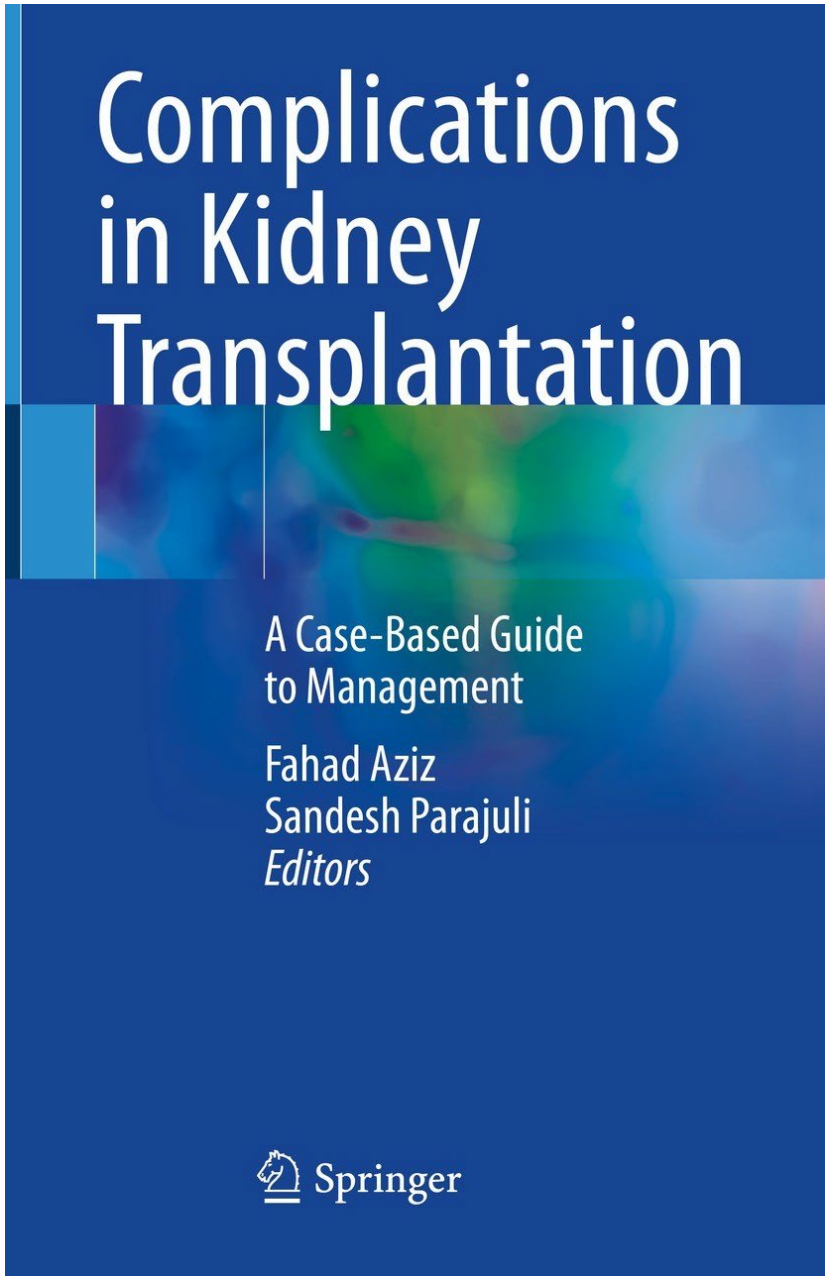
Post kidney transplant complications

NICOLE HAYDE MD,MS
ASSOCIATE PROFESSOR OF PEDIATRICS
CHILDREN'S HOSPITAL AT MONTEFIORE

The Children's Hospital at Montefiore | EINSTEIN Albert Einstein College of Medicine

Objectives

- Vascular Thrombosis
- Hypertension
- Urologic complications
- Graft dysfunction
- Electrolyte abnormalities
- Post-transplant diabetes mellitus


Complications in Kidney Transplantation
A Case-Based Guide to Management
Fahad Aziz
Sandesh Parajuli
Editors
Springer

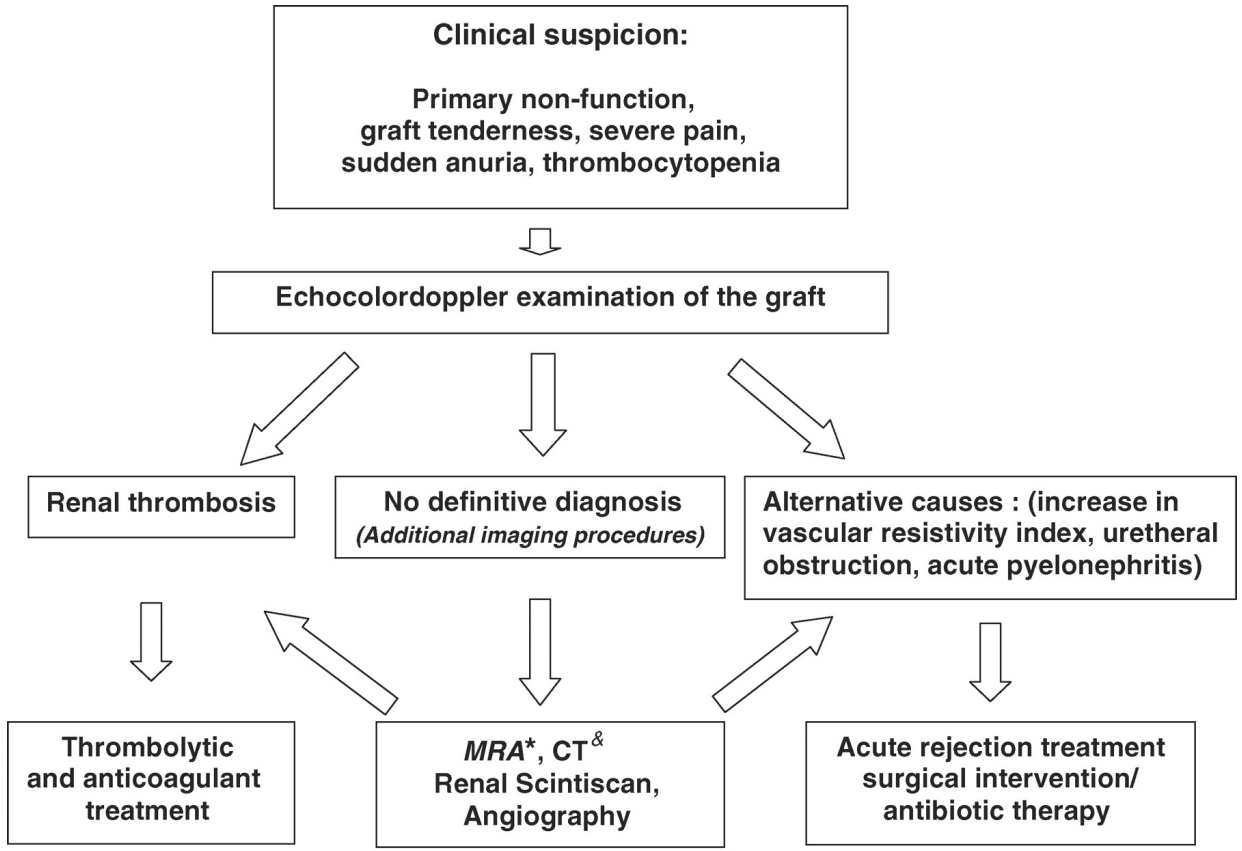
Vascular Thrombosis

- Potentially devastating cause of allograft dysfunction
- Peak incidence at 48 hours post-transplant
- Vein> Artery
- Early recognition is key to prevent allograft loss

Risk Factors for Vascular Thrombosis

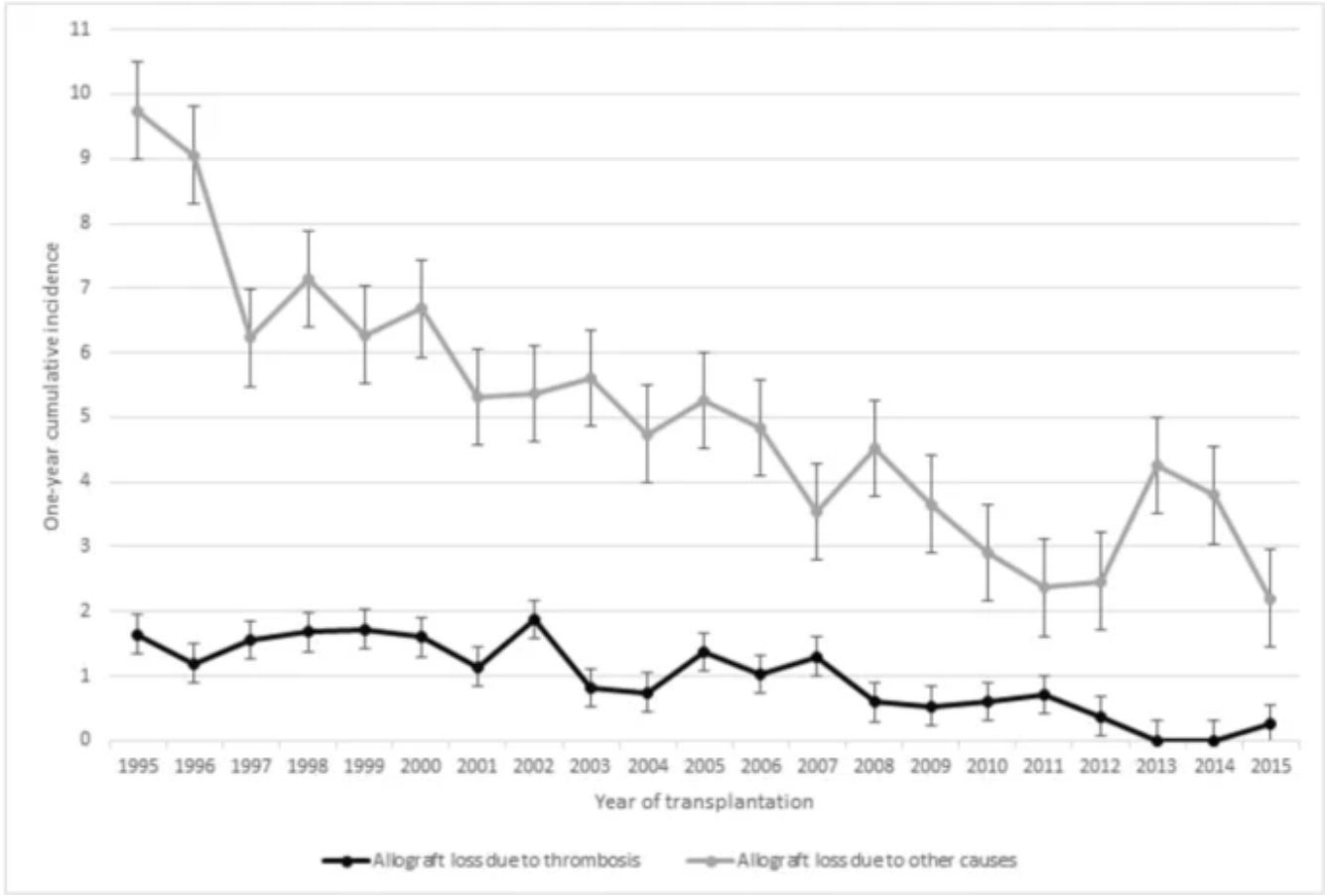
- Young recipient age (<2 years)
- Young donor age (<6 years)
- Long cold ischemia time
- History of peritoneal dialysis
- Hypoperfusion
- Delayed graft function
- Multiple donor vessels
- Technical complications

Algorithm for the diagnosis of allograft thrombosis



Nephrol Dial Transplant, Volume 24, Issue 5, May 2009, Pages 1388–1393,

Trends in Allograft Thrombosis as a Cause of Graft Loss



Wang et. al Pediatric Nephrology 2019

Measures to Reduce Thrombotic Risk

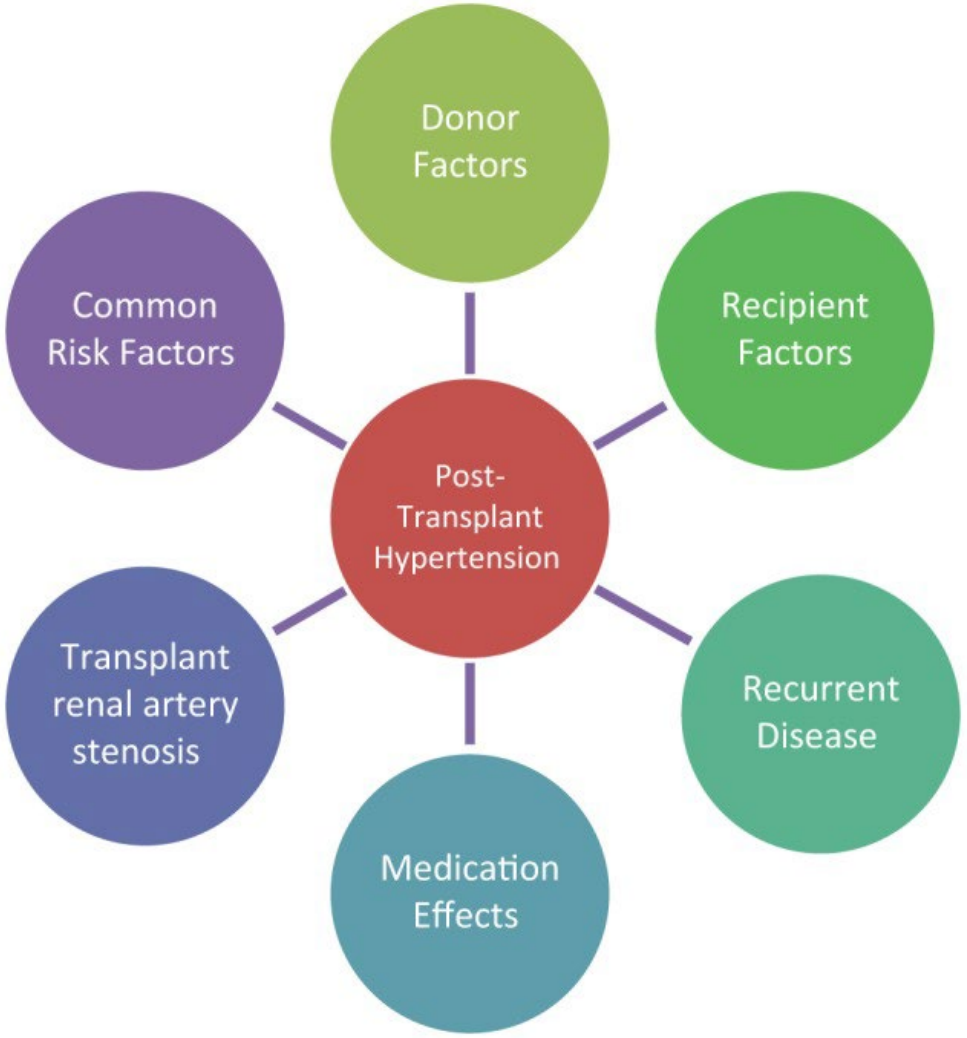
- Pre-transplant screening for congenital and acquired thrombophilia risk factors
- Correct of hypoalbuminemia pre-transplant in patients with nephrotic syndrome
- Hemodynamic monitoring in peri-operative period
- Important to do early post-transplant ultrasound to detect any vascular abnormalities

Hypertension

- ~60-80% of recipients (prevalence highly variable)
- HTN is a risk factor for graft loss
- Masked HTN more prevalent in transplant recipients (both renal and non-renal)
- ABPM is method of choice for diagnosing and evaluating treatment adequacy in HTN

Seeman T. *Pediatr Nephrol* (2009)

Hypertension



Charnaya et al Frontiers in Pediatrics 2017

Etiology of Hypertension & Time Post-Transplant

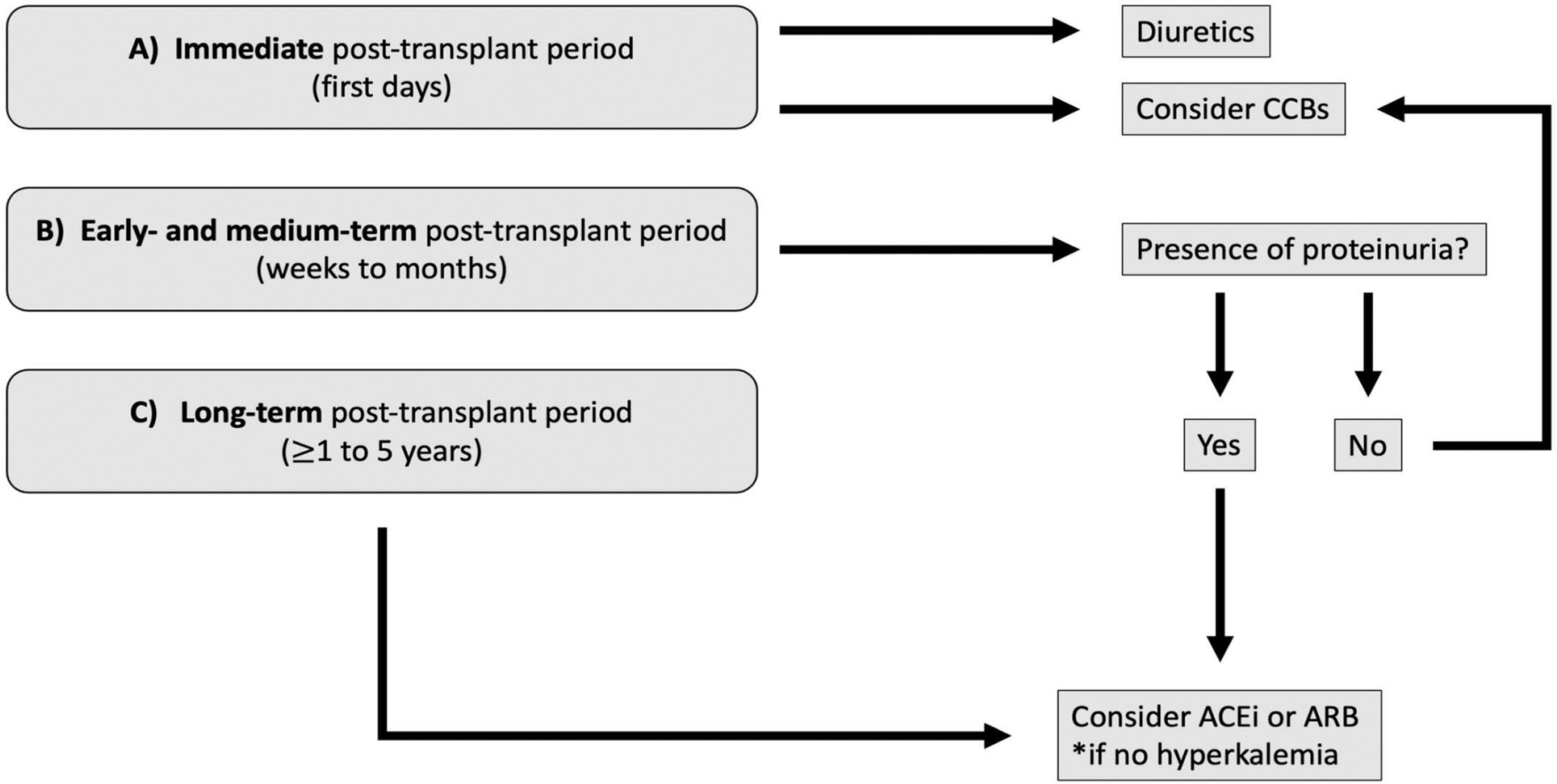
0 – 1 week	1 – 2 Months	2 – 12 Months	1 – 10 Years
Fluid overload	High-dose CNI	Medication effects	Acute rejection
High dose steroids	Recurrent disease	Acute rejection	Chronic transplant glomerulopathy
Delayed graft function	Underlying native kidney disease	Recurrent disease	Renal artery stenosis
Underlying native kidney disease		Renal artery stenosis	Medication effect
Recurrent disease		Obesity	Recurrent disease
		Lifestyle	De novo glomerulonephritis
			Obesity
			Lifestyle
			Nocturnal sleep apnea
			Genetic determinants

Charnaya et al Frontiers in Pediatrics 2017

Case

- 8 yo male with ESRD secondary to PUV received a kidney transplant from his father 3 months ago.
- His BP in clinic today is 120/80
- He was not on any antihypertensives pre-transplant
- What is the best drug to use in this patient?
  - Amlodipine
  - Labetalol
  - Enalapril

HTN Treatment



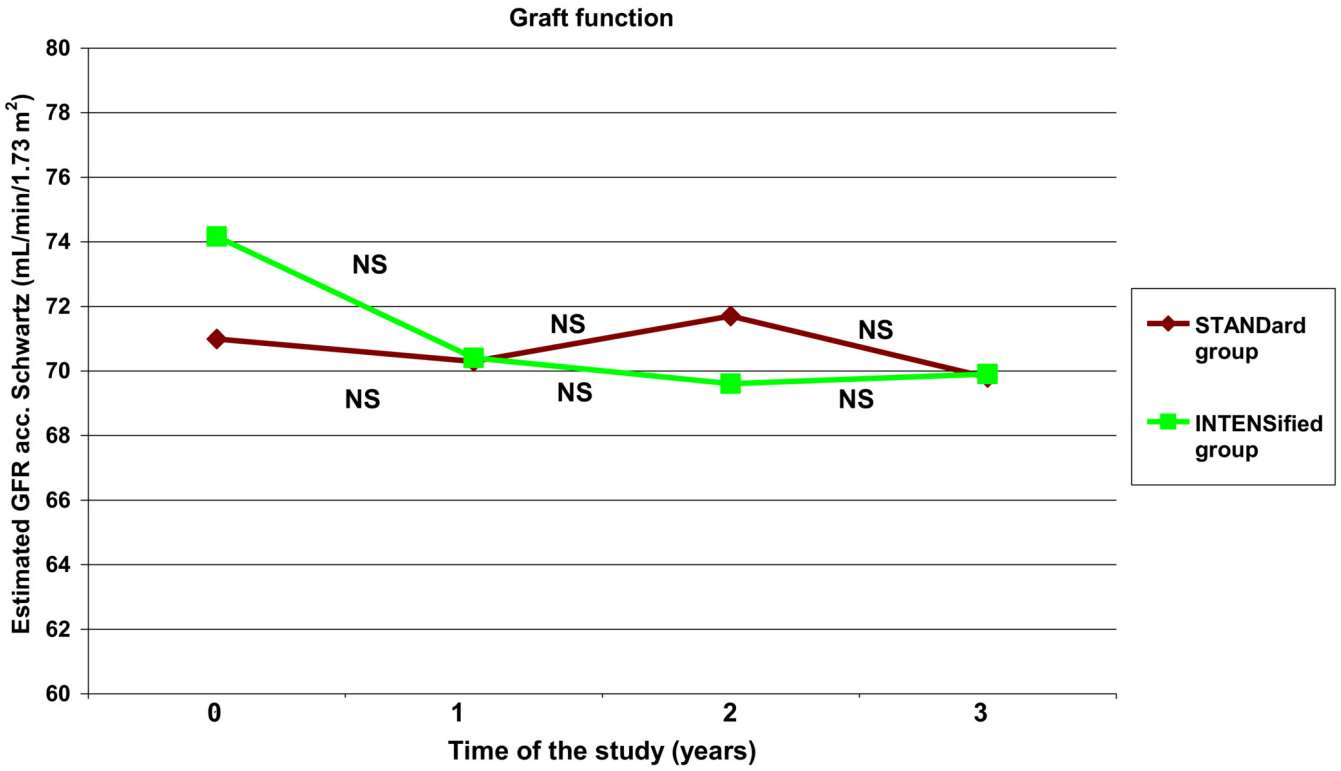
Seeman, Pediatric Transplantation, First published: 28 April 2023

Target Blood Pressure

- Higher BPs are targeted in the immediate post-transplant period to maintain adequate aortic flow

- In pediatric non-transplanted CKD patients, the ESCAPE trial showed that reduction of ambulatory 24-h MAP to <50th percentile led to significantly slower progression of CKD in children compared to children whose 24-h MAP remained between the 50th and 95th percentiles. (Wuhl. et al NEJM 2009)

Graft Function and HTN



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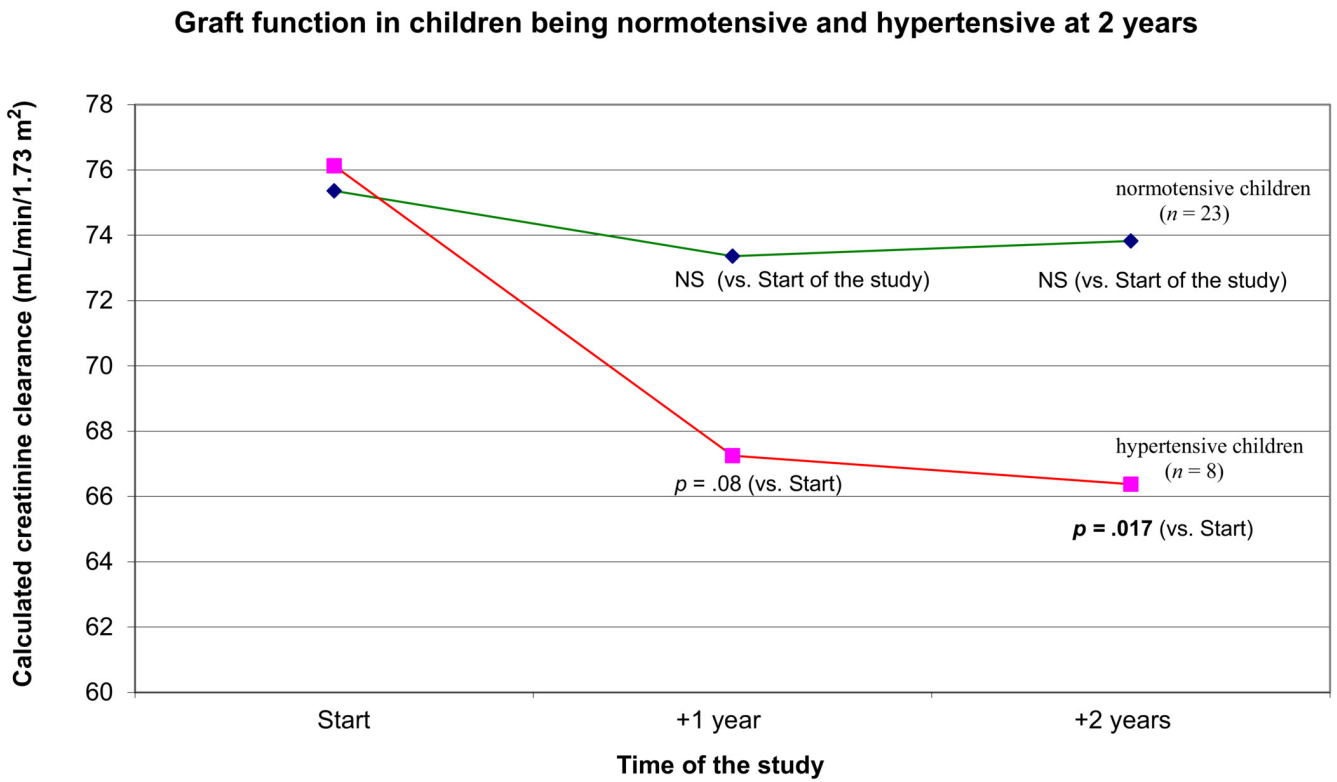


Seeman, Pediatric Transplantation, 2007

Posterior reversible leukoencephalopathy (PRES)

- Neuro-clinical and radiological syndrome associated with hypertension, fluid overload, and/or immunosuppressive treatment
- Tacrolimus > cyclosporine

- Symptoms
  - Headaches
  - Altered mental status
  - Visual disturbance
  - Seizures

PRES

- Neuro-imaging needed for diagnosis
  - CT first line but MRI preferred

- Typical findings are bilateral areas of white matter edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions

- Complications of PRES
  - Ischemia
  - Intracranial hemorrhage

PRES Management

- Blood pressure management
- Seizure management
- ? switch from tacrolimus to cysclosporine

Urologic Complications

- Early complications
  - Urinary leak due to ureteral necrosis, bladder injury, or obstruction
  - Urinary tract obstruction due to clots in the urinary tract postoperative edema, or surgical complication.

- Other complications
  - Transplant reflux nephropathy
  - Recurrent UTI

Stents in Kidney Transplant

- May significantly decrease urinary leak and obstruction with a reduction in overall medical costs
- Increased risk of urinary tract infections especially if the stent remained in place > 30 days post transplant

- At our center: Increasingly less commonly used.
  - Case by case basis

Urinary Tract Infections

- Up to 30% pediatric kidney transplant recipients
- E.coli is most common organism
- More common in children with underlying CAKUT
- VUR into transplant may occur in patients without underlying urologic abnormalities
- Can lead to graft dysfunction
- Underscores importance of urologic evaluation pre-transplant in increased risk patients

John, Pediatric Nephrology 2009
Spiwak Front Pediatr 2022

Lymphocele

- Pseudo-cystic entity filled with lymph fluid, covered with a hard fibrous capsule, localized around the graft
- Well described after pediatric kidney transplantation (~5% mean incidence)
- Risk factors
  - Older age (≥11 yr)
  - Earlier transplant ear
  - Male gender
  - BMI percentile for age ≥95%
  - Prior transplant

Giuliani Pediatric Transplantation 2014

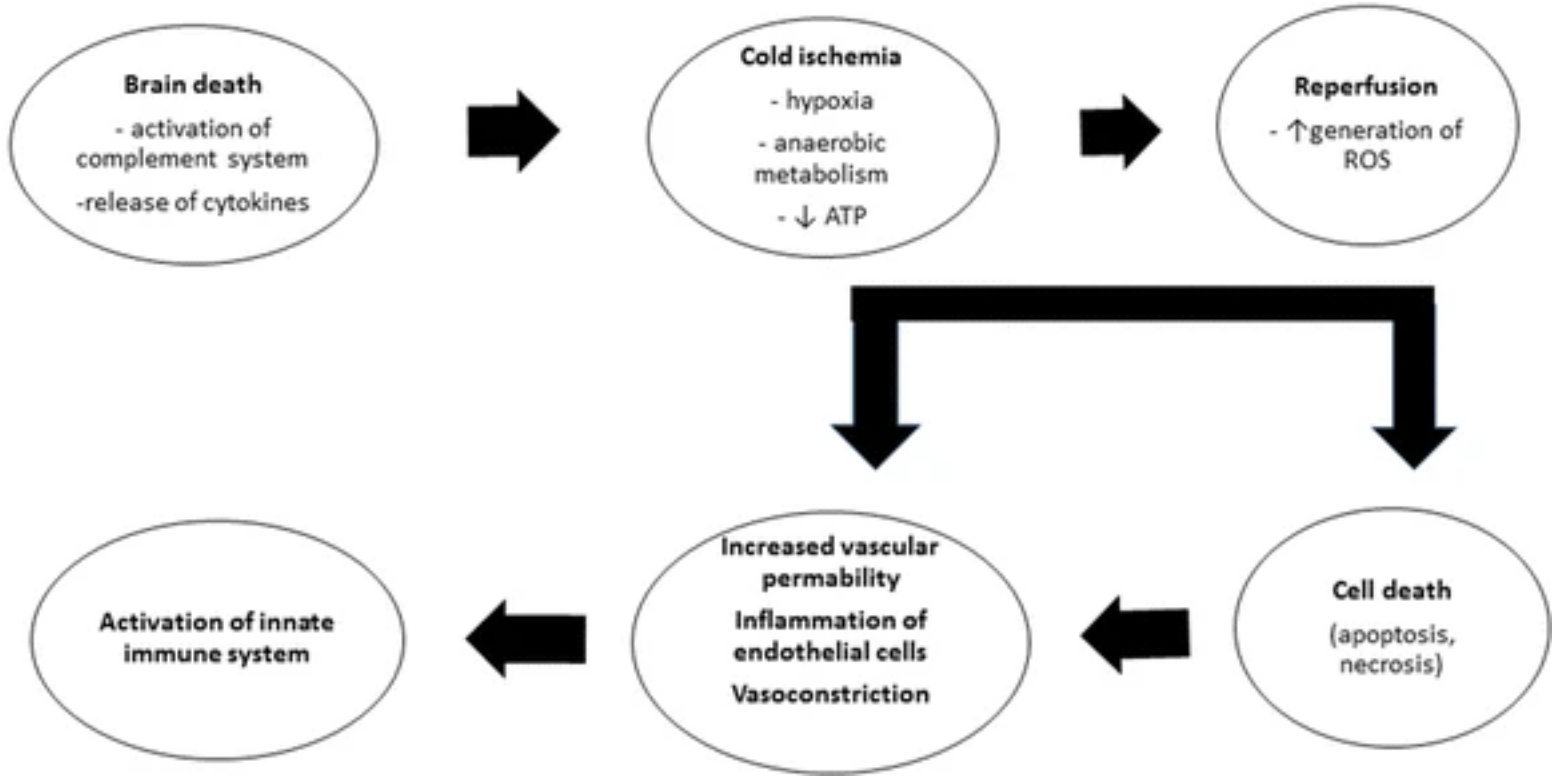
Lymphocele

- Most are asymptomatic and resolve spontaneously
- Pain and discomfort with mass sensation
- More significant symptoms
    - Ureteral obstruction, infection or renal vein thrombosis
        - Secondary graft deterioration or even graft loss

- Treatment involves drainage and/or marsupialization

Graft Dysfunction

ATP – adenozine triphosphate
ROS – reactive oxigen species



Strategies to reduce DGF

- At our center:
  - CIT < 24 hours
  - Donors less than 40 years
  - Limit acceptance of DCD kidneys
  - No donors with renal replacement therapy
  - Start nephrotoxins once kidney function more stable

Calcineurin inhibitor (CNI) toxicity

- Acute kidney injury
- Thrombotic microangiopathy
  - Microangiopathic hemolytic anemia with schistocytes on the blood smear, thrombocytopenia, and acute kidney injury (AKI)
  - CNI-induced injury to the vascular endothelial cells
  - Reduce dose of CNI
- Electrolyte abnormalities
  - Hyperkalemia
  - Metabolic acidosis
  - Hypophosphatemia
  - Hypomagnesemia
  - Hypercalciuria

Post transplant DM

- Up to 40% of adults develop PTDM
- NAPRTCS data- 2.8% children (most within first 6 months)
- DM leads to CVD which causes allograft damage
  - 3 fold increased risk of death (Chanchlani et al NDT 2019)
  - Long term data in pediatrics is lacking

Diagnosis

Diagnostic test	Criteria	Notes
FPG	≥126 mg/dL*	– Simple to perform – Unreliable, as glucocorticoid therapy causes worsening hyperglycemia as the day progresses
Random plasma glucose	≥200 mg/dL	– Simple to perform – Can be done at any time of day
OGTT	≥200 mg/dL**	– Requires the most time and resources – Can diagnose impaired glucose tolerance, which is associated with long-term outcomes in SOT recipients – Better sensitivity than FPG and A1c
A1c	≥6.5%	– Simple to perform – Can be done at any time of day – Unknown if 6.5% cutoff predicts long-term outcomes in PTDM patients – May under- or overestimate mean blood glucose concentrations, especially in the first-year posttransplant

SOT, solid organ transplant; PTDM, post-transplantation diabetes mellitus; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; A1c, hemoglobin A1C. * Fasting with no caloric intake for at least 8 h. ** Two hours after glucose load of 1.75 g/kg of glucose, maximum 75 g.

Mechanisms of Diabetes Mellitus in Transplant Recipients

Immunosuppressant	Diabetogenic mechanism	Notes
Corticosteroids	– Decrease peripheral insulin sensitivity – Decrease number of insulin receptors and their affinity for insulin – Increase hepatic gluconeogenesis – Decrease insulin synthesis – Inhibit pancreatic insulin secretion	– Dose-dependent – Impact of complete withdrawal is unclear
Cyclosporine	– Decrease insulin synthesis – Inhibit pancreatic insulin secretion – Decrease β-cell density	– Dose-dependent – May be associated with decreased risk of PTDM as compared to tacrolimus
Tacrolimus	– Decrease insulin synthesis – Decrease insulin secretion – Increase β-cell apoptosis	– Dose-dependent – β-cell dysfunction may be reversible
Sirolimus	– Decrease peripheral insulin sensitivity – Increase β-cell apoptosis – Impair pancreatic proliferation	– Dose-dependent

SOT, solid organ transplant; PTDM, post-transplantation diabetes mellitus.

Summary

- Although kidney transplant >> dialysis, it is not without complications
- Although less common, vascular thrombosis has significant implications for the allograft
- DGF is much less common in pediatrics
- Electrolyte abnormalities occur early post-transplant and often persist
- Vigilance and close follow-up are essential to prevent and treat complications

Questions/ Thank You!

The Children's Hospital at Montefiore | EINSTEIN Albert Einstein College of Medicine

Immunosuppression in Renal Transplantation

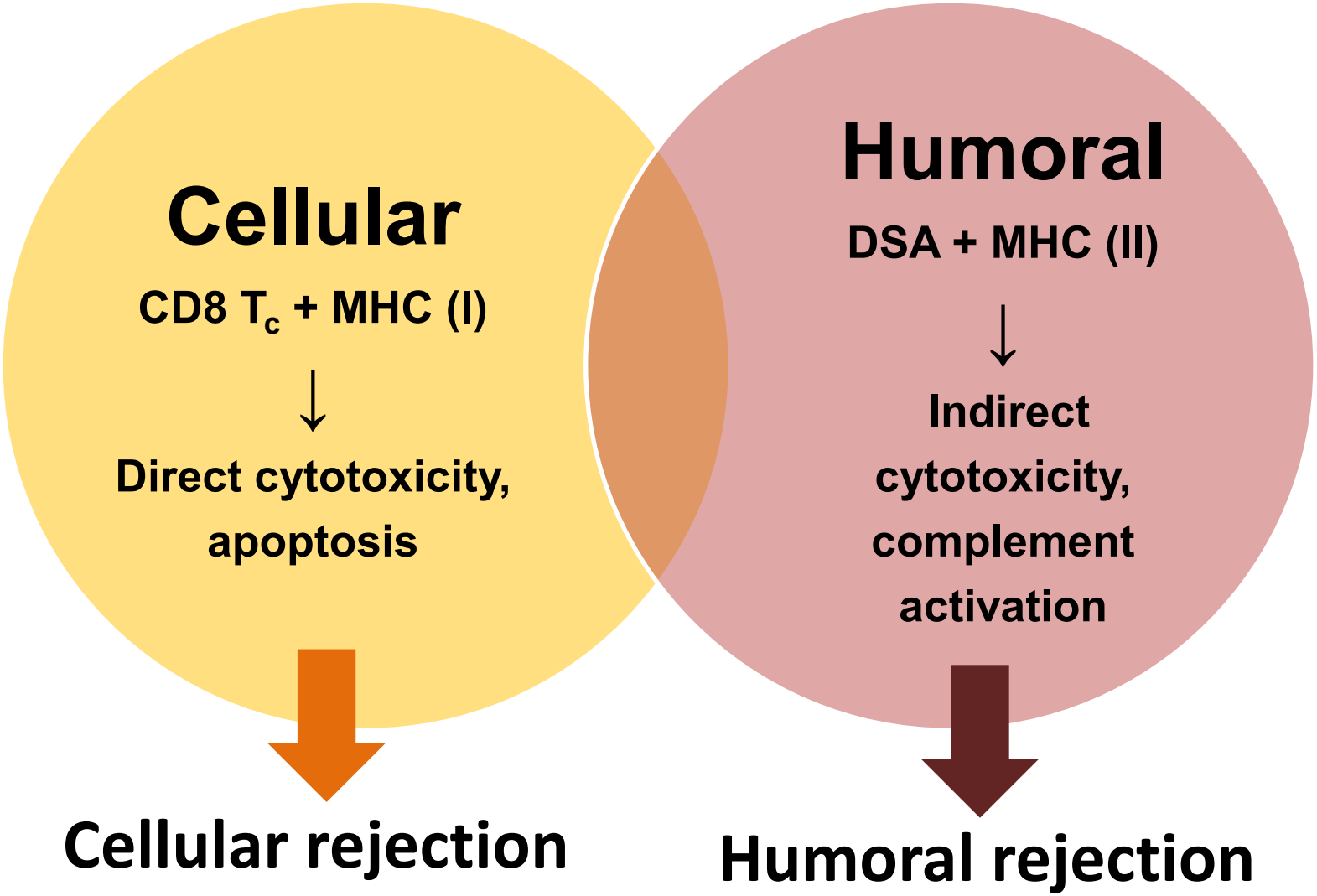
Induction, Maintenance, and Treatment of Rejection

Nicole Hayde MD, MS
Associate Professor of Pediatrics
Medical Director of Pediatric Kidney Transplantation

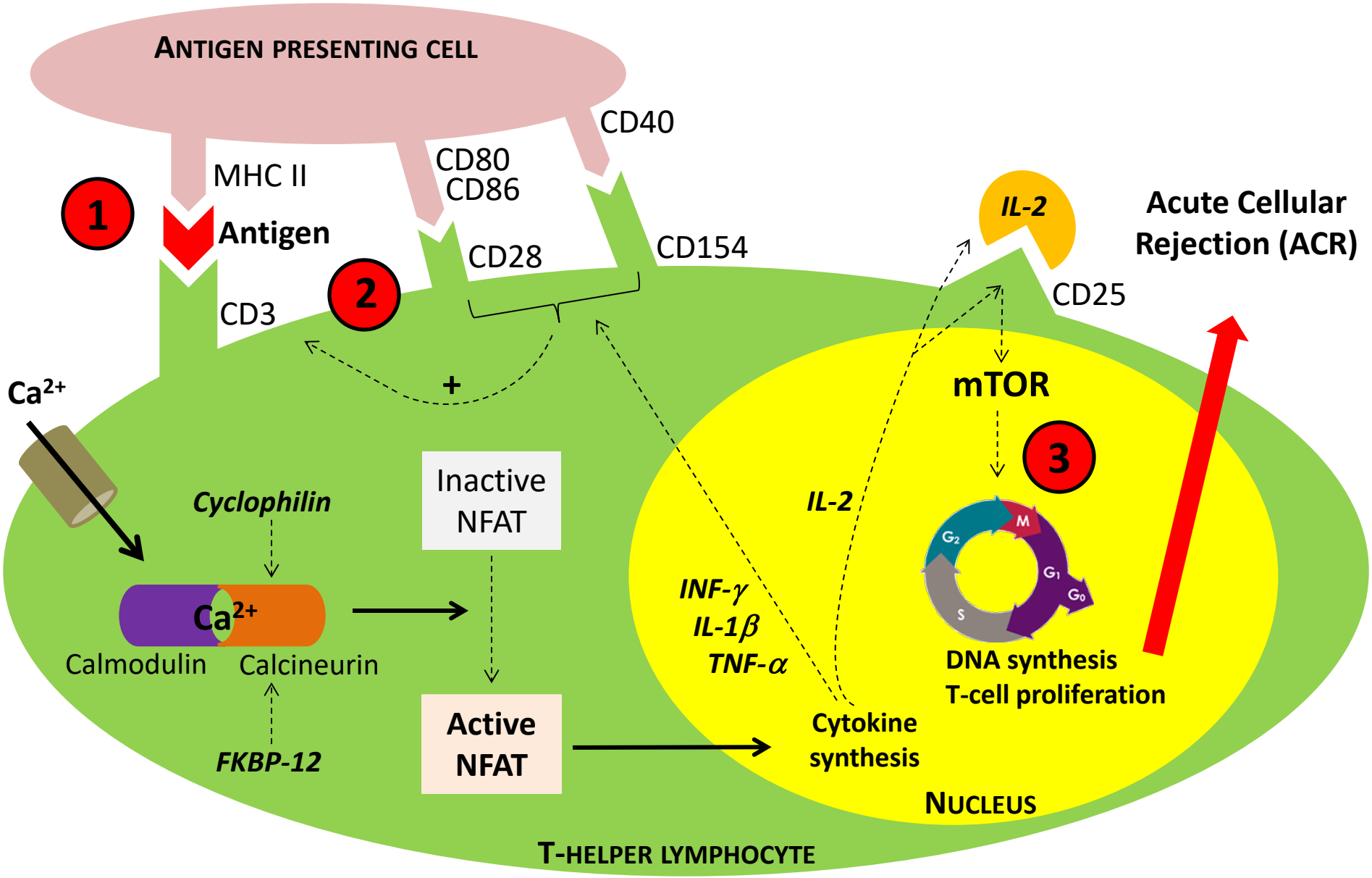
Immunosuppression Balance

- Need to prevent rejection while not causing unwanted side effects from over immunosuppression
  - Infection
  - Medication specific side effects

Types of Immunity



T cell Activation



Phases of Immunosuppression

- Induction
  - Short perioperative course
  - Goal: delay hyperacute/acute allograft rejection
- Maintenance
  - Lifelong
  - Goal: delay acute/chronic allograft rejection
- Treatment of allograft rejection
  - Episodic
  - Goal: preserve allograft function, prevent allograft loss

Factors to Consider When Choosing an Immunosuppression Regimen

- Degree of sensitization
  - Previous transplantation
  - Blood transfusion
  - Pregnancy
- Comorbidities
  - Cardiopulmonary disease
  - Psychiatric conditions
  - Epilepsy
  - Malignancy
- Etiology of kidney disease
  - Glomerular vs. SLE vs. CAKUT
- Age
- Race
- Allergies
- Infectious history
  - Human immunodeficiency virus (HIV)
  - Recurrent/life-threatening multi-drug resistant organisms

Induction Immunosuppression

Induction Immunosuppression Agents used at CHAM

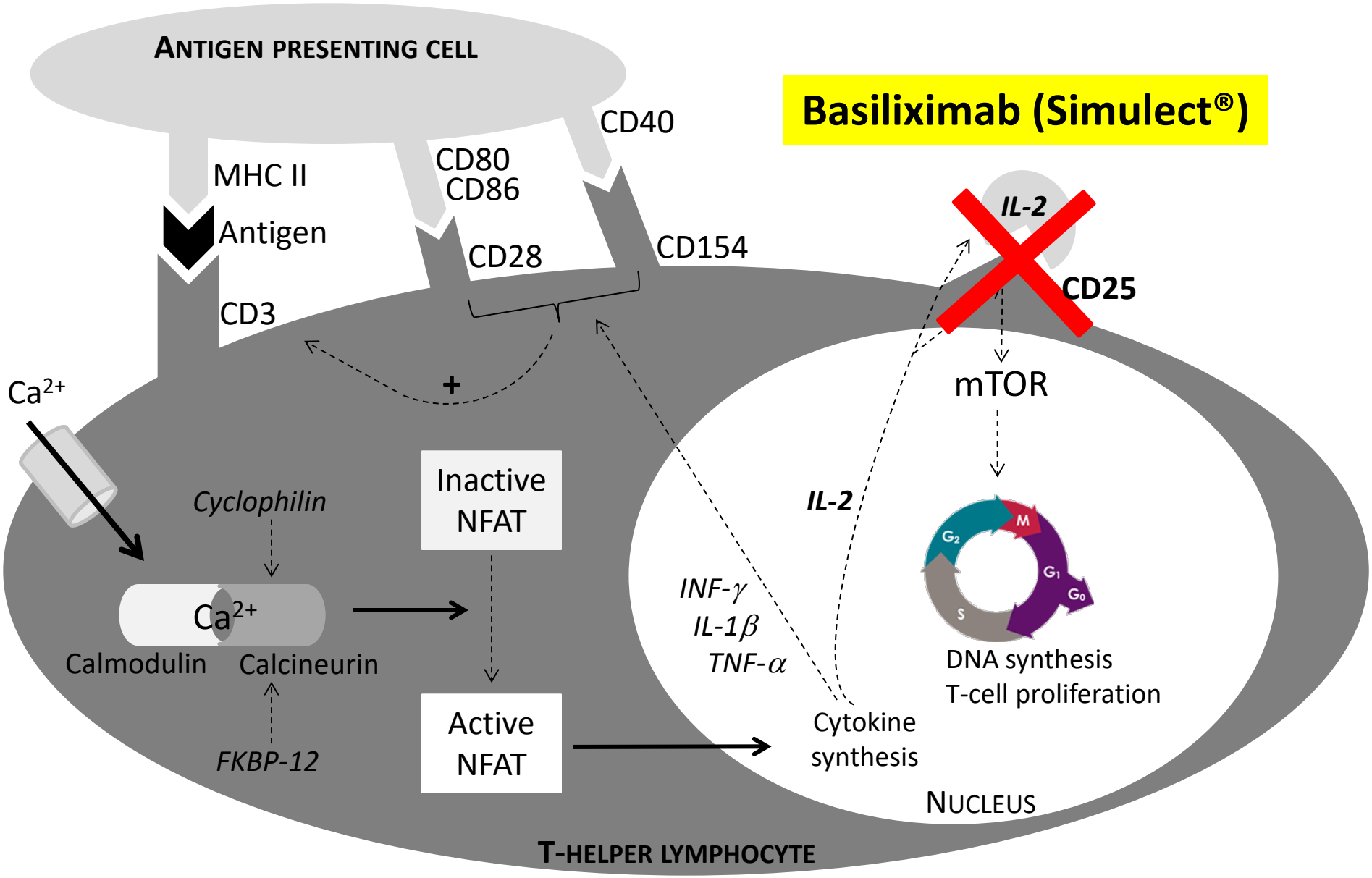
- Non-depleting monoclonal antibody
  - Basiliximab (Simulect®)
- Depleting antibody
  - Rabbit antithymocyte globulin, rATG (Thymoglobulin®)

Other Induction Immunosuppression Agents

- Non-depleting
  - Dacilizumab (no longer in production)

- Alemtuzumab (Campath)

Non-Depleting Antibody Induction



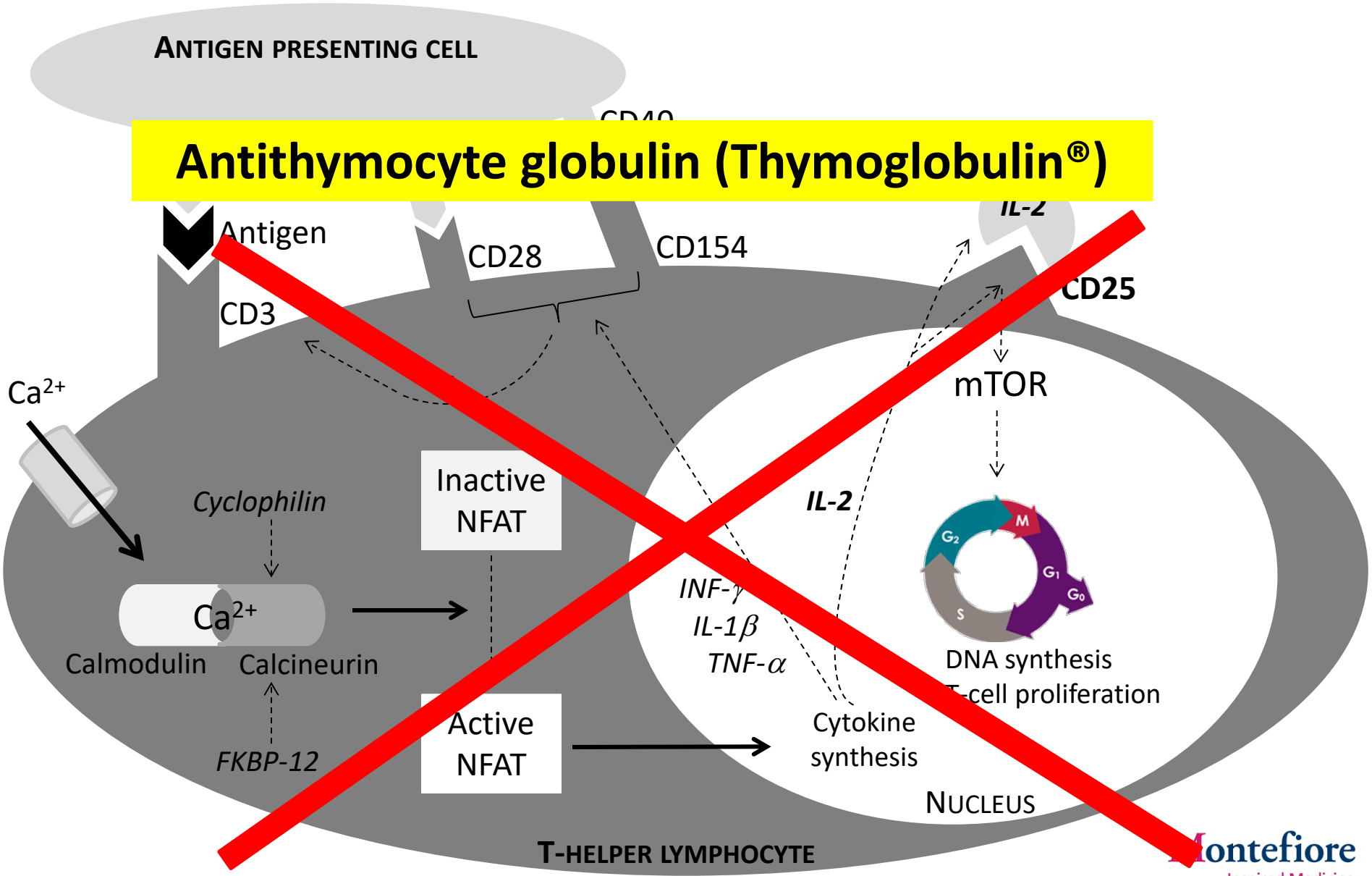
Basiliximab

- Only prevents further proliferation and differentiation of T lymphocytes involved in the cellular immune response; does not cause depletion

- Dose:
  - <20 kg= 10 mg x 2 doses on POD #0 and 4
  - Otherwise 20 mg x 2 doses on POD #0 and 4

- No premedication needed
- Minimal risk of infection

Depleting Antibody Induction



Montefiore
Inspired Medicine

Thymoglobulin

- Primary mechanism is lymphocyte depletion
  - Can persist for 3-12 months
  - complement-dependent lysis and T cell activation–induced apoptosis
- Prone to symptoms consistent with cytokine related to release of natural killer cell and macrophage/monocyte binding of FcR binding as well as cellular cytotoxicity
- Can cause serum sickness
- Long term: infection, prolonged myelosuppression, malignancy, PTLD

Thymoglobulin Dose

- 1.5 mg/kg IV daily for 3-4 doses; maximum 150 mg/dose
- **Pre-medications**: IV solumedrol, acetaminophen, and diphenhydramine prior to each dose
- **Dose adjustments**: ↓ dose 50% if WBC <3, PLT <75; hold if WBC <2, PLT <50

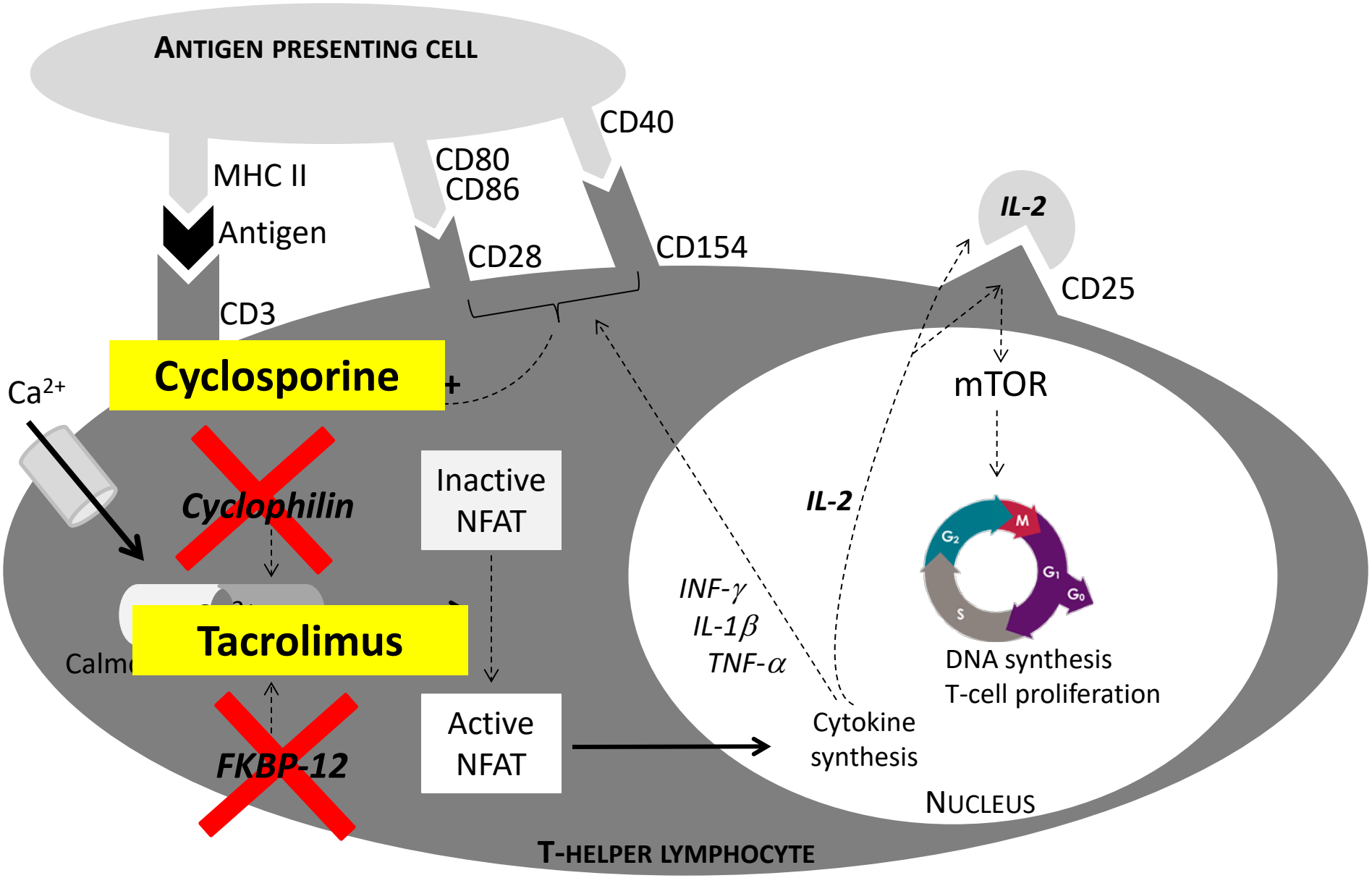
Maintenance Immunosuppression

Maintenance Immunosuppression Agents

- Calcineurin inhibitors
  - ✓ Tacrolimus (Prograf®/Astagraf XL®/Envarsus XR®)
  - Cyclosporine (Neoral®/Gengraf®/Sandimmune®)
- Antimetabolite agents
  - ✓ Mycophenolate mofetil (CellCept®)
  - Mycophenolate sodium (Myfortic®)
  - Azathioprine (Imuran®)
- Corticosteroids
  - ✓ Prednisone
  - Methylprednisolone
- Mammalian target of rapamycin (mTOR) inhibitors
  - Sirolimus (Rapamune®)
  - Everolimus (Zortress®)

Standard regimen = CNI + Antimetabolite +/- Corticosteroid

CALCINEURIN INHIBITORS



TACROLIMUS (Prograf®, Astagraf XL®, Envarsus XR®)	
Dose	▪ 0.05-0.1 mg/kg PO q12h starting dose, titrated to the goal trough level (varies by time post transplant)
Adverse Effects	▪ **Short-term**: afferent arteriole vasospasm, ↑K^+, ↓Mg^{2+}, ↓ Phos, QTc prolongation, RTA, tremors, headaches, behavior/mood changes, GI irritation ▪ **Long-term**: IF/TA, glomerulosclerosis, hypertension, hyperlipidemia, diabetes, alopecia, malignancy, infection, PTLD
Monitoring	▪ **Therapeutic drug monitoring**: target levels dependent on type of organ transplanted and time since transplant ▪ **Drug-drug interactions**: CYP3A4, P-gp inhibitors/inducers, concomitant nephrotoxins and QTc "prolongators"

CYCLOSPORINE (Sandimmune®, Neoral®, Gengraf®)	
Dose	▪ 3-6 mg/kg PO q12h starting dose, titrated to the goal trough level (typically 200-300 ng/mL within the first month of transplant)
Adverse Effects	▪ **Short-term**: afferent arteriole vasospasm, ↑K^+, ↓Mg^{2+}, ↓ Phos, QTc prolongation, RTA, tremors, headaches, behavior/mood changes ▪ **Long-term**: IF/TA, glomerulosclerosis, hypertension, hyperlipidemia, diabetes, hirsutism, gingival hyperplasia, malignancy, infection, PTLD
Monitoring	▪ **Therapeutic drug monitoring**: target levels dependent on type of organ transplanted and time since transplant ▪ **Drug-drug interactions**: CYP3A4, P-gp inhibitors/inducers, concomitant nephrotoxins and QTc "prolongators"

Cyclosporine (Sandimmune,® Neoral®, Gengraf®)

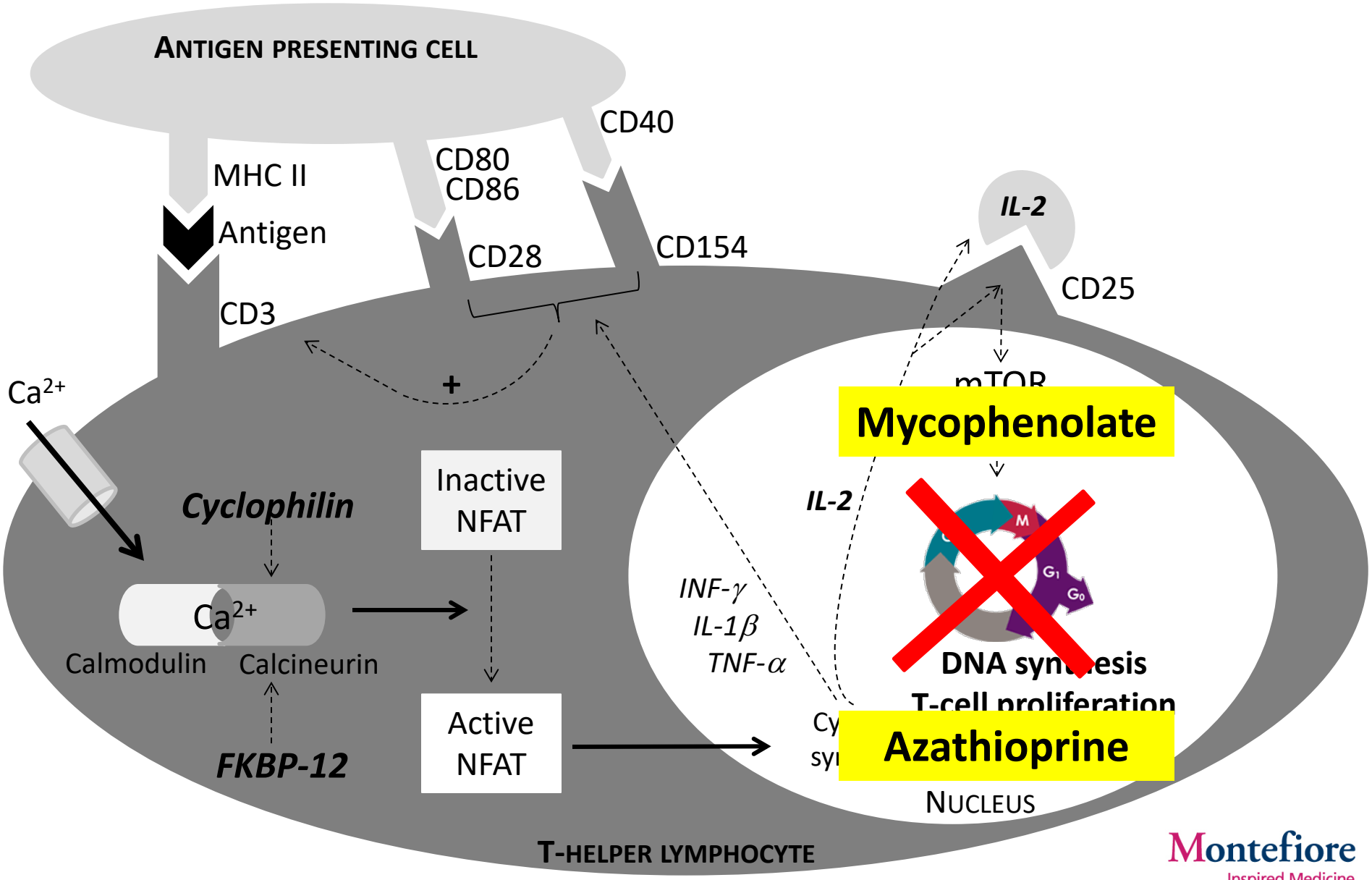
INTERCHANGEABLE

Sandimmune® (non-modified)	Neoral® (modified)	Gengraf® (modified)
• Original formulation • Bile-dependent absorption (poor, inconsistent) • High interpatient variability in drug exposure	• Microemulsion • Bile-independent absorption • Increased systemic absorption, bioavailability	• AB-rated, bioequivalent formulation of Neoral® • Caution: 80-125% bioequivalence acceptance range

NOT INTERCHANGEABLE

Montefiore
Inspired Medicine

ANTIMETABOLITE AGENTS



Montefiore
Inspired Medicine

MYCOPHENOLATE (CellCept®, Myfortic®)	
Dose	▪ **CellCept**: 600mg/m2/dose (max 1000mg q 12h) ▪ **Myfortic**: dose conversion 180mg per 250 of Cellcept (Max 720 mg PO q12h)
Adverse Effects	▪ **Short-term**: dyspepsia, nausea, diarrhea, leukopenia, thrombocytopenia ▪ **Long-term**: myelosuppression, infection, malignancy, PTLD
Monitoring	▪ CBC, pregnancy testing at the start of therapy and routinely throughout therapy ▪ TERATOGENIC

Mycophenolate (CellCept,® Myfortic®)

CellCept® (mycophenolate mofetil)	Myfortic® (mycophenolic acid)
• Original formulation • Absorption dependent on acidic pH in proximal duodenum • Available as oral capsules (250 mg), tablets (500 mg), suspension, and IV injection	• Enteric-coated formulation, potentially less GI irritation • Absorption independent of acidity in distal duodenum • Cannot be crushed/broken • Available as oral tablets (180 mg, 360 mg)

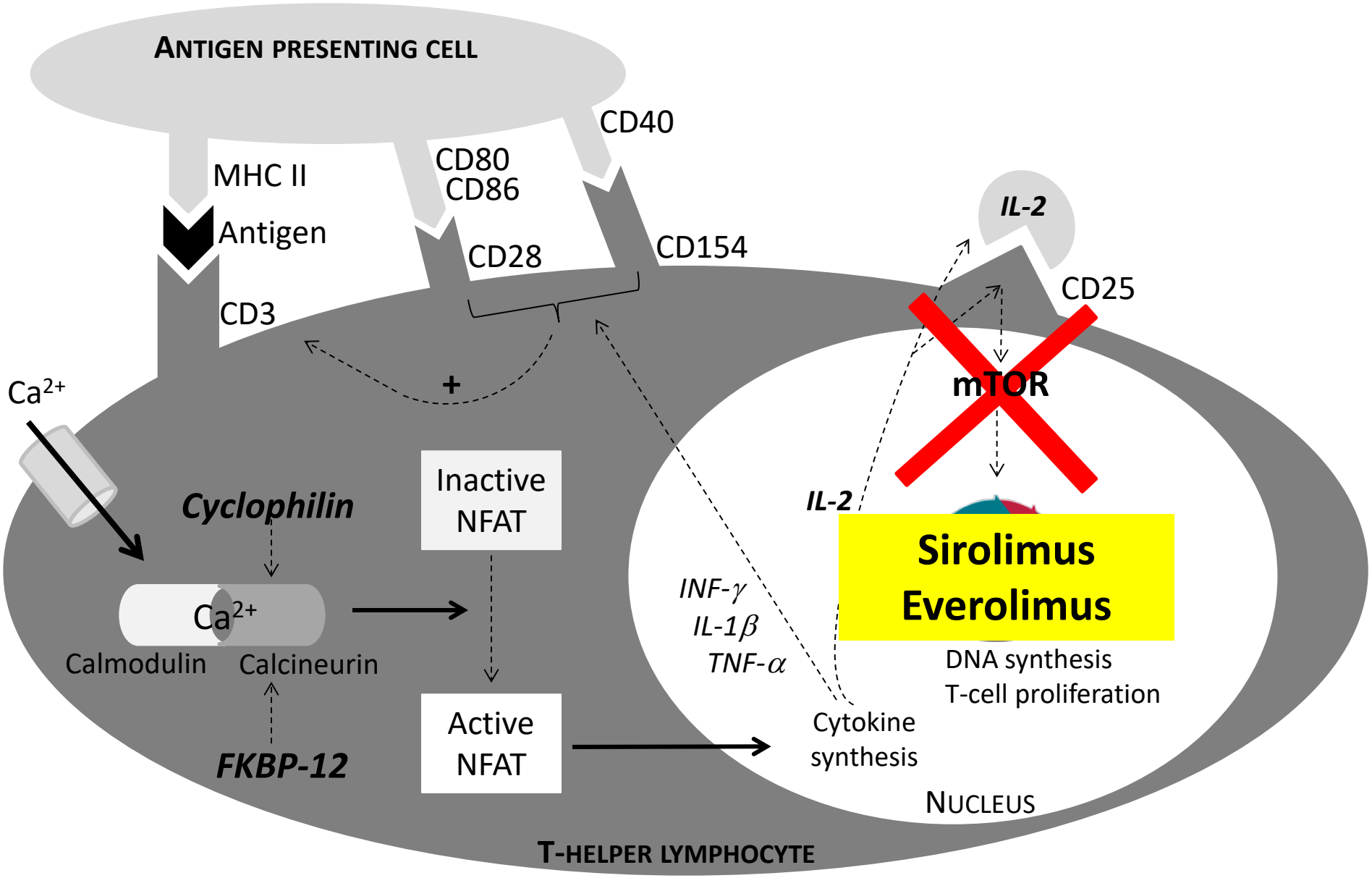
NOT INTERCHANGEABLE

Montefiore
Inspired Medicine

AZATHIOPRINE (Imuran®)

Patient Population	▪ Alternative to mycophenolate in patients who develop intolerable GI toxicity ▪ **Antimetabolite drug of choice in female transplant recipients of child-bearing potential immediately prior to and during pregnancy**
Dose	▪ **Initial**: 3-5 mg/kg PO daily ▪ **Maintenance**: 1-3 mg/kg PO daily
Adverse Effects	▪ **Short-term**: leukopenia, thrombocytopenia, dyspepsia, nausea, diarrhea ▪ **Long-term**: myelosuppression, elevated liver enzymes, myalgia, pancreatitis, infection, malignancy, PTLD TPMT genetic testing recommended if significant myelosuppression Avoid concomitant allopurinol use
Monitoring	▪ CBC, liver enzymes, amylase/lipase

mTOR INHIBITORS

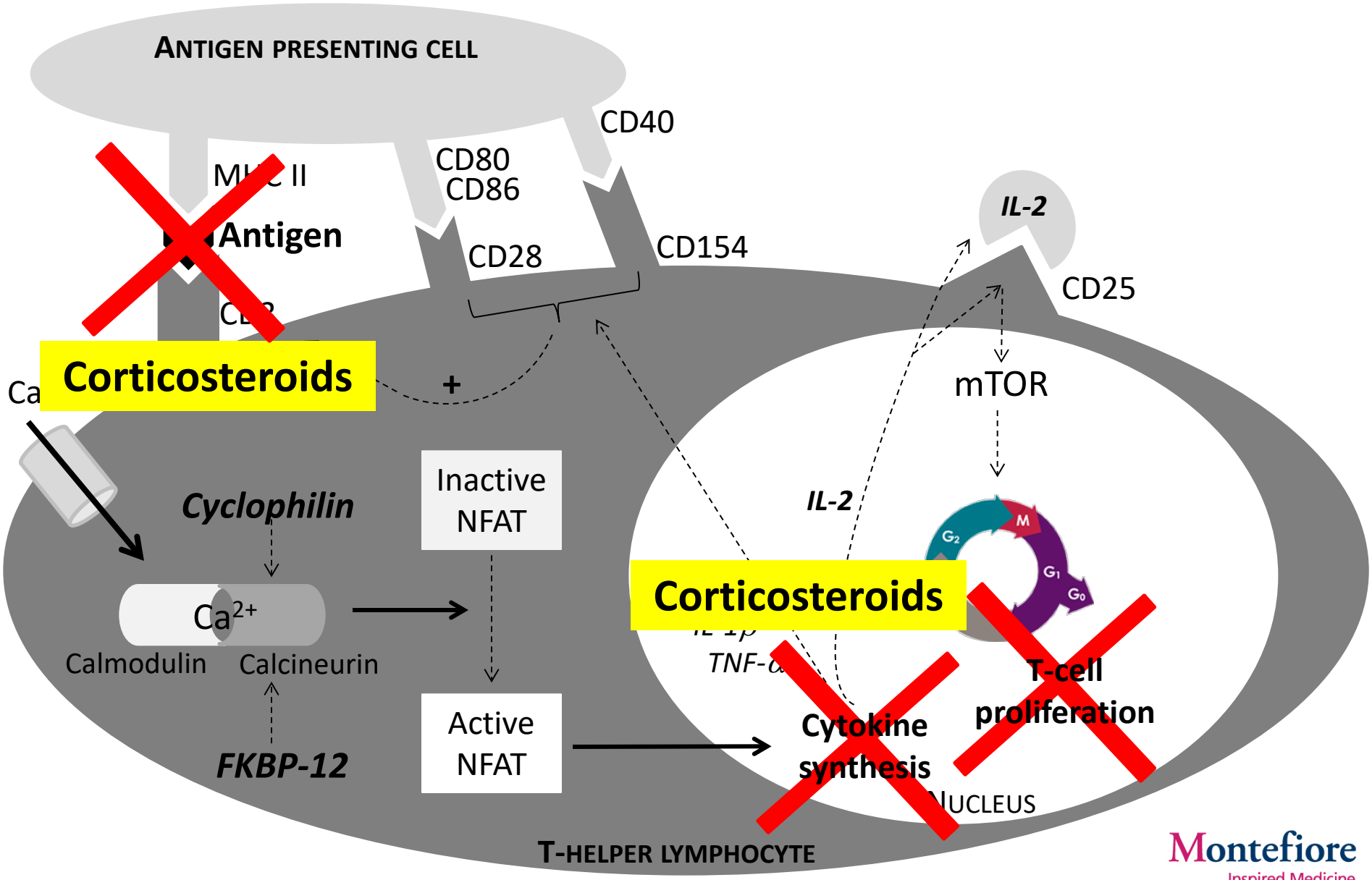


SIROLIMUS (Rapamune®), EVEROLIMUS (Zortress®)	
Patient Population	▪ Patients with history of malignancy or at increased risk for malignancy ▪ Patients at low risk of rejection who may benefit from a CNI-sparing maintenance regimen (neurotoxicity, nephrotoxicity)
Adverse Effects	▪ **Short-term**: thrombocytopenia, impaired wound healing, HAT ▪ **Long-term**: hyperlipidemia, myelosuppression, aggravation of proteinuria, aphthous ulcers (mouth/skin), pneumonitis
Monitoring	▪ CBC, liver enzymes, lipid panel, renal function; **contraindicated within first 30 days post-transplant** ▪ **Therapeutic drug monitoring:** target levels dependent on type of organ transplanted and time since transplant

Antimetabolites
Sirolimus & Everolimus

- Not limited to lymphocyte proliferation intracellular signaling pathway has been described in monocytes/macrophages, dendritic cells, natural killer cells, and endothelial cells
- Used in ADPKD and tuberous sclerosis

CORTICOSTEROIDS



Montefiore
Inspired Medicine

METHYLPREDNISOLONE/PREDNISONE	
Dose	▪ **Initial**: 10/mg/kg IV on POD0, 5 mg/kg on POD1 and 2.5mg/kg on POD2 and 3 ▪ **Maintenance**: weight based (max 20mg q day) ▪ **Rejection**: 3-4 days of 10mg/kg- max 500mg
Adverse Effects	▪ **Short-term**: hyperglycemia, hypertension, edema, impaired wound healing ▪ **Long-term**: cushingoid changes, weight gain, diabetes, infection, cataracts, hyperlipidemia, osteopenia, impaired growth, psychiatric effects

Treatment of Rejection

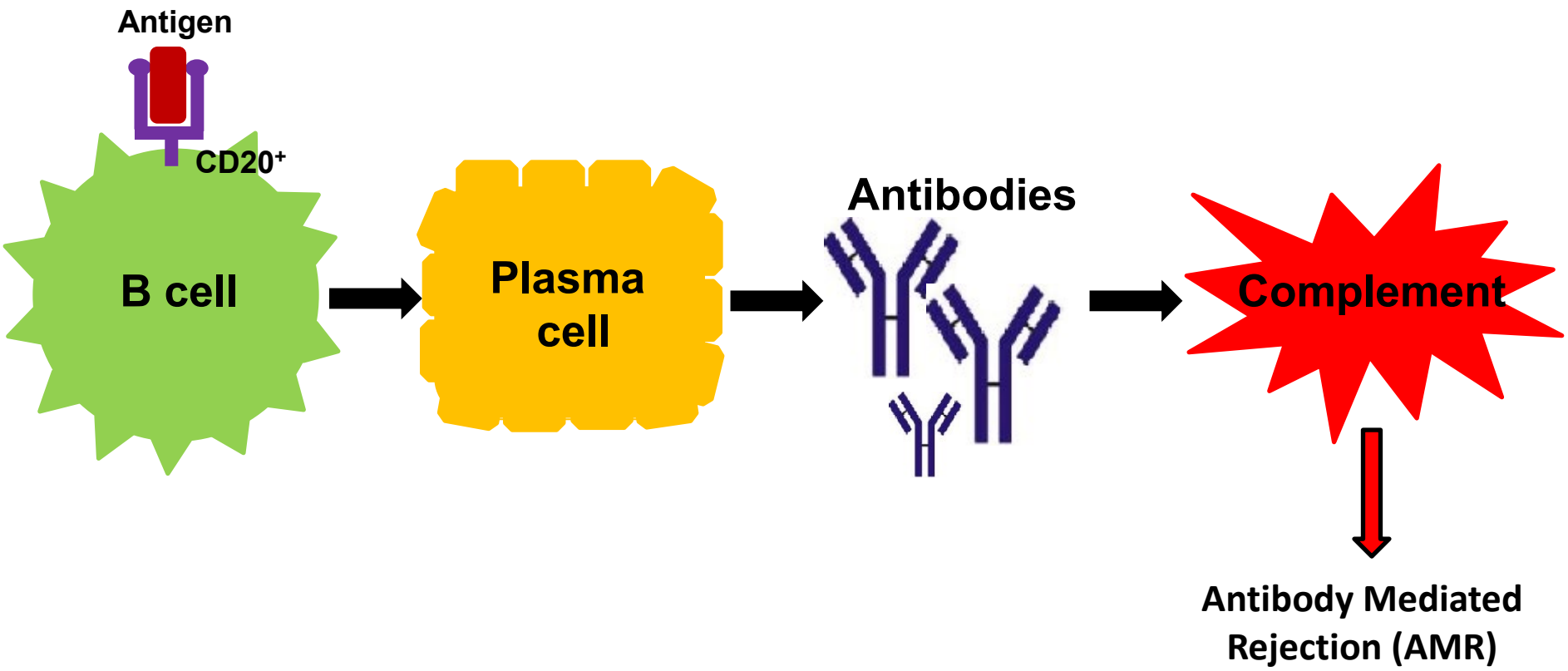
Treatment of Rejection

- Based on the Banff criteria
- Not always black and white
- Guidelines only- evidence for many of the treatment protocols not based on clinical trials

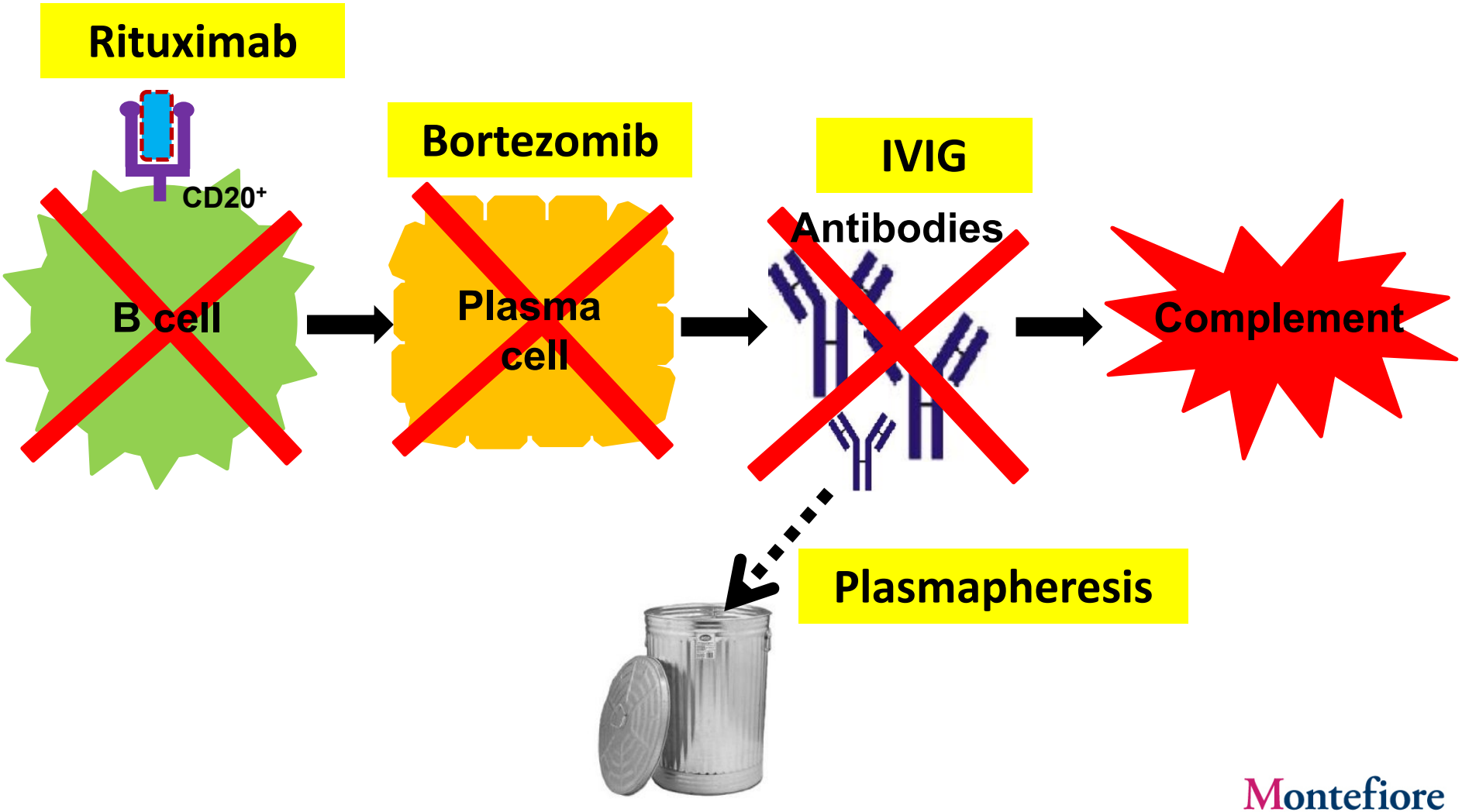
Treatment of Allograft Rejection

- Acute cellular rejection (ACR)
  - High-dose corticosteroids
  - Lymphocyte depleting antibodies: antithymocyte globulin (Thymoglobulin®)
- Humoral/Antibody-Mediated Rejection (AMR)
  - Plasmapheresis
  - Intravenous immune globulin (IVIG)
  - Anti-CD20 antibody (Rituximab – Rituxan®)
  - Proteasome inhibitor (Bortezomib – Velcade®)
  - Eculizumab

Humoral Immunity



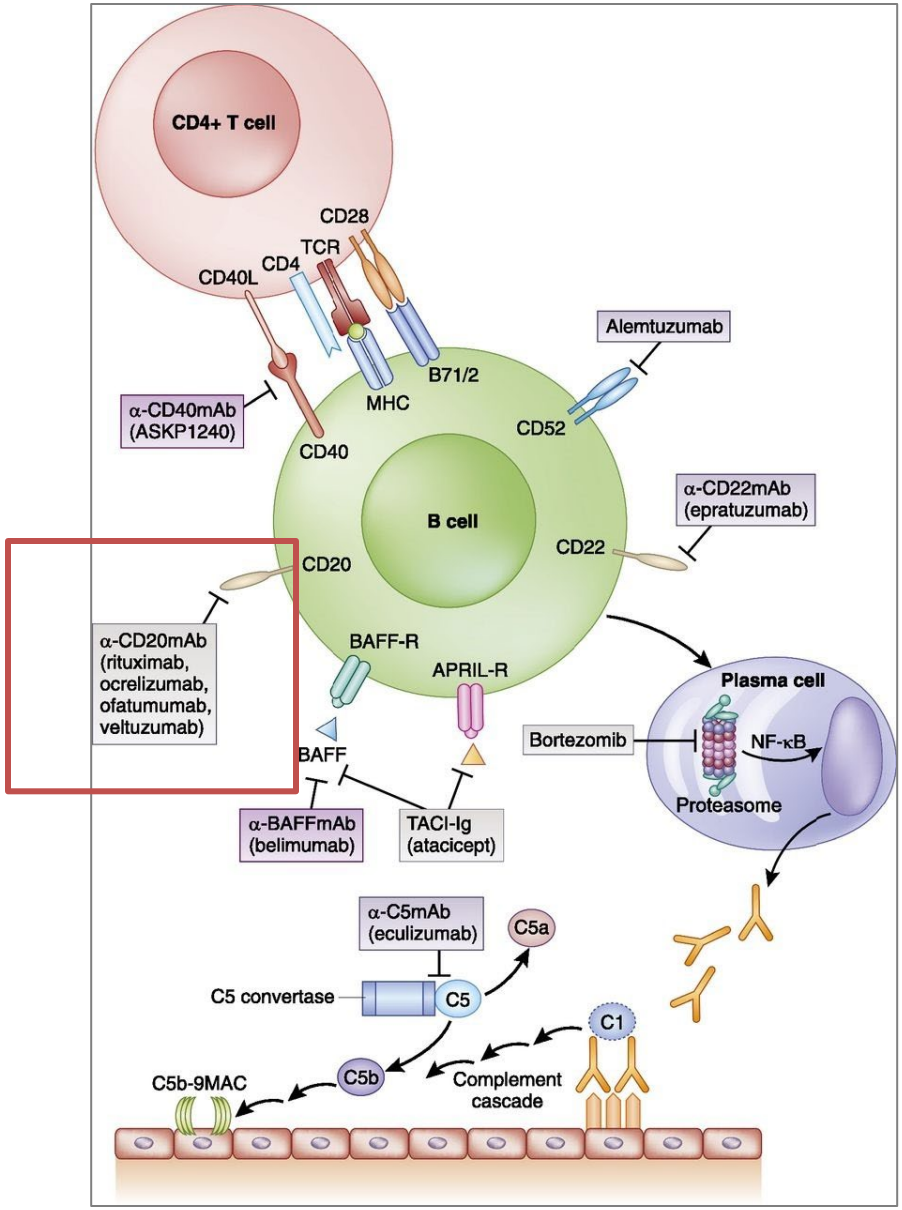
Humoral Immunity



Montefiore
Inspired Medicine

IVIG (multiple formulations)- SUCROSE FREE	
MOA	▪ Neutralizes circulating autoantibodies leading to rapid decrease in anti-HLA antibody titers ▪ Blocks Fc receptors on splenic macrophages, inhibits C3b/C4b-mediated damage, inhibits cytokine synthesis
USE	▪ Patients at high risk of rejection with presence of donor-specific anti-HLA antibodies (DSA) pre-transplant ▪ Patients with antibody-mediated rejection ▪ Patients with post-transplant CMV/Parvo infection
Dose	▪ 1-2 grams/kg cumulative dose, divided over 2-5 doses (typically 4 doses) ▪ Must be administered **AFTER** plasmapheresis
Adverse Effects	▪ **Short-term**: headache, myalgias, fever/rigors, bleeding, hemolysis, infection, osmotic nephrosis (sucrose-containing IVIG products) ▪ **Long-term**: minimal
Monitoring	▪ CBC, renal function, fluid balance, DSA titers

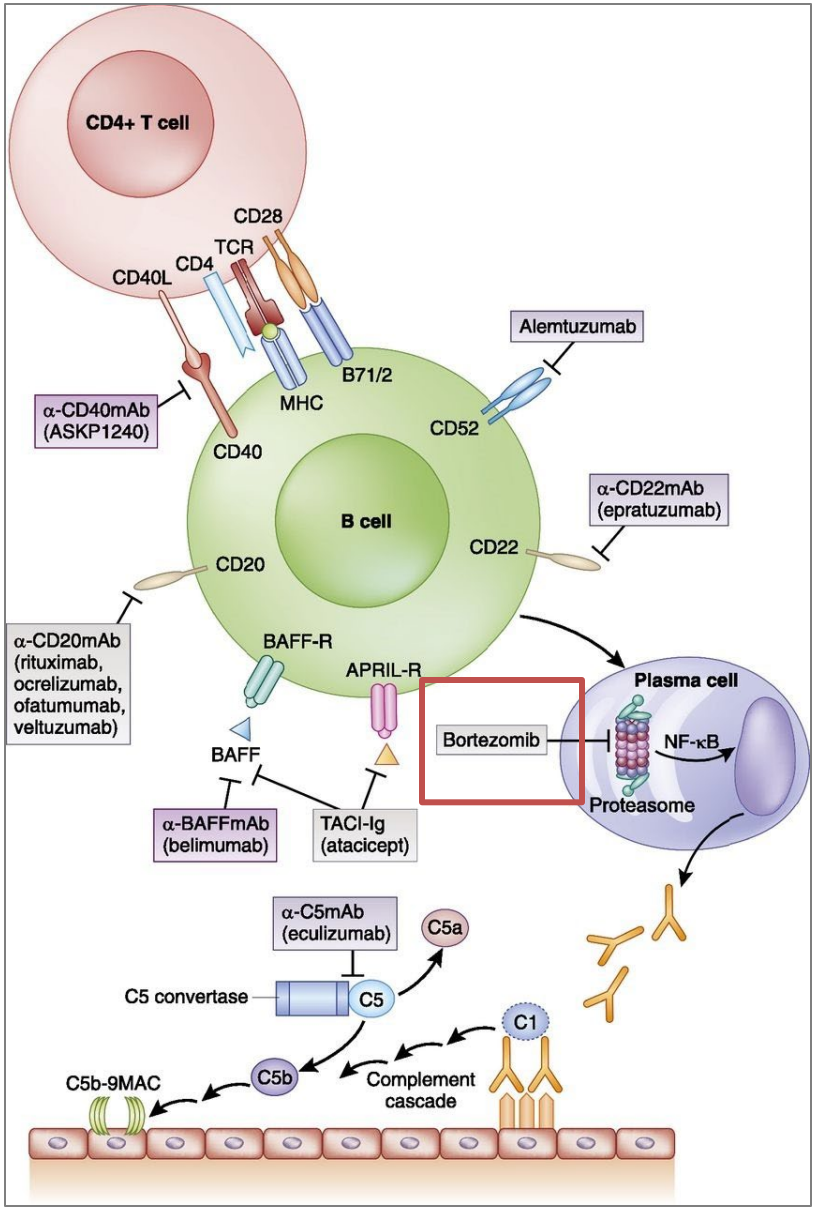
Rituximab



RITUXIMAB (Rituxan®)	
Mechanism of Action	▪ Chimeric murine/human monoclonal antibody against CD20+ on pre-B and mature B lymphocytes; inhibits cell cycle initiation and differentiation, leading to B lymphocyte apoptosis
Patient Population	▪ Patients with AMR ▪ Patients with PTLD
Dose	▪ 375 mg/m^2 weekly for for up to 4 doses ▪ Must be administered **AFTER** plasmapheresis
Adverse Effects	▪ **Short-term**: fever/rigors, rash, bronchospasm, angioedema, neuropathy, myelosuppression, myalgia, cytokine-release syndrome, HBV reactivation, acute hepatitis ▪ **Long-term**: prolonged myelosuppression, infection, PML, serum sickness
Monitoring	▪ CBC, liver enzymes, DSA

- B cell counts can be suppressed for 6-9 months

Bortezomib

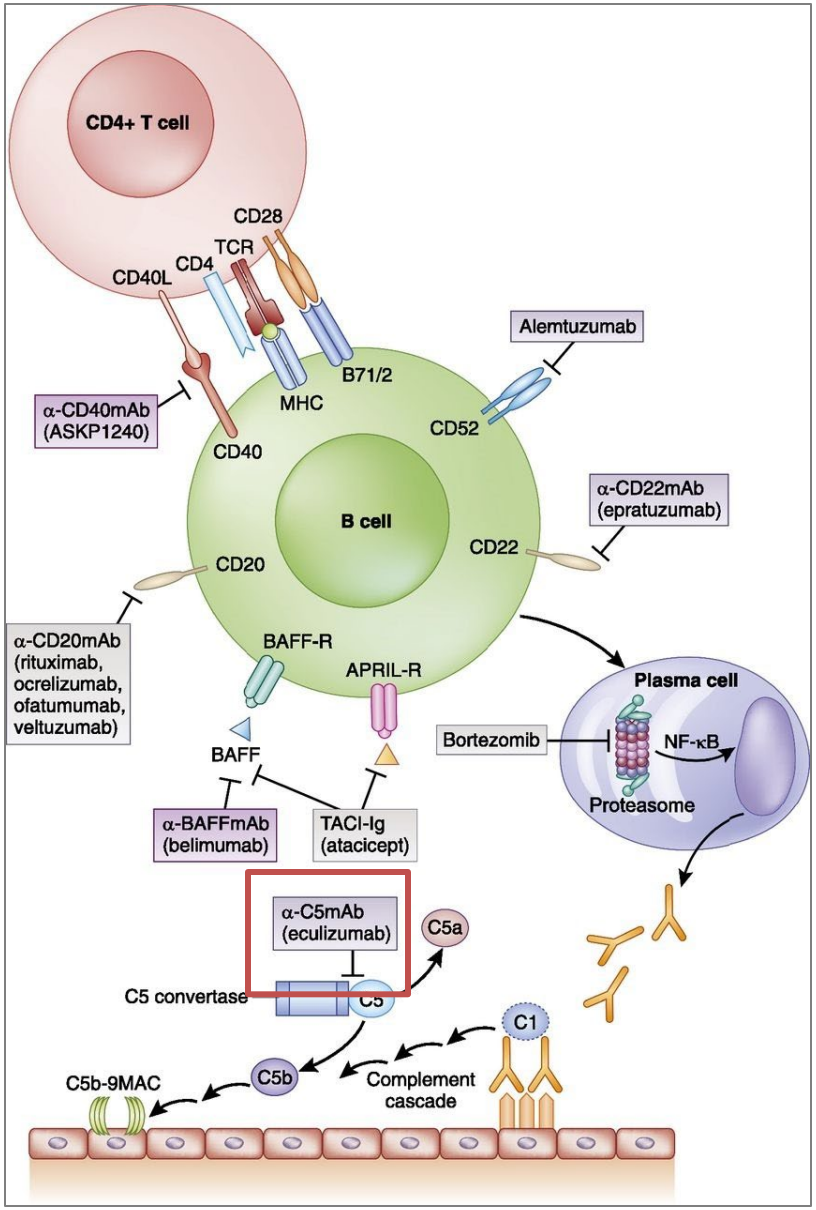

CD4+ T cell
CD28
TCR
CD4
CD40L
Alemtuzumab
α-CD40mAb
(ASKP1240)
B71/2
MHC
CD52
CD40
B cell
α-CD22mAb
(epratuzumab)
CD22
CD20
α-CD20mAb
(rituximab,
ocrelizumab,
ofatumumab,
veltuzumab)
BAFF-R
APRIL-R
Plasma cell
Bortezomib
NF-κB
BAFF
Proteasome
α-BAFFmAb
(belimumab)
TACI-Ig
(atacicept)
α-C5mAb
(eculizumab)
C5a
C5 convertase
C5
C1
C5b
C5b-9MAC
Complement
cascade

BORTEZOMIB (Velcade®)	
Dose	▪ 1.3 mg/m^2 SQ on days 1, 4, 8, and 11 ▪ May consider repeating cycle in 28 days if treatment-resistant rejection
Adverse Effects	▪ **Short-term**: nausea/vomiting, neuropathy, elevated liver enzymes, HSV reactivation (rare with single-course therapy) ▪ **Long-term**: myelosuppression, infection
Monitoring	▪ CBC, liver enzymes, DSA

Other Immunosuppressive Agents

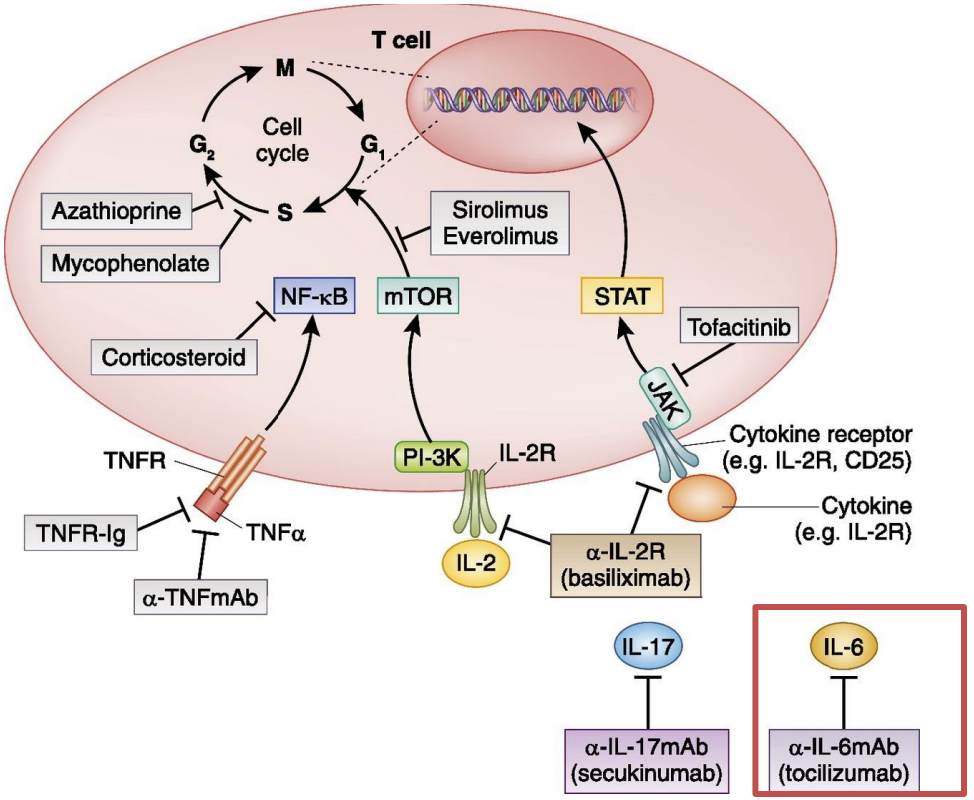
Eculizumab

- Inhibition of the complement cascade increases the risk of serious infection from encapsulated bacteria:
  - Vaccination for Neisseria meningitis, Streptococcus pneumonia, and Haemophilus influenza type b should be performed before therapy.



Tocilizumab

- IL-6 is expressed in response to inflammatory stimuli and contributes to CD8 T cell differentiation, B cell differentiation, and activation of the hepatic acute-phase response
- Used in refractory ABMR



QUESTIONS?

Thank you!

Kidney Transplantation in Children:
An Overview and the Pre-Transplant Evaluation

Lorraine Hamiwka, MD FRCPC
Pediatric Nephrologist, Associate Professor

Alberta Children's Hospital
UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

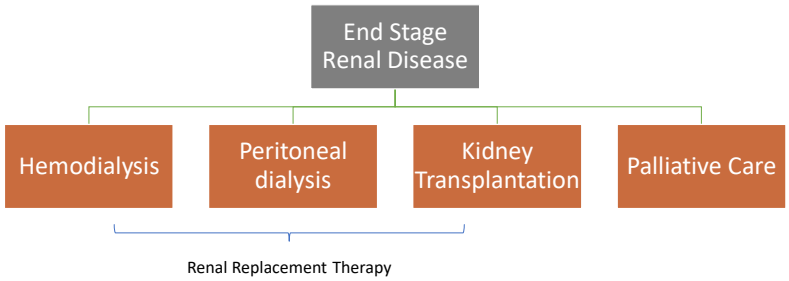
1

Objectives

1. Transplant as Treatment for Children with ESRD
2. Challenges in Pediatric Kidney Transplantation
3. The Pre-Transplant Evaluation
4. Types of Kidney Donors
5. Pediatric Kidney Transplant Outcomes

2

Options for Patients with ESRD



3

Kidney transplantation

Treatment of choice for children with end-stage renal disease

- offers improved survival, growth potential, cognitive development, social adjustment
- improved quality of life over dialysis therapy
- economically advantageous
  - *initial higher cost but long-term costs are less*

4

Transplant-Related Quality-of-Life Benefits

- Lifestyle free of dialysis constraints
- Freedom to travel
- Relatively unrestricted diet
- Engage in strenuous training for athletic sports
- Improved ability for pregnancy/bearing children

5

Pediatric Kidney Transplant History

Prior to the 1980's infants and small children

- were generally *not* considered for transplant
- only *select* patients were chosen for dialysis
- experienced *poorer* patient and graft survival rates than adult patients

6

Pediatric Kidney Transplantation

Refined pre and post–transplant management has contributed to enhanced outcomes:

- vaccinations for preventable diseases
- attention to cognitive and growth delays
- effective dialysis and nutrition prior to transplant
- improved donor selection
- improvements in pediatric surgical techniques and postoperative care
- more potent immunosuppression
- better antiviral prophylaxis

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Pediatric Kidney Transplantation

- Worldwide >1300 pediatric kidney transplants are performed annually
- Since the *first* transplant, pediatric outcomes have dramatically improved
- Pre-emptive living donor transplantation has become more common
- *And now* pediatric kidney recipients' outcomes are equal or better when compared to adults *(except in the adolescent age group)*

8

Challenges in Pediatric Kidney Transplantation

9

Kidney Transplantation Children vs Adults

10

<u>Similarities</u>: Pediatric and Adult Kidney Transplantation

1. Same immunosuppressive medications used
2. Creatinine is the serum biomarker
3. Rejection is determined by kidney biopsy
4. Rejection mechanisms and treatments are similar

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<u>Differences</u>: Pediatric and Adult Kidney Transplantation

1. Different spectrum of primary kidney disease
2. Different pharmacokinetics of immunosuppressive agents
3. Different immunologic responsiveness in young children
4. Higher risk of vascular thrombosis
5. Liquid formulations (compounding) of medications
6. Diagnosis of acute rejection more difficult in disproportionate graft size
7. Non-adherence with medication, especially adolescents
8. More recurrence of original disease
9. Impaired growth before *as well as* after transplantation
10. Child more often naïve to viral infection (CMV, EBV, BK, etc)
11. More need for urologic evaluation
12. *All children need transition to adult clinics*

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Slide 10

JH7 Are you adding more to this slide? If not, I'd suggest making the picture larger
Jolene Haddad, 1/14/2019

Differences: Pediatric and Adult Kidney Transplantation
Causes of Kidney Failure

Young children - congenital or inherited disorders:
- renal dysplasia
- obstructive uropathies
- VUR/reflux

Older children - acquired glomerular diseases:
- focal segmental glomerulosclerosis (FSGS)
- lupus nephritis/rheumatological
- IgA nephropathy

Adults:
- diabetic nephropathy
- hypertension
- ADPKD

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Adult-sized Kidneys into Small Pediatric Recipients: Challenges

Cardiac output: renal blood flow regulation: -
- Higher risk of ATN
- Higher risk of graft thrombosis
  small vascular caliber → highest among <2yrs
- Space for organ within abdominal cavity

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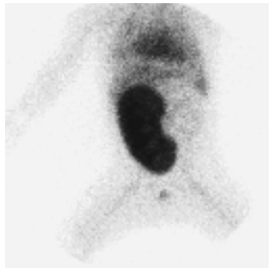
A temporary contraindication for pediatric transplantation may be recipient size



15

Adolescent Adherence

- Transplant *does not* release a patient from lifelong medical follow-up
- Adolescents and young adults developing increased independence and responsibilities, including management of immunosuppressive therapy
- Adolescents and young adults have the highest graft failure rates of any age group
  - Regardless of age at transplant, graft failure rates begin to increase around 12 years, peak at 17–24 years and decline thereafter

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TRANSITION OF CARE

Adolescents *must* eventually graduate to adult care

As transfer to adult care occurs during the "high-risk" period, it is important to have good transition plan and follow-up or a transplant transition program

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Pre-Transplant Evaluation: Preparing Patients and Families for Transplantation

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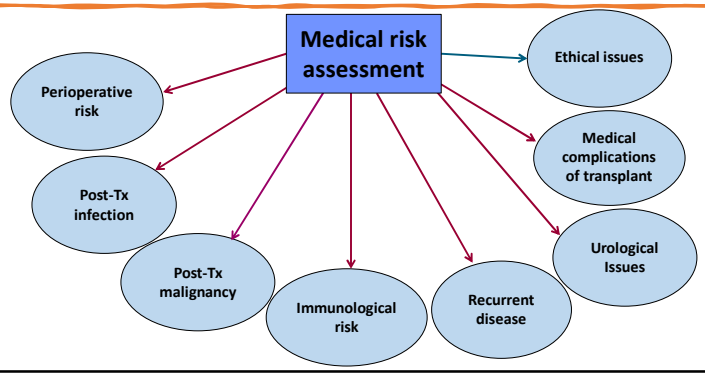
Pre-Transplant Recipient Evaluation



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Pre-Transplant Evaluation

- To assess and optimize current health status
- To ensure the patient is healthy enough to undergo transplantation
- To identify any risk factors that could compromise kidney transplant (clotting disorder, urological issues, etc)
- To provide education for patient and families

⇨ To ensure best outcomes after kidney transplantation; both short and long-term

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Benefits and Risks

Benefits of transplant
- Improved quality of life without need for dialysis
- Decreased mortality and morbidity

Risks of transplant
- Risks involved with surgery
- Lifelong immunosuppression
- Potential for serious infections and cancers

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Preparing for Transplantation

- Encouraging families to learn about transplantation improves outcomes
  - Teaching session with multidisciplinary team
- Transplantation can be preemptive
  - Identify potential living donors
- Coordinating all pre-transplant care and testing
  - e.g. vaccines, other subspecialty referral, tests, etc.

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Timing of Transplantation

- Pre-emptive transplantation is increasingly recommended
- Time spent on dialysis before transplant is shown to have negative effects on patient survival and possibly graft survival
- *2020 Kidney Disease: Improving Global Outcomes* guidelines recommend "referral of potential kidney transplant candidates for evaluation at least 6–12 months before anticipated dialysis initiation to facilitate identification and workup of living donors and to plan for possible pre-emptive transplantation"

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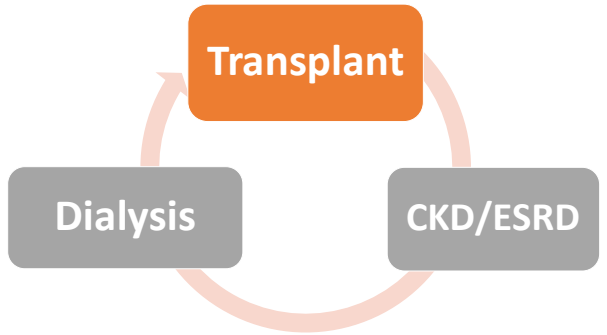
The ESRD Treatment Cycle



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Managing Expectations

TRUTH **Kidney Transplant is another form of Renal Replacement Therapy**

- ***More intensive monitoring*** early on, compared to dialysis
- ***Increased mortality*** in first year
- ***Greater dependence & need for adherence*** to medications

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Pre-transplant Recipient Evaluation

Routine testing

- Full medical history and physical exam
- Blood type
- CBC
- Chemistry, liver panel
- PTH (bone health)
- PT and PTT
- HBV and HBC serology
- HIV screen
- CMV & EBV testing
- Vaccine serology
- Chest X-ray
- ECG and echocardiogram
- HLA tissue typing and antibody screening
- Abdominal ultrasound
- Vascular ultrasound
- +/-Pap smear
- Transplant surgery referral

Kasiske BL, et al. *Am J Transplant.* 2001;1 (suppl 2):1-95

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Pre-transplant Recipient Evaluation

Elective testing as needed

- Voiding cystourethrogram
- Upper GI series and upper endoscopy
- Toxoplasmosis titer
- Lipid profile
- PPD tuberculin test
- Subspecialty referrals

Siddqi N, et al. In: Danovitch GM, ed. *Handbook of Kidney Transplantation.* 2005:169-192

27

Conditions Requiring Therapy Prior to Transplant

Active infections
- Bacterial, fungal, viral etc.
  - Hepatitis
  - Tuberculosis

Cardiovascular disease
- Cardiology assessment as needed

Malnutrition

Urological issues

Substance abuse

Kasiske BL, et al.

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Pre-Transplant Nephrectomy

- ~25% of children undergo native nephrectomies prior to transplant
- Nephrectomies are considered for
  - high-grade VUR, recurrent pyelonephritis, refractory hypertension, significant polyuria
- Certain conditions: congenital nephrotic syndrome generally require bilateral native nephrectomy and a period of dialysis despite normal renal function to prevent protein malnutrition, sepsis, and vascular thrombosis

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Vaccines

All vaccines required should be completed prior to transplant

Generally *after* transplant:

- inactivated vaccines safe
- live vaccines are "not" safe
- Reduced immune response on immunosuppression

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Malignancy and Transplantation

- Previous recommendation was a standard waiting time of 2 years for most cancers
- Recently a approach based on the understanding of the malignancy
- Oncological consultation should be sought as part of the evaluation of a transplant patient with a history of malignancy

Danovitch GM, 6thed. 2017:218-219. Kiberd BA, et al. *Am J Transplant.* 2003;3:619-625.

31

Contraindications to Pediatric Transplantation

Very few absolute

- Active malignancy
- Untreated current infection

Others to consider

- Severe, irreversible *extra*renal disease
  - severe heart or lung disease
- Aggressive recurrent native kidney disease (relative)
  - primary oxalosis (unless combined liver/kidney transplant an option)
- *Nonadherence with medical management*

Temporary contraindication *for pediatrics may be "recipient size"*

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Types of Kidney Donors

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Kidney Transplant Donors

Living Donors
- Related or unrelated "emotionally close" donor
- Altruistic anonymous living donor
- Paired exchange living donor (when AB0 incompatibility)

Deceased Donors
- Donation after neurological death (NDD) – heart beating
- Donation after cardio-circulatory death (DCD) – *non* heart beating
- Expanded criteria deceased donor (ECD)
  - > 60 years or a donor > 50 years with two comorbidites

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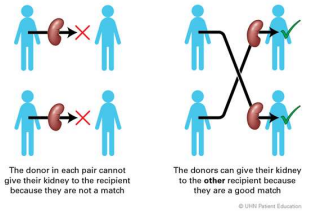
Advantages/Disadvantages: Living Donor Transplant

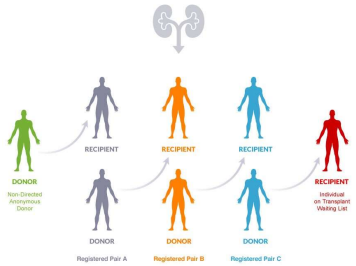
Advantages	Disadvantages
• Preemptive transplant option • Better outcomes • Minimal delayed graft function • No wait for deceased-donor kidney; can time transplant for convenience • Immunosuppressive regimen may be less aggressive • Emotional gain to donor	• Psychological stress to donor • Long donor evaluation process • Donor recovery time – work, family, etc • Operative donor mortality (3-4/10,000 nephrectomies) - major complications (3-6%), minor complications (22%) • Potential donor hypertension, proteinuria • Risk of unrecognized donor covert renal disease • Donor risk of gestational hypertension or preeclampsia

Lentine and Patel *Adv Chronic Kidney Dis*. 2012 July ; 19(4): 220–228

35

Kidney Paired Donation





Canadian Kidney Paired Donation Program was established in 2008
- Program completed 1000 transplants as of May 2023
- Farthest distance a kidney was shipped was approximately 3,965 km; between Vancouver and Quebec City

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Waiting List for a Deceased-Donor Kidney

- Usually when a living donor cannot be identified
- Administered by an established Donation Agency
- Transplant center will list the patient after a completed pre-transplant evaluation with surgical approval
- Wait can be longer for blood types O and B

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Deceased Donor Kidney Allocation to Children

Allocated by an established Donation Agency
- listed when GFR <15 mL/min

Children given priority on deceased donor waiting list in most countries
- waiting times may be as short as weeks to a few months

Allocation policies have preferentially allocated higher-quality kidneys from deceased donors to children
- children make up a small fraction of those on the waiting list
- children need to live longer *than* their transplant
- children may need multiple transplants over their lifetime

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Pediatric Kidney Transplantation Outcomes

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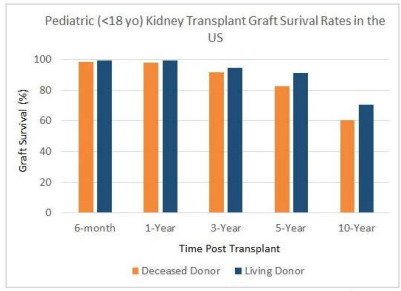
Graft Survival Rates Good and Getting Better



Pediatric kidney transplant graft survival rates in the United States (2017). Adapted from: Scientific Registry of Transplant Recipients (SRTR/OPTN Annual Data Report 2018)

Shapiro R, Sarwal MM. Pediatric kidney transplantation. Pediatr Clin North Am 2010;57:393

1-year:
Patient survival 98%
Graft survival 97%

5-year:
Patient survival: 94%
Graft survival of 89%

40

Survival Rates of Pediatric Patients Undergoing Kidney Transplantation

1-year:

Patient survival 98%
Graft survival 97%

5-year:

Patient survival: 94%
Graft survival of 89%

Graft half-life of children transplanted between 2002-2016:
Living-donor: 15-20 years
Deceased-donor: 12-17 years

Shapiro R, Sarwal MM. Pediatric kidney transplantation. Pediatr Clin North Am 2010;57:393

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Causes of Graft Failure for Pediatric Renal Transplants

	Index graft failures		Subsequent graft failures		All graft failures	
	N	%	N	%	N	%
Total transplants with graft failure	2,585	100.0	335	100.0	2,920	100.0
Cause of graft failure						
Death with functioning graft	238	9.2	25	7.5	263	9.0
Primary nonfunction	58	2.2	2	0.6	60	2.6
Vascular thrombosis	247	9.6	38	11.3	285	9.8
Other technical	29	1.1	4	1.2	33	1.1
Hyperacute rejection	15	0.6	4	1.2	19	0.7
Accelerated acute rejection	33	1.3	8	2.4	41	1.4
Acute rejection	342	13.2	44	13.1	386	13.2
Chronic rejection	913	35.3	126	37.6	1,039	35.6
Recurrence of original kidney disease	170	6.6	32	9.6	202	6.9
Renal artery stenosis	15	0.6	0	0.0	15	0.5
Bacterial/viral infection	47	1.8	5	1.5	52	1.8
Cyclosporine toxicity	13	0.5	0	0.0	13	0.5
De novo kidney disease	8	0.3	2	0.6	10	0.3
Patient discontinued medication	120	4.6	8	2.4	128	4.48
Malignancy	34	1.3	2	0.6	36	1.2
Others/unknown	303	11.7	35	10.5	338	11.6

50.9%

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NAPRTCS: Pediatric Causes of Patient Death

	Total			Living Donor			Deceased Donor		
	N	%	Func graft	N	%	Func graft	N	%	Func graft
All deceased patients	591	100.0	285	260	100.0	131	331	100.0	154
Cause of Death									
Infection,Viral	47	8.0	25	26	10.0	14	21	6.3	11
Infection,Bacterial	75	12.7	38	35	13.5	16	40	12.1	22
Infection, Not Specified	46	7.8	15	23	8.8	8	23	6.9	7
Cancer/malignancy	68	11.5	49	38	14.6	28	30	9.1	21
Cardiopulmonary	86	14.6	39	31	11.9	15	55	16.6	24
Hemorrhage	33	5.6	12	9	3.5	2	24	7.3	10
Recurrence	10	1.7	1	4	1.5	1	6	1.8	0
Dialysis-related Complications	18	3.0	0	8	3.1	0	10	3.0	0
Other	149	25.2	76	64	24.6	35	85	25.7	41
Unknown	59	10.0	30	22	8.5	12	37	11.2	18

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Transplantation

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Conclusions

- Pediatric kidney transplant is the optimal choice for children with ESRD
- Pediatric kidney transplant differs from adult transplant
- Preparation of the child and family play an important role in successful outcomes
- In the past decades, innovations in pediatric kidney transplantation led to increased graft and patient survival
- Despite a subsequent improvement in graft survival, there are still challenges to face

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HLA Typing, Crossmatching and Immune Monitoring

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1

Objectives

1. How does the immune system recognize a transplanted organ
2. HLA Typing and Crossmatching
3. The main components of the immune response after transplant
4. Immune Monitoring Post - Transplant

2

Introduction

In addition to the medical and surgical challenges in kidney transplantation,

a major biological *barrier* is immunological

This barrier may lead to graft rejection and graft loss

The recipient's immune response against a transplanted graft is largely dependent on the degree of genetic similarity between the donor and recipient

3

Kidney Transplant Immunology

4

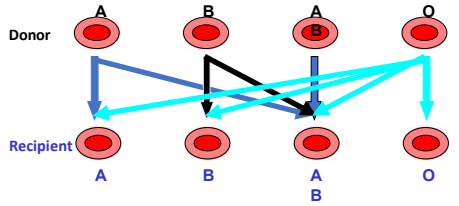
Immunologic Barriers to Transplantation

I. ABO Blood Group Antigens

II. HLA (Human Leukocyte Antigens)

5

ABO Compatibility



ABO group mismatching

- Blood group mismatches result in hyperacute rejection
- AB0 incompatible transplant protocols exist
  - plasmapheresis, immunoadsorption, plasma exchange, rituximab, splenectomy
  - Paired kidney donor programs

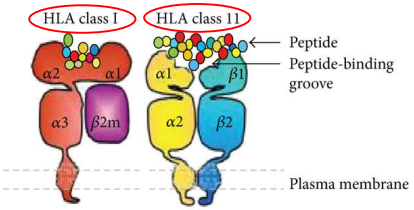
6

How Does a Transplant Kidney get Rejected?

Organs comes with unique fingerprints that can trigger the immune system after transplantation

7

The *fingerprints* of the transplant kidney: Human Leukocyte Antigens

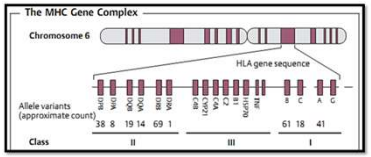


- Glycoproteins composed of 2 polypeptide chains; on cell surfaces
- Responsible for recognition of the graft as *similar* or *foreign*
- Incompatibility of HLA between donor & recipient of an allograft leads to *graft rejection*

8

Human Leukocyte Antigen (HLA)

Genes that encode for HLA antigens - found in the genetic region located on the short arm of chromosome 6, region p21.3 called the *Major histocompatibility complex* (MHC)

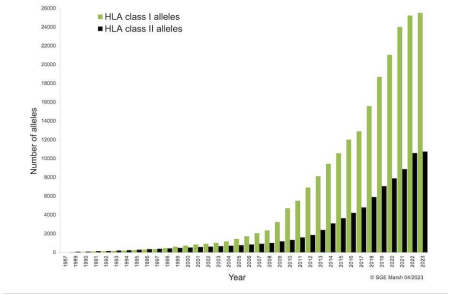


- HLA genes are polymorphic; many different variations at each gene locus
- In total, there are >20,000 unique HLA alleles

9

Number of HLA class I and class II alleles discovered from 1987 to 2023

DNA typing methods have increased the number of discovered alleles



Graph showing the number of alleles named by year from 1987 to the end of March 2023.

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Sensitization: anti-HLA Antibodies

If our body is exposed to "foreign" HLA
→ HLA antibodies will be produced

The more foreign HLA
→ higher sensitization → harder to find a "match"

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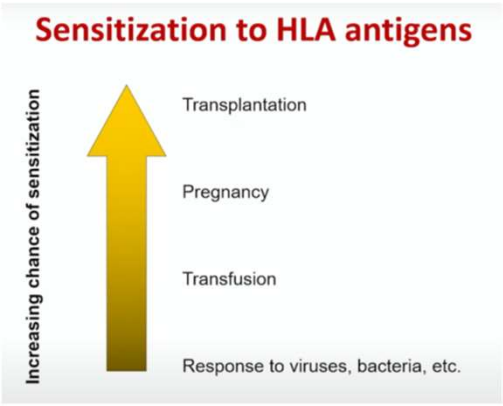
Sensitization to HLA antigens



Antibodies produced cross react with HLA

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HLA Typing and Cross Matching

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Transplantation: HLA Typing and Cross Matching

HLA Typing refers to determination of class I and class II specificities (the HLA phenotype) of both the potential donor and the recipient

Crossmatching is a test that determines the immunologic risk of a recipient with a potential donor; to ensure the recipient has no antibodies directed against donor antigens

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HLA Typing

Historically, HLA typing was performed using *serological* methods utilizing
(1) sera with known HLA specificity to identify HLA antigens
(2) cells with known HLA antigens to identify anti-HLA antibodies in patient sera

Use of newer molecular HLA typing techniques includes *DNA sequencing*, allows for higher resolution typing using
(1) extraction of genomic DNA
(2) amplification of segments of the gene of interest
(3) detection of the sequence polymorphisms that define the alleles

➡ improvement in graft survival

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Tissue Typing (HLA Testing)

"Tissue typing" of recipient & donor determines their HLA match
- Superior HLA matching is associated with improved outcomes

Everybody has 11 HLA genes:
3 HLA Class I: -A,-B, -C
8 HLA Class II: -DRB1, -DRB3, -DRB4, - DRB5,
-DQA1, -DQB1, -DPA1, -DPB1
⇒ 2 copies of each gene = **22 alleles**

Traditionally in solid organ transplantation, only HLA-A, -B, and -DR antigens considered

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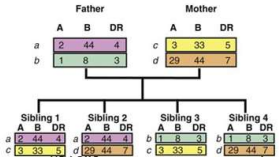
HLA Inheritance

HLA loci inherited together (Mendelian inheritance)



- parent and child have *at least* a 50% chance of matching
- siblings could have a 0 to 100% match
- unrelated donors would be less likely to match at all

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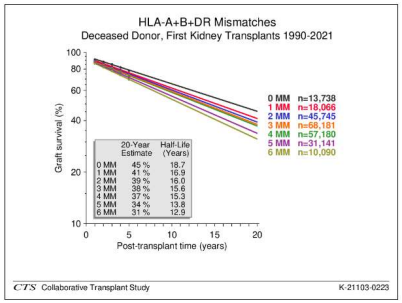
How important is HLA matching?

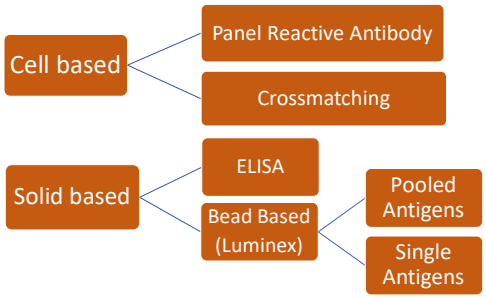


Traditionally in solid organ transplantation, only HLA-A, -B, and -DR antigens considered

18

HLA TESTING: The Role of the HLA Laboratory

- To assess & monitor immunological risk of a donor-recipient pair



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"Virtual Crossmatch" in Kidney Transplantation

- Used to assess immunologic compatibility between recipient and potential donor by analyzing the results of 2 *independent* physical laboratory tests
  —patient anti-HLA antibody and donor HLA typing
- Solid-phase assays for detecting circulating antibodies in the *recipient* directed against individual HLA and DNA-based methods for typing *donor* HLA specificities at a higher resolution makes routine use of VXM a reality
- As of 2020, approximately 20% of kidney were transplanted using a virtual crossmatch; resulting in reduced cold ischemia times

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Organ Allocation and HLA

- HLA donor–recipient match is desirable
  - extent of *mis*matches is associated with poorer graft outcome
- Consequence of HLA mismatch is the potential generation of antibodies against the mismatched HLA antigen
- Incorrect HLA typing can lead to hyperacute rejection and graft failure
- HLA mismatches are less important short-term given current immunosuppression

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The Immune System After Transplantation

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Normal Immune Function

An individual's survival depends on the ability of our immune system to recognize and respond to a multitude of foreign substances

- Recognition of "non-self" or "abnormal self"
- Protection from pathogens (bacteria, viruses, etc)
- Surveillance for tumors

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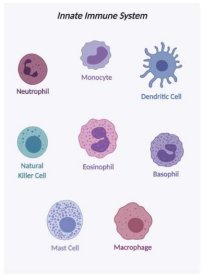
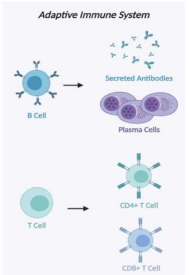
Two Basic Parts of the Immune System

Surveillance: INNATE
- macrophages, neutrophils, complement and natural antibodies (IgM)



SWAT Team: Adaptive
- dendritic cells (antigen presentation), T cells (helper and cytotoxic T cells, natural killer (NK) cells, cytotoxic B cells (antibody generation & memory)



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Innate Immunity

- Non-specific response to tissue injury
- Potentiates adaptive immunity but not reject the allograft itself

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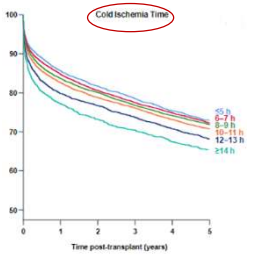
Innate Immunity

Early after transplant: ischemic- reperfusion injury

Releases DAMPS (damage associated molecular patterns); bind to pattern recognition receptor (Toll like receptors) → proinflammatory cytokines, upregulation of MHC and costimulatory "ready for the fight"



CTS Collaborative Transplant Study

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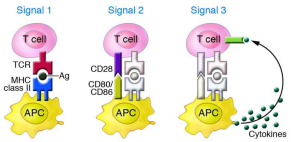
Adaptive Immunity

3 different signal are required for full T cell activation

- Signal 1: antigen-specific
- Signal 2: co-stimulation
- Signal 3: cytokines and additional signals



Animal models: without T cells are unable to reject an allograft

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Immunosuppressant Targets

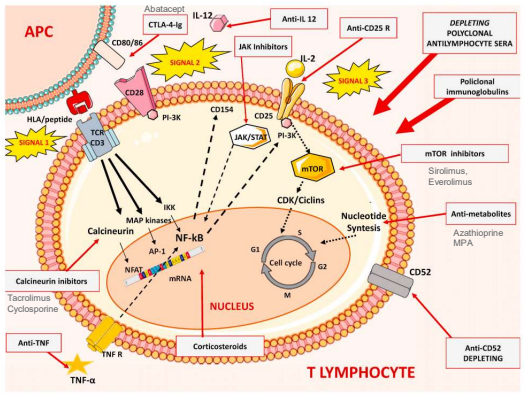

Fig. 1. Cell targets on T cells and antigen presenting cells and their interactions and immunosuppressive agents. Adapted from the book: Hernando Nefrología Clínica, 5th edition, Panamericana.

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Rejection

Activation of T cells → coordinated immune response between the adaptive and innate immune response against the allograft

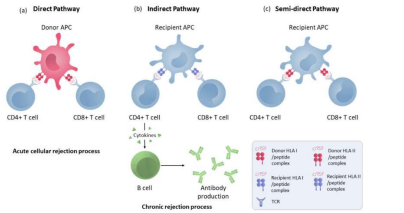

Figure 1. Direct, indirect and semi-direct allorecognition pathways. (**a**) T-lymphocyte direct pathway activation by HLA molecule presentation by donor APCs to the recipient's T cells. (**b**) Indirect pathway recognition by T CD4 and CD8 cells in which the alloantigens presented as peptides processed by recipient APCs through self-HLA molecules. CD4+ lymphocytes activate B cells to make antibodies. (**c**) T-cell semi-direct pathway activation: T cells recognise intact HLA molecules from the donor, but their own APC presents them.

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Immune Monitoring

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Immune Monitoring

Immune monitoring is *critically* important in prolonging allograft survival

- Our current challenge is to improve *long-term* allograft outcomes
- Current practices have improved outcomes, but *rejection* remains a significant barrier to long-term allograft survival
- Current and emerging non-invasive methods of post transplant immune monitoring are being developed

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Immune Monitoring

In order to improve long-term graft function and survival, a more *personalized immunosuppressive treatment*, according to individual anti-donor immune response status, is needed

- identification of potentially "high-risk" patients likely to develop acute rejection episodes or display an accelerated decline of graft function
- patients who might need immunosuppression intensification
- operationally "tolerant" patients suitable for immunosuppression minimization or weaning off

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Types of Immune Monitoring

1) Immunosuppression Drug Level Monitoring
   i. Calcineurin inhibitor
   ii. Mycophenolate mofetil
2) Protocol Transplant Biopsies
3) Blood HLA antibody Monitoring
4) Immune-based Biomarkers
   i. Urine
   ii. Blood

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Monitoring Immunosuppression

- CNI drug monitoring is vital in transplantation, given the narrow therapeutic index
- Due to inter- and intrapatient variability, drug monitoring allows for individualization of drug dosing in order to ensure efficacy and limit toxicity
  - Under-dosing is associated with higher rates of acute rejection
  - Over-dosing increases the risk of electrolyte disturbances, metabolic derangements, and nephrotoxicity

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Monitoring Immunosuppression

- CNI pharmacokinetics can be inconsistent and dependent on variables:
  - presence of meals, variability of gastrointestinal motility (diarrhea), concurrent usage of medications affecting CYP450 3A4 activity, decreased renal function
- More frequent monitoring of immunosuppression levels is necessary during periods of rejection, pregnancy, treatment for malignancy, infection and when medications that alter the pharmacokinetics of immunosuppressive agents are administered
- Pediatric patients may also require more frequent monitoring given their higher rates of rejection and nonadherence to medication regimens

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Immunosuppression monitoring

Calcineurin Inhibitors

- Antibody-based and high-performance liquid chromatography (HPLC) assays
- Targets are set depending on time post-transplant
- Assay turn around time needed is within 24 -36 hours; to make appropriate changes, especially early post-transplant

Mycophenolate mofetil

- Trough level is not reliable
- AUC measurement cumbersome but useful
- Dose in mg/m2

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Kidney Transplant Biopsies

- Serum creatinine has limited sensitivity in detecting early rejection or other pathologic processes occurring in the allograft
- Biopsy is the gold standard for diagnosing renal allograft rejection
- Transplant allograft biopsies are invasive but generally considered safe
  - complications (hemorrhage, graft loss, etc) reported in <1%
  - mostly performed in outpatient settings with high compliance from patients

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Protocol Transplant Biopsies

- The purpose of *surveillance (protocol)* biopsies is to detect the presence of early rejection or chronic allograft changes
  - Allows for more timely therapies and improve allograft outcomes
- Histologic evidence of rejection with a stable serum creatinine has been seen with the implementation of protocol biopsies

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Anti-HLA: Donor Specific Antibodies

Antibody mediated rejection is caused by circulating anti-HLA antibodies

- categorized as hyperacute, acute, or chronic
- Hyperacute rejection rates seen less often due to crossmatching, whereas acute and chronic rejection remain an obstacle to long-term allograft survival
- Monitoring of donor-specific antibodies (DSA) remains the cornerstone of antibody mediated rejection assessment

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Anti-HLA: Donor Specific Antibodies

- Formation of *de novo* DSA following transplant occurrs in up to 20% in the first 5 years after transplant
- *de novo* DSA are related to higher rates of AMR and allograft failure
- DSA monitoring should be considered with graft dysfunction, immunosuppression change or nonadherence, or suspicion of AMR
- If DSA is detected, a biopsy should be performed, and subsequent treatment given based on the biopsy results

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Immune monitoring - Kidney transplantation

The search for biomarkers continues….

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Conclusions

- New technologies have made HLA matching *more precise* and allows detection of lower titers of potentially clinically relevant anti-HLA antibodies resulting in improved short-term outcomes, but rejection remains a significant barrier to long-term allograft survival
- Therapeutic drug monitoring, serial serum creatinine measurements, protocol biopsies and HLA monitoring lack the refinement and practicalities needed to risk-stratify patients, guide immunosuppression therapy, and follow treatment responses
- Novel modalities in immune monitoring offer the possibility of noninvasive prediction and detection of rejection and allograft survival

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Kidney Transplantation and Infections

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1

Introduction

The fundamental purpose of immunosuppression is to *modulate* the immune system's ability to recognize the transplanted organ

But an overly suppressed immune system increases the risk of certain infections in pediatric solid organ transplant recipients

2

Introduction

- Modern immunosuppression regimens have reduced the rate of acute rejection BUT with more potent immunosuppression, infectious complications have become more frequent

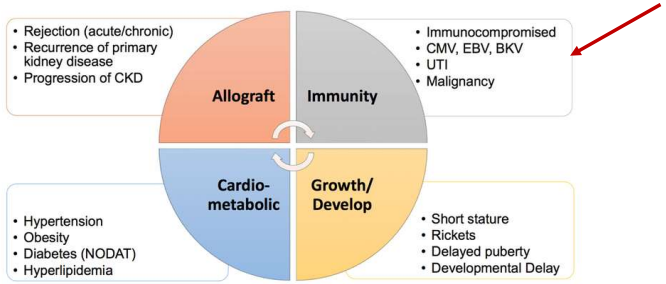
3

Objectives

1. Infection as a Complication in Pediatric Kidney Transplant Patients
2. Importance of Pre-Transplant Infection Evaluation and Vaccinations
3. Common Post-Transplant Infections
4. Brief Review of Emerging Post-Transplant Infections

4

Complications of Pediatric Kidney Transplant



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Introduction

- Pediatric transplant recipients are at risk for routine childhood illnesses *in addition* to infections related to immunosuppressed state
- Pediatric recipients are at risk for vaccine preventable infections due to suboptimal response to vaccines before and after transplant
- ~70% of kidney transplant recipients experience an infection episode within the first 3 years after transplant
- Hospitalization for vaccine preventable infections occurs in >15% of pediatric solid organ transplant recipients

6

Causes of Graft Failure

	Index Graft Failures		Subsequent Graft Failures		All Graft Failures	
	N	%	N	%	N	%
Total transplants with graft failure	2702	100.0	343	100.0	3045	100.0
Cause of Graft Failure						
Death with functioning graft	249	9.2	27	7.9	276	9.1
Primary non-function	63	2.3	2	0.6	65	2.1
Vascular thrombosis	252	9.3	39	11.4	291	9.6
Other technical	30	1.1	4	1.2	34	1.1
Hyper-acute rejection	15	0.6	4	1.2	19	0.6
Accelerated acute rejection	33	1.2	8	2.3	41	1.4
Acute rejection	352	13.0	44	12.8	396	13.0
Chronic rejection	960	35.5	129	37.6	1089	35.8
Recurrence of original kidney disease	179	6.6	33	9.6	212	7.0
Renal artery stenosis	15	0.6	0	0.0	15	0.5
Bacterial/viral infection	47	1.7	6	1.8	53	1.7
Cyclosporine toxicity	13	0.5	0	0.0	13	0.4
De novo kidney disease	8	0.3	2	0.6	10	0.3
Patient discontinued medication	125	4.6	8	2.3	133	4.4
Malignancy	34	1.3	2	0.6	36	1.2
Other/Unknown	327	12.1	35	10.2	362	11.9

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Cause of Death in Pediatric Transplant

Cause of Death	*n* (%)	Time to Death in Years,[a] Median (IQR)	Age at Death in Years, Median (IQR)
All cause	431	10 (4–20)	24 (18–35)
Cardiovascular	174 (40)	10 (4–21)	25 (18–36)
Cardiac arrest	51 (12)	6 (0–13)	27 (21–34)
Myocardial infarction	31 (8)	12 (23–27)	39 (26–43)
Stroke	26 (6)	5 (2–15)	17 (15–25)
Malignancy	50 (12)	19 (11–26)	33 (24–43)
Gastrointestinal	10 (2)	24 (18–30)	40 (34–36)
PTLD	10 (2)	10 (2–12)	19 (13–26)
Infection	74 (17)	6 (1–13)	21 (15–29)
Other	133 (31)	10 (4–20)	23 (18–33)
Withdrawal of treatment	36 (8)	16 (9–24)	23 (16–30)

Clin J Am Soc Nephrol. 2020 Mar 6; 15(3): 392–400.

8

Timeline of Infections after Kidney Transplant

Within the first 30 days of transplant:

- bacterial infections such as urinary tract infections
- bloodstream infections

May be associated with underlying pre-transplant conditions, nosocomial exposures or surgical complications

≤ 1 month	1-6 months	≥ 6 months
-Nosocomial infection	-Donor derived infection	-Community acquired pneumonia
-Technical, anastomotic complications	-Urinary tract infection	-Influenza
-Infection with antibiotic resistant organisms (MRSA, VRE, CRE)	-Adenovirus	-Urinary tract infection
-*Clostridium difficile* colitis	-Influenza	-Late onset CMV
-Donor derived infection	-Polyoma virus BK	-EBV (PTLD)
	-HCV	-HBV, HCV
	-*Mycobacterium tuberculosis*	-JC polyoma virus (PML)
	-Endemic mycoses	-Aspergillus, Mucormycosis
	Without PJP and antiviral prophylaxis -Pneumocystis	-Nocardia species
	-Herpesvirus infection (CMV, HSV, VZV, EBV)	
	-HBV	

P. Nambiar et al.

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Timeline of Infections after Kidney Transplant

1-6 months post-transplant:

- Latent pathogens from donor organs
- Reactivation of latent infection in recipient
- "Opportunistic infections"

Often due to lack of primary infection to transplant or an organ from a seropositive donor

≤ 1 month	1-6 months	≥ 6 months
-Nosocomial infection	-Donor derived infection	-Community acquired pneumonia
-Technical, anastomotic complications	-Urinary tract infection	-Influenza
-Infection with antibiotic resistant organisms (MRSA, VRE, CRE)	-Adenovirus	-Urinary tract infection
-*Clostridium difficile* colitis	-Influenza	-Late onset CMV
-Donor derived infection	-Polyoma virus BK	-EBV (PTLD)
	-HCV	-HBV, HCV
	-*Mycobacterium tuberculosis*	-JC polyoma virus (PML)
	-Endemic mycoses	-Aspergillus, Mucormycosis
	Without PJP and antiviral prophylaxis -Pneumocystis	-Nocardia species
	-Herpesvirus infection (CMV, HSV, VZV, EBV)	
	-HBV	

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Timeline of infections after kidney transplant

> 6 months post-transplant:

- community acquired infections
- ongoing risk of viral infections

Risks vary with degree immunosuppression and exposures

≤ 1 month	1-6 months	≥ 6 months
-Nosocomial infection	-Donor derived infection	-Community acquired pneumonia
-Technical, anastomotic complications	-Urinary tract infection	-Influenza
-Infection with antibiotic resistant organisms (MRSA, VRE, CRE)	-Adenovirus	-Urinary tract infection
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	-HCV	-HBV, HCV
	-*Mycobacterium tuberculosis*	-JC polyoma virus (PML)
	-Endemic mycoses	-Aspergillus, Mucormycosis
	Without PJP and antiviral prophylaxis -Pneumocystis	-Nocardia species
	-Herpesvirus infection (CMV, HSV, VZV, EBV)	
	-HBV	

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Pre-transplant evaluation

- A *thorough* infection evaluation of the donor and recipient is essential to minimize infections prior to, during, and after transplantation
- Detailed history and serologic assessment for both *vaccination responses* and *infections that risk reactivation* is necessary to assess eligibility and timing of transplantation
- Other risk factors for infection include:
  - chronic malnutrition, underlying anatomic defects, and young age at the time of transplantation

12

Vaccination

- Pediatric patients with CKD should receive standard immunizations as recommended by local and national authorities
- Transplant recipients are at a higher risk with *more severe* courses of vaccine-preventable infections
- Immunization of the patient and their close contacts is important *pre-transplant*

13

Vaccination

- 60-70% of children do not receive age-appropriate vaccinations prior to solid organ transplantation
- Pre-transplant immunization is strongly advised; mandatory in many centers
- With availability of dialysis, transplantation may be delayed until the appropriate vaccinations are complete
- Serologic assessment for vaccine responses can guide pre-transplant immunization recommendation

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Anti-microbial Use for Infection Prevention in Pediatric Kidney Transplantation

Anti-microbial prophylaxis is routinely used

- Skin (surgical) – standard
- PJP – trimethoprim-sulfamethoxazole
- CMV (HSV) – valganciclovir (acyclovir)
- Oral thrush - nystatin

UTI prophylaxis – not routinely recommended, but may be required in select patients

15

Major Infections

- Cytomegalovirus (CMV)
- BK Virus (Polyomavirus)
- EBV and Post-Transplant Lymphoproliferative Disease (PTLD)
- UTIs
- Infectious diarrhea
- Pneumocystis jirovecii pneumonia (PJP)

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Cytomegalovirus (CMV)

Table 1.
The Human Herpesvirus Family[1,a]

HHV	Common Name of Virus or Associated Illness	Subfamily
1	Herpes simplex virus type 1	α
2	Herpes simplex virus type 2	α
3	Varicella zoster virus	α
4	Epstein-Barr virus	γ
5	Cytomegalovirus	β
6/7	Exanthem subitum (roseola infantum)	β
8	Kaposi's sarcoma	γ

[a]HHV = human herpesvirus.

17

Cytomegalovirus (CMV)

CMV is one of the *most* important opportunistic pathogens in solid organ transplantation

- In healthy individuals CMV primary infection can present asymptomatic or as a nonspecific viral illness
  → Establishes life-long latency
- In transplant patients, can adversely affect outcomes for both allograft and recipient survival, increase the cost of transplantation and negatively impact health-related quality of life

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Cytomegalovirus (CMV)

Pre-transplant CMV immunoglobulin (IgG) serological testing in both donor and recipient establishes CMV disease risk and guides infection prevention strategies

1) Primary infection or re-infection
   - Usually transmitted via graft: CMV seronegative recipient with donor derived disease
2) Reactivation
   - CMV seropositive recipient

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CMV Risk Factors

Major risk factor is *mismatch* between Donor and Recipient

D/R Serostatus	Risk Factor
D+/R-	High Risk
D+/R+ D-/R+	Intermediate Risk
D-/R-	Low Risk (<5% incidence of CMV disease)

Use of highly immunosuppressive therapies ie. after rejection therapy
Younger age

20

Cytomegalovirus (CMV)

Infection
- CMV replication regardless of signs or symptoms
- PCR testing has rendered serology, antigen and culture-based testing obsolete

Disease
- CMV infection with attributable symptoms or signs
- Viral syndrome (fever, leukopenia, malaise, thrombocytopenia) or as tissue invasive disease

21

CMV management following transplantation

Currently 2 principal approaches:

1) A *prophylactic strategy* involved administration of antiviral agents:
- Prophylaxis for 6 months with valganciclovir post-transplant
- Prophylaxis after rejection therapy

2) A *preemptive strategy* involved periodic monitoring for viremia
- Treatment if develop CMV viremia
- Increased lab cost, coordination of blood testing

➢ CMV may be a factor in causing rejection

22

Cytomegalovirus (CMV) Treatments

- Valganciclovir and ganciclovir
  - first-line agents → CMV-DNA polymerase inhibitors
- Foscarnet/Cidofovir/CMVIg
  - reserved for refractory resistant organisms
- Cell therapy for CMV
  - In development

⟶ CMV resistance

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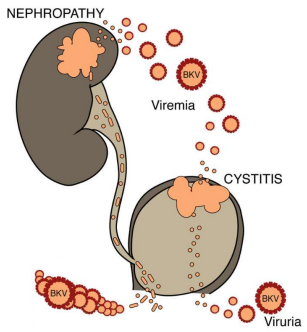
CMV Summary

- Children are at *higher* risk for CMV due to *higher* rates of seronegative status at time of transplant
- CMV disease risk is highest in recipients with no preexisting CMV-specific immunity (Donor+/Recipient-)
- Universal CMV prophylaxis or pre-emptive therapy reduces incidence of CMV infection and CMV disease with substantial reduction in morbidity and mortality
- Blood PCR or antigenemia should be used for monitoring of CMV infection

24

BK Virus (Polyomavirus)



- Small, non-enveloped, double stranded DNA polyomavirus
- Named with initials of the first patient diagnosed with the virus

25

BK Virus (Polyoma)

- Generally asymptomatic in immunocompetent hosts, who therefore rarely have clinical disease
- 90% have BK virus as a child - *"carried by many, bothered by few"*
- Establishes latency in uroepithelium after primary infection

➢ *BUT* BK polyomavirus poses a "unique challenge" after renal transplantation

26

BK Virus (Polyoma)

- Risk of invasive disease with immunosuppression and Donor-Recipient BKV "mismatch"
- Lysis of tubular cells releases BKV into renal tubules; virus particles leak into the interstitium and gain access to capillaries → viremia
- Reactivation or primary infection after transplantation can result in BK nephropathy and allograft loss

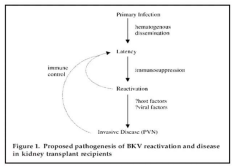


Figure 1. Proposed pathogenesis of BKV reactivation and disease in kidney transplant recipients

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Reported Risk Factors for BK viremia in Kidney Transplant Patients

Overall degree of immunosuppression (likely *most* influential)

High risk with uroepithelial injury

- Ischemia
- Acute rejection
- Ureteral trauma – ureteral stent

Donor is BK positive and recipient negative

Graft is from a deceased donor

- Peak time for BK reactivation is ~ 3 months post transplant

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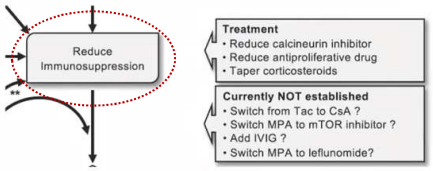
BK Virus Management

Can be hard to distinguish from rejection

Difficult to treat

Guidelines generally state



Hirsch et al, Clin Transplant 2019 Sep

29

Which is more nephrotoxic for kidney transplants: BK nephropathy or rejection?

Sandesh Parajuli[1] | Brad C. Astor[1,2] | Dixon Kaufman[3] | Brenda Muth[1] | Maha Mohamed[1] | Neetika Garg[1] | Arjang Djamali[1] | Didier A. Mandelbrot[1]

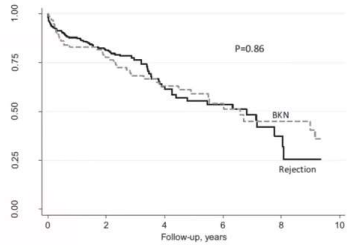


FIGURE 2 No difference in graft survival (uncensored) between rejection and BKN

Clinical Transplantation 2017

30

EBV (Epstein-Barr Virus)

Gamma herpesvirus which is a ubiquitous cause of infection in humans with a seroprevalence of over 90–95% of adults worldwide

- Exposure to EBV begins early in life with approximately 50% of children in developed countries becoming seropositive by age 5 years
- Timing of EBV infection varies with socioeconomic status; earlier acquisition occurs in developing countries and in those from lower socioeconomic conditions

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EBV (Epstein-Barr Virus)

- Pediatric organ transplant recipients are at greater risk of acquiring primary EBV infection compared to adult recipients given age seroprevalence
- EBV exposure after transplant may occur by “passenger” leukocytes from an EBV seropositive organ donor, through blood products or via typical community exposures
- Primary EBV infection is a major risk factor for developing symptomatic EBV disease including PTLD; pediatric recipients are at greater risk
- Nucleic acid amplification test (NAT) such as PCR of peripheral blood to quantitate viral load has revolutionized the ability to monitor and help diagnose EBV infection

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Spectrum of EBV Infection After Transplant

- Asymptomatic infection
- Non-specific viral syndrome
- Mononucleosis
- EBV hepatitis
- EBV enteritis
- PTLD
- EBV+ spindle cell (smooth muscle) tumors

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Post Transplant Lymphoproliferative Disease (PTLD)

- 85% are EBV infection associated
- *Range from asymptomatic to reactive hyperplasia (mono-like illness) to lymphoma like disease*
- Polyclonal lesions (usually earlier) have a better prognosis than late lesions (may be monoclonal)
- Highest rate of EBV+ PTLD is in the 1st year post-transplant

34

PTLD Treatment

Treatment consists of:

- Reducing or removing immunosuppression
- Rituximab in many cases
- Chemotherapy in extreme circumstances

➢ *Ganciclovir (Valgan) and acyclovir*

- Inhibit *lytic* EBV DNA replication *in vitro*
- Neither agent has *in vitro* activity against EBV latently infected B cells nor have been effective in treating healthy individuals with acute EBV infection
- Majority of EBV infected cells within PTLD lesions are transformed B cells that are *not* undergoing lytic infection

35

PTLD Outcomes

- Successful regression in 23-86% of patients who undergo reduction of immune suppression alone or in combination with other therapies
- Treatment failures due to tumor unresponsiveness
- Graft rejection is a complication of reduction or withdrawal of immune suppression

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Urinary Tract Infections (UTIs)

- UTI is a common complication after renal transplant, accounting for 45–72% of all infections and 30% of sepsis hospitalization in adults
- Febrile UTI reported in 28% of pediatric kidney transplant recipients
- Highest risk for UTI is within the first 6 months post-transplant
- Common risk factors for post-transplant lower and/or upper urinary tract infections include:
  - female sex, young age, reflux prior to transplant, deceased donor, extended duration of bladder catheter or stent, other instrumentation

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Urinary tract infection (UTIs)

Most common causative pathogen post-transplant is E. coli, accounting for 70% of cases;

- Other organisms include gram-negative and gram-positive bacteria - Pseudomonas, Enterococcus, coagulase-negative Staphylococcus
- Reflux post-transplant
- Neurogenic bladder is a known risk factor for bacteriuria and recurrent UTI, placing these children at higher risk for UTI post-transplant

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Infectious Diarrhea

- Gastrointestinal issues are common
- Diarrhea occurs in up to 22% of kidney recipients in the first 3 years post-transplant
- Increasing incidence is Clostridium difficile
  - A single US center reported up to 12% of pediatric transplant patients develop C. difficile infection
- Antimicrobial exposure is a risk factor for the development of CDI
  - ampicillin, clindamycin, cephalosporins, and fluoroquinolones being most commonly associated with the development of disease

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Infectious diarrhea

- Other commonly reported bacterial pathogens include nontyphoidal Salmonella species, Campylobacter jejuni, other enteric pathogens such as Shigella, Yersinia, and Escherichia coli
- Viral etiologies such as norovirus, etc

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Pneumocystis jirovecii pneumonia (PJP)

- Opportunistic and prevalent fungal infection in immunocompromised hosts, including kidney transplantation
- *Life-threatening* infection after kidney transplantation
- Before implementation of prophylaxis, PJP developed in up to 15% of SOT recipients
- Less common with effective prophylaxis, but remains an issue among kidney transplant recipients during the 1st year
- Occurrence of PCP >1 year after transplant *with* effective prophylaxis is rare, but cases up to 13 years after transplant have been reported

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Pneumocystis jirovecii pneumonia (PJP)

- Definite diagnosis requires identification of the microorganism either by microscopy or PCR with the sample taken from BALF
- Risk factors: highly immunosuppressed patients, infected with CMV, prolonged neutropenia and higher-dose corticosteroid therapy
- *2020 Kidney Disease: Improving Global Outcomes (KDIGO)* guidelines recommend TMP-SMX as a first-line therapy for 3–6 months after KTx and at least 6 weeks during and after treatment for acute rejection

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Other infections

- HSV
- Fungal
- Nocardia
- West Nile
- COVID-19

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Human Immunodeficiency Virus (HIV)

- Kidney transplantation is an appropriate therapeutic option for HIV-infected patients with ESRD
- Infections are a major source of morbidity and mortality in the post-transplant period
- Infections in HIV-infected recipients during the post-transplant period are similar to those seen in non-HIV-infected patients
  - although the incidence rates of tuberculosis and fungal infections seem to be higher
- After transplantation, HIV-infected SOT recipients follow same antimicrobial prophylaxis and transplant and anti-HIV immunization
- Antiretroviral regimen is based on those medications that prevent pharmacokinetic interactions between antiretroviral drugs

44

Emerging infections

- New or re-emerging pathogens may impact transplant patients at any time
- Infections from atypical Mycobacterium species are more common in the immunocompromised patients
- Cerebral toxoplasmosis has been reported in the adult kidney recipients with up to 50% mortality
- In the past few years, arboviral illnesses such as Chikungunya, Dengue, and Zika virus that are transmitted via the bite an infected Aedes aegypti mosquito have become a concern in transplant patients
- Increasing infections due to multidrug resistant organisms

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Conclusion

- Infection complications are common and rising among kidney transplant recipients; including pediatric patients
- Infections commonly seen in children include CMV, EBV, BKV, UTIs and infectious diarrhea, but many other infections can occur
- There is significant morbidity, mortality and costs from infections including those that are vaccine preventable, demonstrating the importance of immunizing all transplant candidates and recipients

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Conclusion

- If we win the battle with prevention of rejection, we may further increase the risk of infectious complications
- Guidelines provide a framework on screening, work-up, and management for many infections encountered in the post-transplant period although much of the literature is based on *adult populations*
- Approaching an infectious evaluation in a pediatric kidney recipient requires practitioners to be up-to-date on the literature and collaboration with other experts in the field to best manage this complex population

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Peritoneal Dialysis

Prof. 'Tola Odetunde
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Learning objectives

- Describe the principle of dialysis
- Understand the access to the peritoneal cavity for PD
- Indications and contraindication of Acute PD
- Describe the key factors for successful PD access management
- Describe the main components of PD catheters
- List the different insertion techniques

Generally :

Dialysis refers to the diffusion of small molecules down their concentration gradient across a semipermeable membrane.

There are two types of dialysis:

1. Haemodialysis
2. Peritoneal dialysis

- Acute or Chronic

What are the types of dialysis ?

Choice of modality:

- Available facilities
- Both PD., & HD can be used for acute RRT.
- HD will reverse metabolic abnormality much rapidly than PD.
- There may be contraindications to acute PD, such as recent abdominal surgery, aortic vascular graft, abdominal drains, …etc,
- Acute PD is associated with an increase risk of morbidity (especially peritonitis).

- **CHOICE OF RRT**
- Renal unit

- Peritoneal dialysis

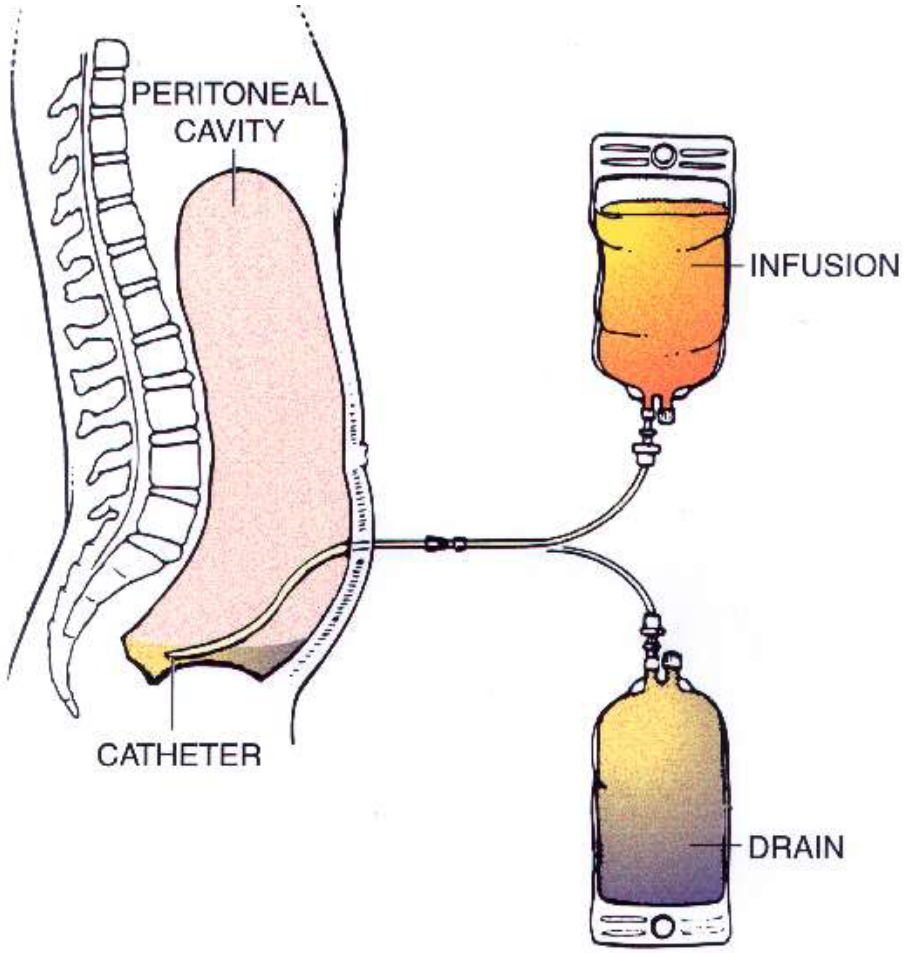
-Haemodialysis

- .Picu

-Peritoneal dialysis

-Various forms of CRRT

Peritoneal Dialysis


PERITONEAL
CAVITY
INFUSION
CATHETER
DRAIN

Indications for Acute dialysis:

- Uremic symptoms (e.g., anorexia, nausea, vomiting, encephalopathy)
- Electrolytes or acid-base abnormalities refractory to medical therapy, especially:

1. Hyperkalemia
2. Metabolic acidosis
3. Hyponatremia

Indications for Acute dialysis:

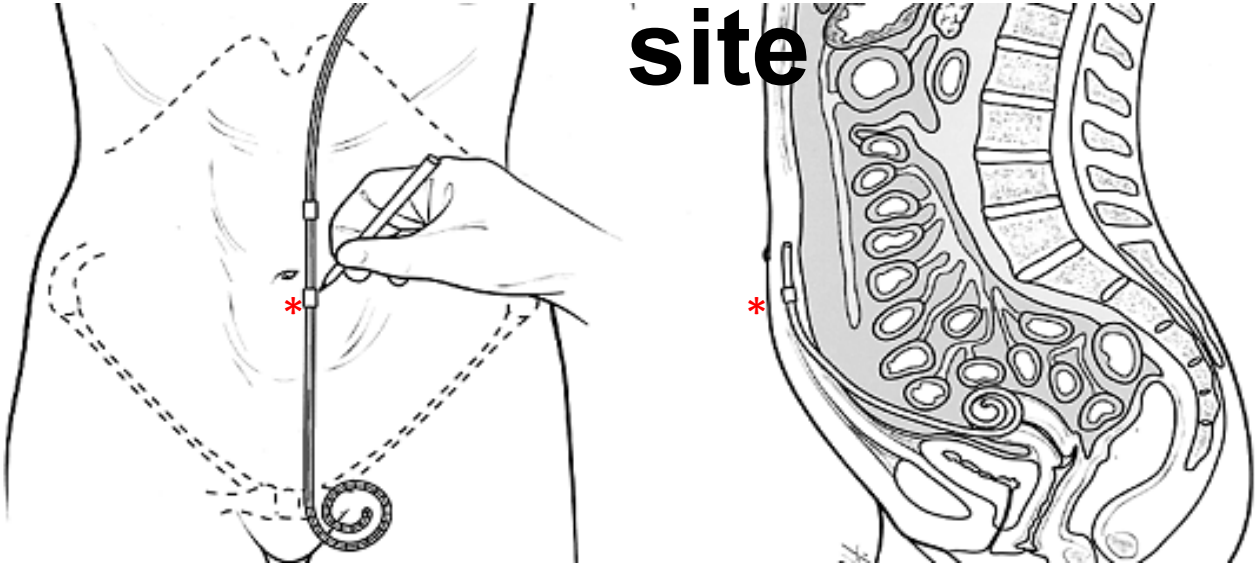
- Fluid overload or pulmonary oedema refractory to diuretic therapy.
- Uremic pericarditis
- Others:

1. Poisoning (Lithium, methanol, ethylene glycol), PPD.
2. Hypothermia
3. Hyperuricemia
4. Metabolic alkalosis.

Pre-dialysis preparation:

- Good physical examination. e.g. Abdominal exam. is a prerequisite to proceeding with P.D.
- Pt with lung diseases tend to tolerate excess fluid less well &can become short of breath when only mildly overloaded.
- Pts. with pericarditis, IHD. shoud be given special consideration.
- Serological examination.e.g hepatitis B positive pt must be isolated if in HD.
- Insertion of acute vascular access in H.D &peritoneal dialysis catheter if in P.D.
- Internal jugular venous catheter become the preferred temporary venous access.
- Obtain baseline RFT.

Choice of catheter insertion site



- For each style and size of catheter, the insertion site is determined by noting the deep cuff position * when the upper border of the catheter coil is aligned with the upper border of the pubic symphysis.
- Determine whether mid abdominal, high abdominal or pre sternal location is most appropriate for individual patient
- Catheter insertion exit-site location must be done patient seated and standing
- Mark exit-site location with indelible ink using stencils or actual catheter

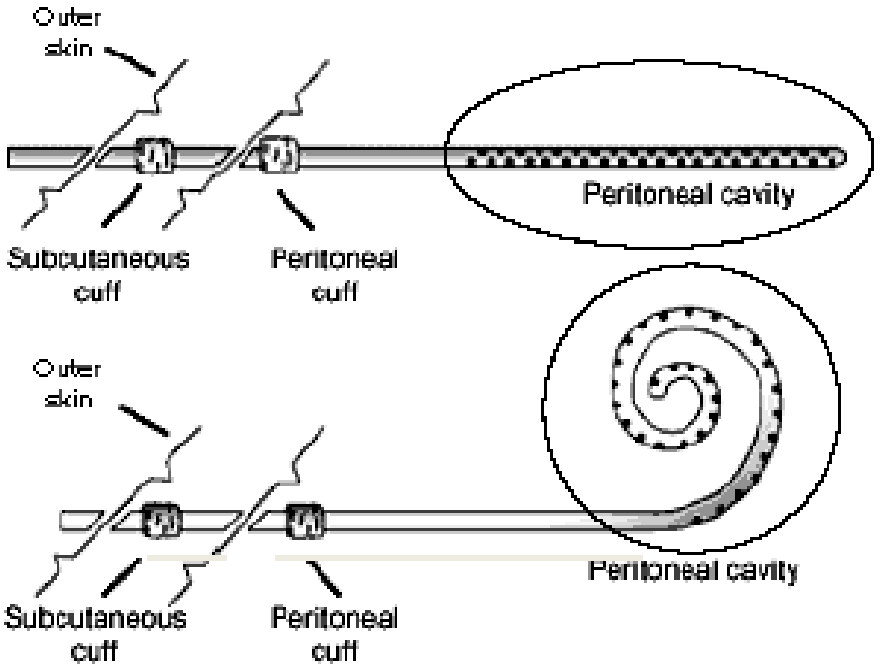
ISPD PD Access Guidelines 2005

PD Catheters / The choice

- The ideal catheter provides reliable, rapid dialysate flow rates without leak or infection*
- Successful outcome of a catheter is very much dependent on meticulous care and attention to detail.*
- The ideal catheter should be safe, simple an long-lasting.**
- No particular catheter has been definitely shown to be better than standard silicone Tenckhoff
- **Double cuff has shown superior survival / single cuff**

*Peritoneal Catheters and exit site practices toward optimum ,Peritoneal access: a review of current developments,
*PDI, Vol 25; 2005***PD Today; Contrib Nephrol, Basel Karger 2003 Vol 140*

Catheter design

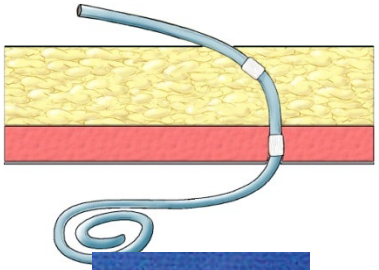


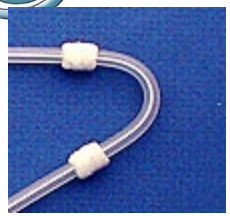
3 parts:

- **Intraperitoneal segment**
  - Straight or coiled
- **Intramural segment (within the abdominal wall tunnel)**
  - Straight or bend
  - Bead and flange
  - Cuffs (Single or dual)
- **External segment (outside the skin)**

With an important radio-opac stripe

Extra-peritoneal segment



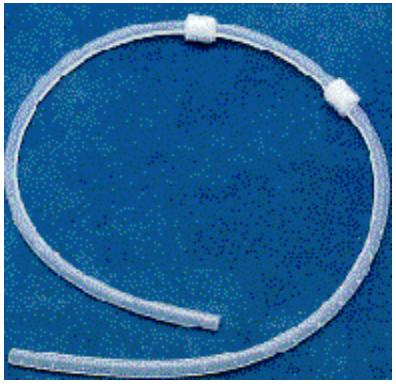


- Straight: ideally for lateral exit site. Straight tube inserted in arcuate configuration can cause catheter tip migration
- Must be implanted in a tunnel that exactly “reflects this shape
- Arcuate: preformed bend to provide a caudal directed exit site without strain on the cuffs and to balance the extrusion forces on the deep cuff
- Straight: is the most common design, presence of side holes to enhance in-and outflow

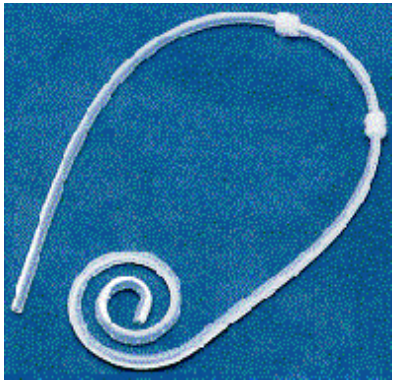
Intra-peritoneal segment

- Coiled: Increased bulk of tubing to separate parietal and visceral layers of peritoneum.Tip is more protected, less inflow pain, less risk for catheter migration and omental wrapping.(opinion)

Types of catheters

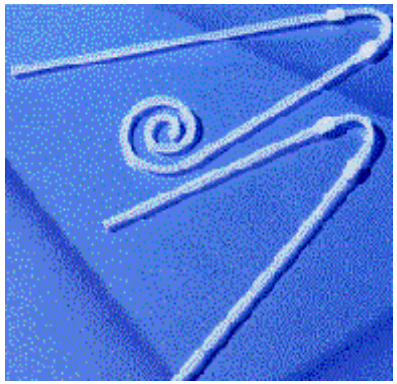


Straight Tenckhoff cath.
2 cuffs

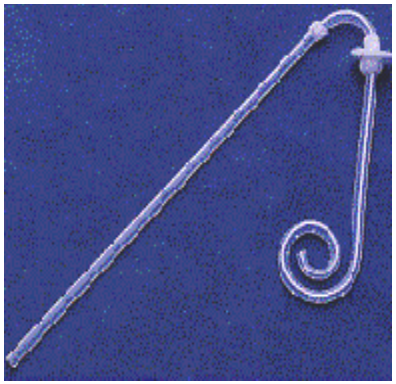


CoiledTenckhoff cath.
2 cuffs

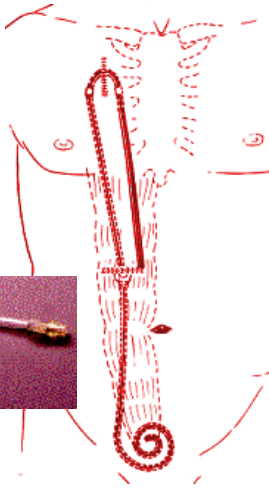
Coiled
1 cuff



Swan Neck Tenckhoff
Permanent bend (180^{o})
between the 2 cuffs



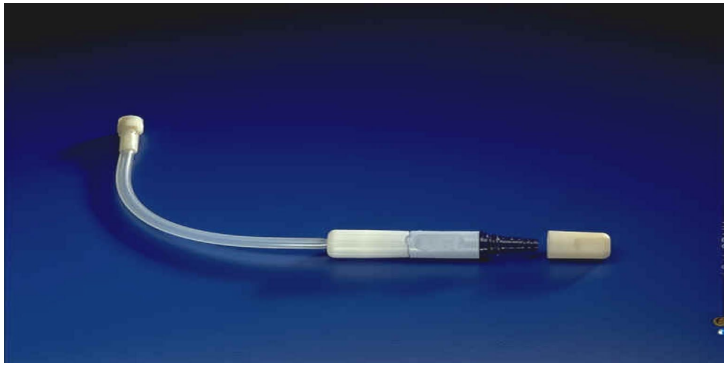
Swan Neck Missouri
2 cuffs



Pre sternal
1 cuff

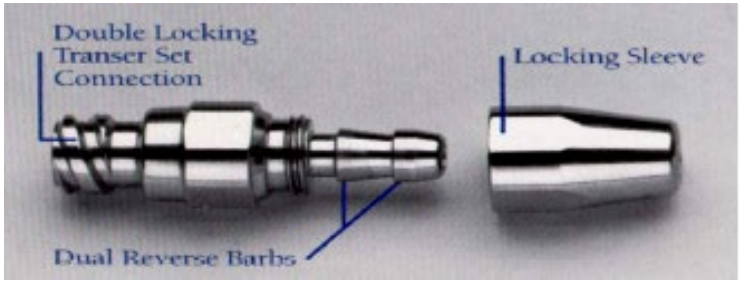
Accessories of PD catheter

- Important to have the accessories being connected before leaving the operating room.



Transfert set

Minicap

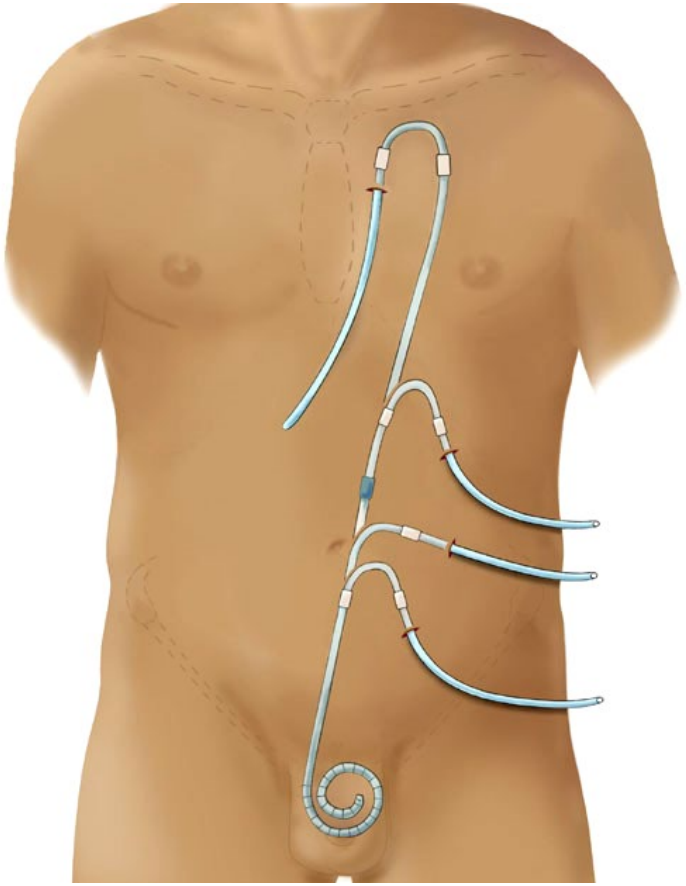


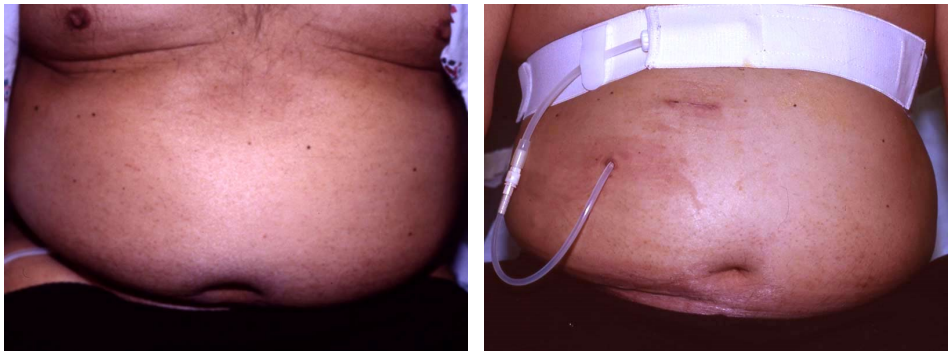
Titanium adaptor:

Secure seal and reduces risk of peritonitis

- One size for all ? -
There Must be flexibility in the choice of exit site

- Presternal
- Sternal (high)
- Abdominal central
- Abdominal low

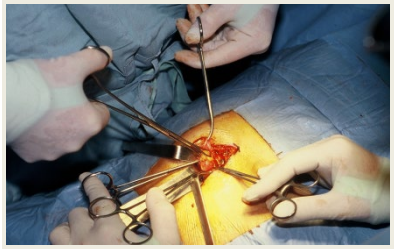




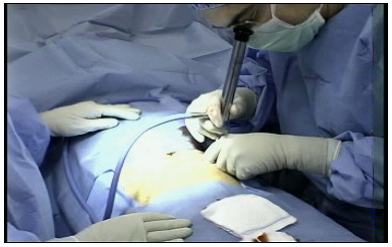
Courtesy Dr Crabtree, CA, USA

Implantation methods

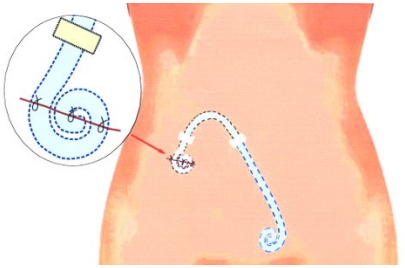
- Open dissection



- Laparoscopic



- Percutaneous (Seldinger): Peritoneal cavity is entered with a priming needle (catheter over a needle) into the superior aspect of the wound and through the linea alba.



- Moncrief :The external segment is completely buried in a subcutaneous tunnel . The entire wound is then closed for 4–6 weeks with no exit site.

There is no technique of insertion of a peritoneal dialysis catheter that has consistently proven to be superior in the prevention of peritonitis. (Level II evidence): *Guidelines* **NEPHROLOGY** 2004; **9,** S65–S71

Catheter insertion Recommandation

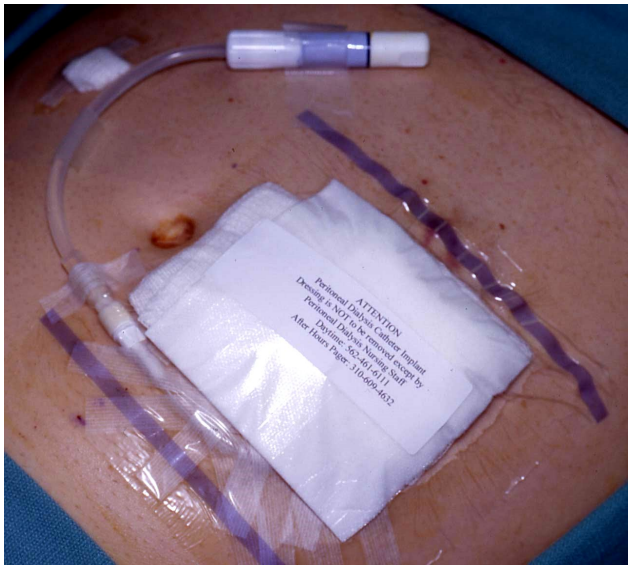
- Before inserting the catheter, eliminate air from catheter cuffs prior to implantation by soaking and gently squeezing cuffs in saline solution
- A residual of 250 to 300 ml is left in the abdomen to reduce the likely-hood of intra-peritoneal structures sucking up against the catheter toward the end of the drainage phase
- Catheter anchoring sutures at exit site should never be used

ISPD PD Access Guidelines 2005

Post insertion recommendation (1)

- Dressing should not be changed more than once a week during the healing period and must be performed by experienced PD nurses.
- Use of mupirocine or gentamicin cream at the exit site is recommended to reduce exit site infections.

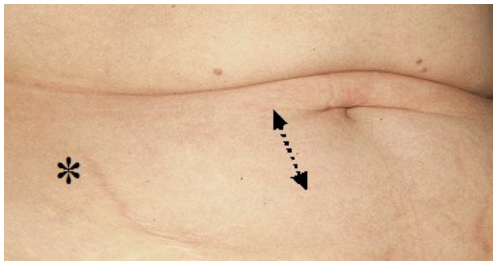
(Evidence level A) European guidelines 2005



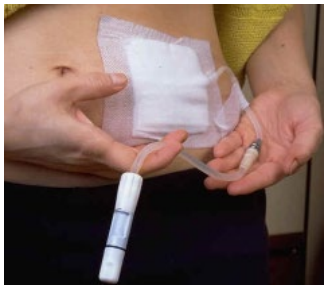
- Always keep the catheter well immobilized to the skin: this reduces the incidence of trauma and promotes tissue growth.
- Shower allowed (not soaking in bath) when the exit site is classified as good: usually after 4 weeks to 6 weeks

Clinical Key activities * (ISPD recommendation)

- **Pre-operative**
  Pre-dialysis patient education
    Exit site marking
    Pre-op preparation



- **Intra-operative**
  Prepare patient
    Prepare material
    Check catheter patency
    Dressing
- **Post-operative**
  Dressing
    Patient education: hygiene, nutrition,
    PD procedures



- **Chronic**
  Immobilization
    Dressing
    “Monitoring”

Contraindication for peritoneal dialysis:

- **Absolute:**
- Loss of peritoneal function
- Adhesions that limit dialysate flow
- Recent abdominal wounds
- Abdominal fistulas
- Abdominal wall defects that prevent effective dialysis or increase infection risk (eg, irreparable inguinal or diaphragmatic hernia, bladder extrophy)
- Patient's condition not amenable to dialysis

Contraindication for peritoneal dialysis:

- **Relative:**
- Abdominal wall infection
- Frequent episodes of diverticulitis
- Inability to tolerate large volumes of peritoneal dialysate
- Inflammatory bowel disease
- Ischemic colitis
- Morbid obesity
- Peritoneal leaks
- Severe undernutrition

COMPLICATIONS OF P.D:

1- mechanical include pain with dialysate inflow or outflow,dialysate leakage ,scrotal edema, intestinal perforation & lower back pain .

2- cardiovascular include fluid overload , hypertension ,hypotension .

3-neurologic , include seizures and rarely DDS

4- infections include peritonitis .

5-metabolic include hypreglycemia,hyper-or hypokalemia , hyper-or hyponatremia protein depletion .

FURTHER PLAN :

According to the pt state and the underlying causes .

If the pt is in acute renal failure ___ treat the underlying cause .

If the pt is in chronic renal failure ___ regular follow up ,perminant vascular access , preparations for transplantation.

THANK YOU

Uninary Tract Infections in Children

Rick Kaskel, MD PhD
Chief Emeritus Professor, Nephrology

IPNA Teaching Course
ISN Sister Ceners
Port Harcourt-NY and Ibadan-Calgary
19-21 June 2023

The Children's Hospital at Montefiore

THE PEDIATRIC HOSPITAL FOR:
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

- A 4-year-old girl presents to the emergency department with vomiting, fever to 39° C (102.2° F), and right flank pain. Laboratory evaluation reveals: white blood cell count, 22,000/mm^3 with 10% bands and 70% segmented neutrophils; urine dipstick, positive for nitrite and leukocyte esterase; and greater than 100 white blood cells per high-power field in an unspun urine.
- Of the following, the MOST appropriate therapy is

- A. intravenous ampicillin
- B. intravenous cefotaxime
- C. intravenous ciprofloxacin
- D. oral nitrofurantoin
- E. oral trimethoprim/sulfamethoxazole

Answer: B

- Cefotaxime is the most appropriate single-agent parenteral antibiotic for the treatment of APN. It has a broad spectrum of coverage that includes aerobic Gram-negative organisms (eg, E coli, Proteus, Serratia), anaerobic Gram-negative organisms (eg, Bacteroides), and Gram-positive organisms (eg, group B streptococci).

- Because about one third of the organisms causing urinary tract infections are resistant to ampicillin, this would not be adequate initial therapy for pyelonephritis.

- If ampicillin is to be administered intravenously, it should be combined with an aminoglycoside (eg, gentamicin or tobramycin). Such a broad-spectrum combination covers Gram-negative organisms, including Pseudomonas, enterococci, and other Gram-positive cocci.

Journal of Pediatric Urology (2021) 17, 200–207

Review Article

Update of the EAU/ESPU guidelines on urinary tract infections in children

Lisette A. 't Hoen [a,*], Guy Bogaert [b], Christian Radmayr [c], Hasan S. Dogan [d], Rien J.M. Nijman [e], Josine Quaedackers [e], Yazan F. Rawashdeh [f], Mesrur S. Silay [g], Serdar Tekgul [d], Nikita R. Bhatt [h], Raimund Stein [i]

Review > Pediatrics. 2021 Feb;147(2):e2020012138. doi: 10.1542/peds.2020-012138.

Contemporary Management of Urinary Tract Infection in Children

Tej K Mattoo [1], Nader Shaikh [2], Caleb P Nelson [3]

Affiliations + expand

PMID: 33479164 DOI: 10.1542/peds.2020-012138

Epidemiology

- The prevalence of UTI is approximately 5% in infants and children <2 years of age with unexplained fever.
- The incidence of 1st time UTI is highest during the first year of life.
- During the first few months of life, the incidence of UTI in boys exceeds that in girls.
- By the end of the first year and thereafter, both first-time and recurrent UTIs are most common in girls.
- Caucasian children have a two- to fourfold higher prevalence of UTI compared to African American children.
- Based on data from Hoberman, A, Chao, HP, Keller, DM, et al. Prevalence of urinary tract infection in febrile infants. J Pediatr 1993; 123:17 and Shaw, KN, Gorelick, M, McGowan, KL, et al. Prevalence of urinary tract infection in febrile young children in the emergency department. Pediatrics 1998; 102:e16.

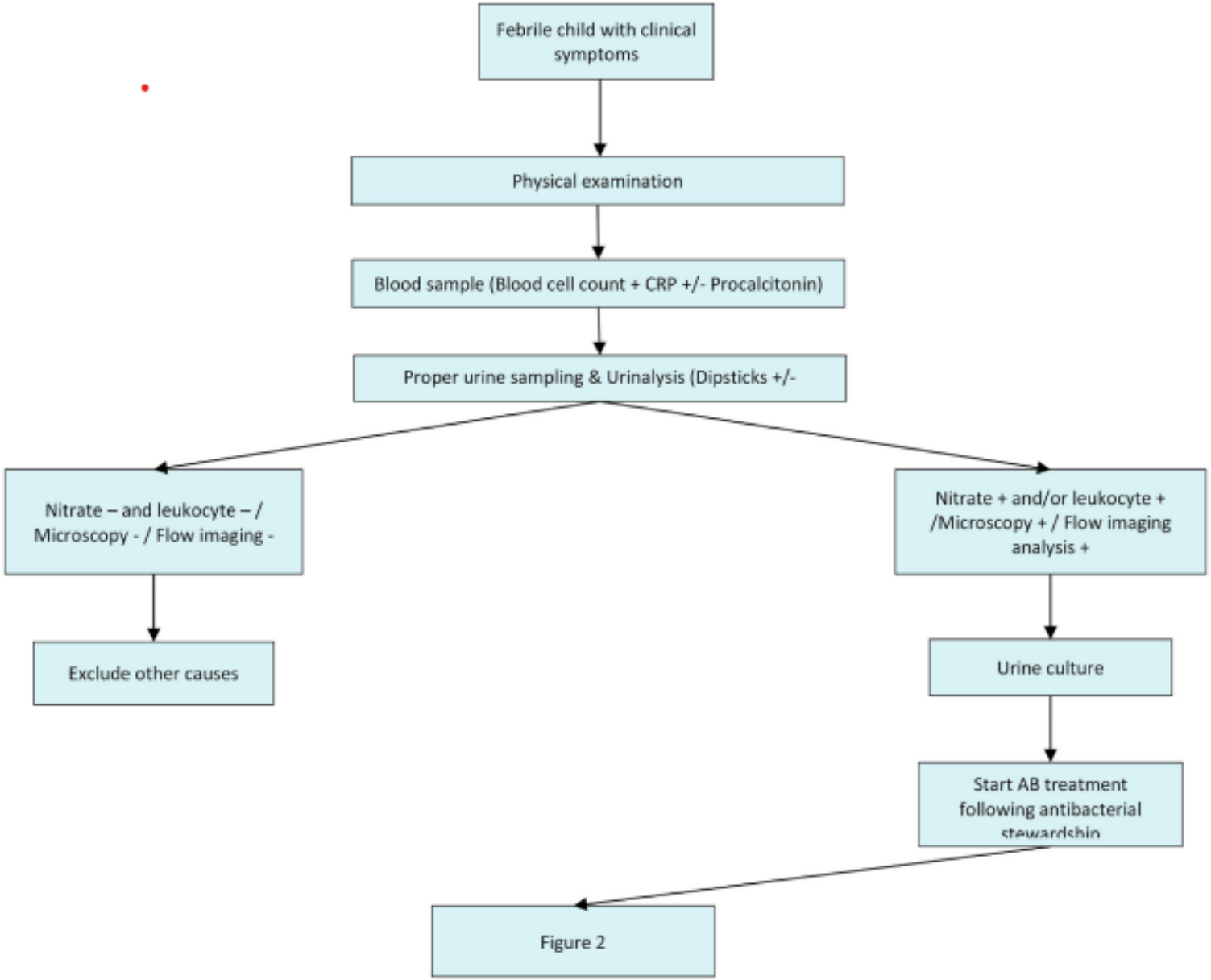


Fig. 1 Flowchart for basic diagnostic evaluation and subsequent management of UTI.

Classification of Urinary Tract Infection

- *Acute pyelonephritis (APN)* - upper tract infection
- *Cystitis* – lower-tract infection
- *Asymptomatic bacteriuria* – positive urine culture without any manifestations of infection and occurs almost exclusively in girls

Clinical Features

- **Younger children**
  - Fever
  - GI symptoms - Vomiting, diarrhea, poor feeding, jaundice
  - Irritability
  - Foul smelling urine

- **Older Children**
  - Fever
  - Urinary symptoms – dysuria, urgency, frequency, incontinence, macroscopic hematuria
  - Abdominal Pain
  - FTT

History

- Duration of fever
- Recent illnesses, antibiotics administered
- Chronic constipation
- Chronic urinary symptoms – incontinence, lack of proper stream, frequency, urgency, withholding maneuvers
- Previous UTIs
- Vesicoureteral reflux
- Family history of frequent UTIs, VUR, and other genitourinary abnormalities

Physical Exam

- General appearance
- Vital signs: Blood pressure, temperature
- Abdominal Findings:
  - Mass may indicate obstruction, hydronephrosis, or another anatomic abnormality.
  - Costovertebral angle tenderness
  - Suprapubic tenderness.
- Back Findings:
  - Sacral dimple or birthmarks overlying the spine may be associated with an underlying anomaly of the spinal cord.
- External genitalia:
  - vulvovaginitis, STDs, signs of abuse, pinworms
  - Anatomic abnormalities

Causes

- *Escherichia coli* - By far the most common organism, causing more than 75-90% of all UTIs.
- *Staphylococcus saprophyticus* - female adolescents
- *Klebsiella oxytoca* and species
- *Proteus* species
- *Enterococcus faecalis*
- Group B *Streptococcus*
- Adenovirus

Collection of Urine Specimen

- Clean catch midstream urine – toilet trained children.
- Catheterized specimen – children in diapers.
- Suprapubic aspiration
  - Catheterization is not feasible (eg, penile and labial adhesions).
  - Results from catheterized specimen are inconclusive

The use of a sterile bag is generally not recommended for dipstick, microscopic analysis, or culture. Up to 85% of positive cultures from bag urine specimens will represent false+ results; therefore, results are useful only if negative.

Urine Culture: Interpretation in Diagnosis of a UTI

Method of Collection	UTI Present
Suprapubic Aspiration	Gram negative bacilli: any number Gram positive cocci: $>2x10^3$ CFU/mL
Catheterization	Febrile infants or children usually have $>50x10^3$ CFU/mL or a single urinary pathogen, but infection may be present with counts from $10x10^3$ to $50x10^3$ CFU/mL
Midstream clean catch, voided	$>10^5$ CFU/mL of a single urinary pathogen

From Hellerstein S. Pediatr Clin North Am 1995; 42:1142
CFU/mL, Colony-forming units per milliliter

- **You are seeing an 11-year-old girl who had a previous history of urinary tract infection at age 2. Previous radiographic studies have included renal ultrasonography and voiding cystourethrography, both of which yielded normal results. She has no complaints at this time. Urinalysis reveals 1+ nitrites, but is otherwise negative. Results of a urine culture from a clean catch specimen reveal greater than 100,000 cfu/mL Escherichia coli.**
- **Of the following, the MOST appropriate treatment for this patient is:**

- A. intramuscular ceftriaxone
- B. observation
- C. oral ciprofloxacin
- D. oral nitrofurantoin
- E. oral trimethoprim-sulfamethoxazole

Answer: B

- Several prospective studies have shown that there is no value to identifying or treating asymptomatic children who have bacteriuria, such as the girl in the vignette.
- Unnecessary treatment only leads to the emergence of resistant strains of bacteria; many patients clear the bacteriuria uneventfully.

Comparison of Urinary Diagnostic Tests

TABLE 1. Sensitivity and Specificity of Components of the Urinalysis, Alone and in Combination (References in Text)

Test	Sensitivity % (Range)	Specificity % (Range)
Leukocyte esterase	83 (67–94)	78 (64–92)
Nitrite	53 (15–82)	98 (90–100)
Leukocyte esterase *or* nitrite positive	93 (90–100)	72 (58–91)
Microscopy: WBCs	73 (32–100)	81 (45–98)
Microscopy: bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase *or* nitrite *or* microscopy positive	99.8 (99–100)	70 (60–92)

PEDIATRICS Vol. 103 No. 4 April 1999

Other Laboratory Tests

- **WBC casts** – suggests renal involvement but are rarely seen.
- **Renal function testing -** An increased BUN and/or creatinine level should raise the suspicion for hydronephrosis or renal parenchymal disease
- **Electrolyte measurements** – abnormalities 2^{o} to vomiting and diarrhea, secondary pseudohypoaldosteronism
- **Leukocytosis** - nonspecific and does not help in distinguishing lower UTI from upper UTI.
- **ESR** - in the presence of a febrile UTI, > 30 mm/h is highly predictive of acute pyelonephritis
- **Elevated C-reactive protein** - sensitive but nonspecific markers of renal parenchymal involvement in the febrile infant and child with UTI.
- **Blood culture**

- A 2-year-old girl is admitted to the hospital with fever and vomiting. Findings include right costovertebral tenderness; white blood cell count, 20,000/mm3; creatinine, 0.3 mg/dL; and urinalysis, >100 white blood cells per high-power field. Symptoms resolve after receiving parenteral antibiotic therapy. Urine culture grows >100,000 colonies/mm3 of Escherichia coli.
- Of the following, the most appropriate INITIAL evaluation for this girl is

- A. intravenous pyelography
- B. renal arteriography
- C. Tc99-diethylenetriaminepentaacetic acid renal scintigraphy
- D. urodynamic studies
- E. voiding cystourethrography

Answer: E

- It has been reported that 25% to 30% of girls younger than 10 years of age who develop UTIs have vesicoureteral reflux.

- VCUG is indicated for this age group, including the girl described in the vignette. Some physicians recommend a VCUG for all boys; girls younger than 5 years of age after the first UTI episode, irrespective of site; and all pediatric patients who have acute pyelonephritis.

Childhood UTI
Goals of Imaging

- Primary
  - Identify risk factors for infection
  - Identify risk factors for renal damage
- Secondary
  - Confirm diagnosis of acute pyelonephritis
  - Detect renal scarring
  - Assess renal function

Imaging

- Routine imaging is recommended for:
  - Children younger than 5 years of age with a febrile UTI.
  - Girls younger than 4 years of age with a first UTI.
  - Males of any age with a first UTI.
  - Children with recurrent UTI.
  - Children with UTI who do not respond promptly to therapy.

Imaging Tools

- Sonography: anatomy
- Tc-99m DMSA: renal function, scar, infection
- VCUG: grade reflux, bladder function/anatomy,
  image urethra (males)
- Functional MRI urography

Renal Ultrasonography

- Non-invasive test that can determine the
  - size and shape of the kidneys.
  - Presence of duplication and dilation of the ureters.
  - Existence of gross anatomic abnormalities
- Demonstrates only 30% of renal scars.
- Does not provide information regarding renal function.
- Useful in the diagnosis of renal or perirenal abscess, urolithiasis, hydronephrosis, hydroureter, ureteroceles, and bladder distension.

- A 3-year-old girl presents with fever, left flank pain, and dysuria. On physical examination, blood pressure is 100/58 mm Hg, temperature is 39° C (102.2° F), and there is left costovertebral angle tenderness. A catherized urine culture grows more than 100,000 CFU/mm3 of Escherichia coli. Results of renal ultrasonography are normal, and voiding cystourethrography shows bilateral grade 3 vesicoureteral reflux (VUR). You prescribe antibiotics for 10 days.
- Of the following, the next BEST step is

- A. no prophylaxis
- B. periodic urine cultures for 6 months
- C. prophylaxis with antibiotics for 6 months
- D. prophylaxis with antibiotics until the VUR resolves
- E. referral to a urologist for surgical correction

Answer: D

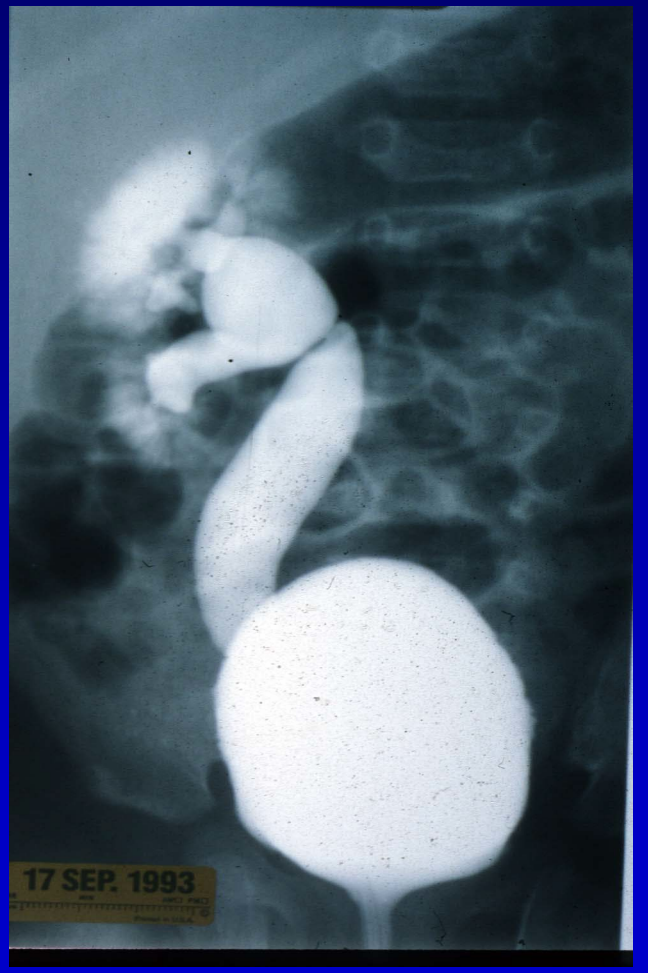
- Long-term prophylactic antibiotics are recommended for children in whom VUR is documented.

- Usually the antibiotic is continued until the reflux resolves. Prophylactic antibiotics could be stopped in children who have low grades of VUR or who have reached 5 to 6 years of age without any breakthrough infection while receiving prophylaxis.

- Children who have bladder instability, abnormal voiding patterns, or neurogenic bladder in conjunction with recurrent UTIs may benefit from antibiotic prophylaxis.

Voiding Cystourethrogram (VCUG)

- Useful for visualizing the urethral and bladder anatomy.
- Establishes the presence and degree of vesicoureteral reflux (VUR) and posterior urethral valves.
- Involves catheterization to fill the bladder with a radioopaque liquid and recording of VUR during voiding.
- May be performed after 3-4 days of therapy to ensure that bladder irritability has resolved and that the urine is sterilized.
- Should be performed at the earliest convenient time.

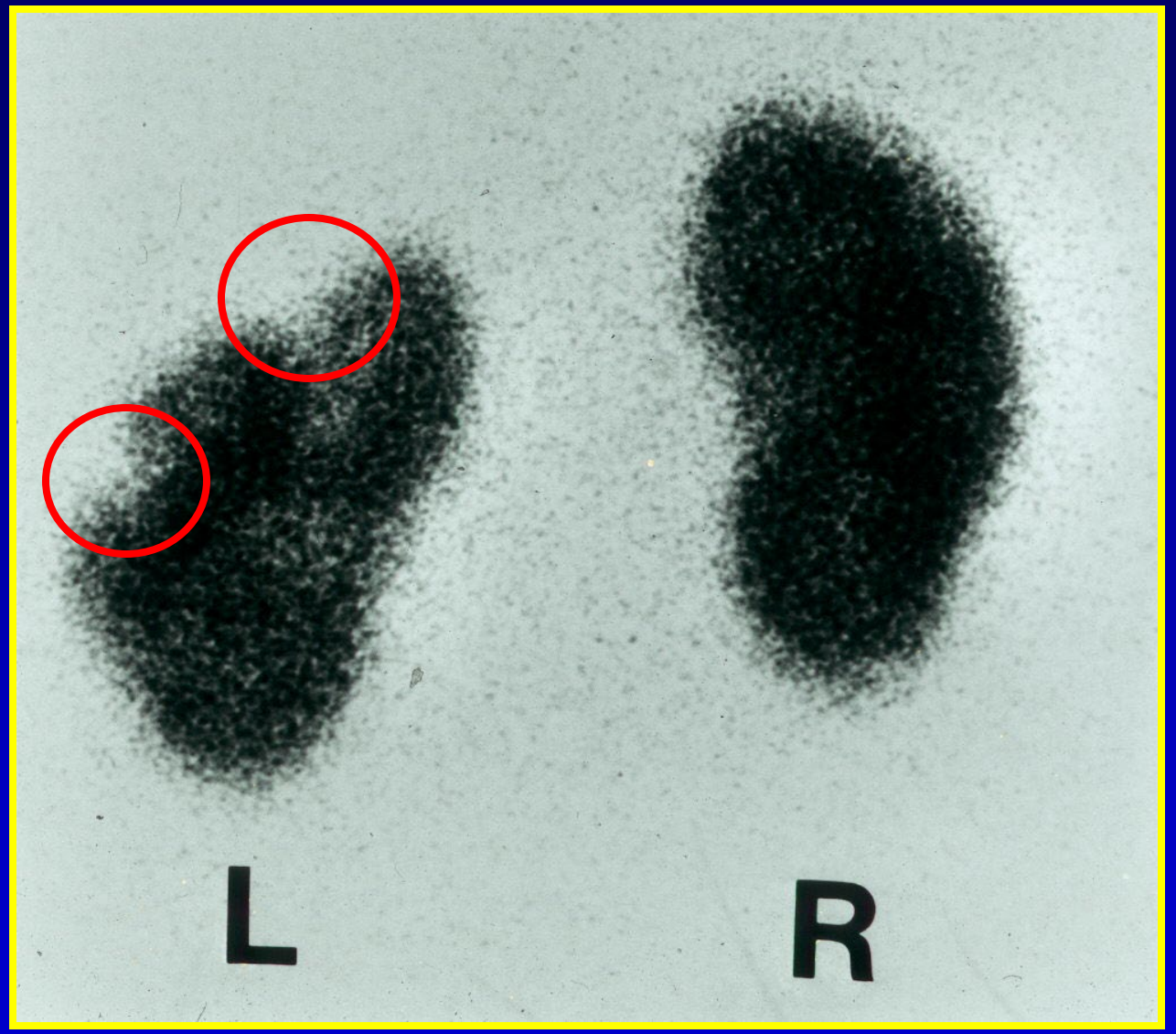


Renal Scintigraphy

- When the diagnosis of APN is uncertain, renal scanning with technetium-labeled DMSA is useful.
- DMSA is injected intravenously, and uptake by the kidney is measured two to four hours later.
- An area of decreased uptake represents an area of pyelonephritis or scarring.
- DMSA scans can help in determining the cause of fever in children with chronic bacteriuria, such as patients with spinal cord injury and those who undergo intermittent catheterization.

DMSA Scan

- Assesses APN & renal scarring
- Assesses differential renal function
- Predicts presence of “significant” VUR
- Can detect “significant” hydronephrosis
- Does not usually require sedation
- More renal radiation, but less gonadal radiation than VCUG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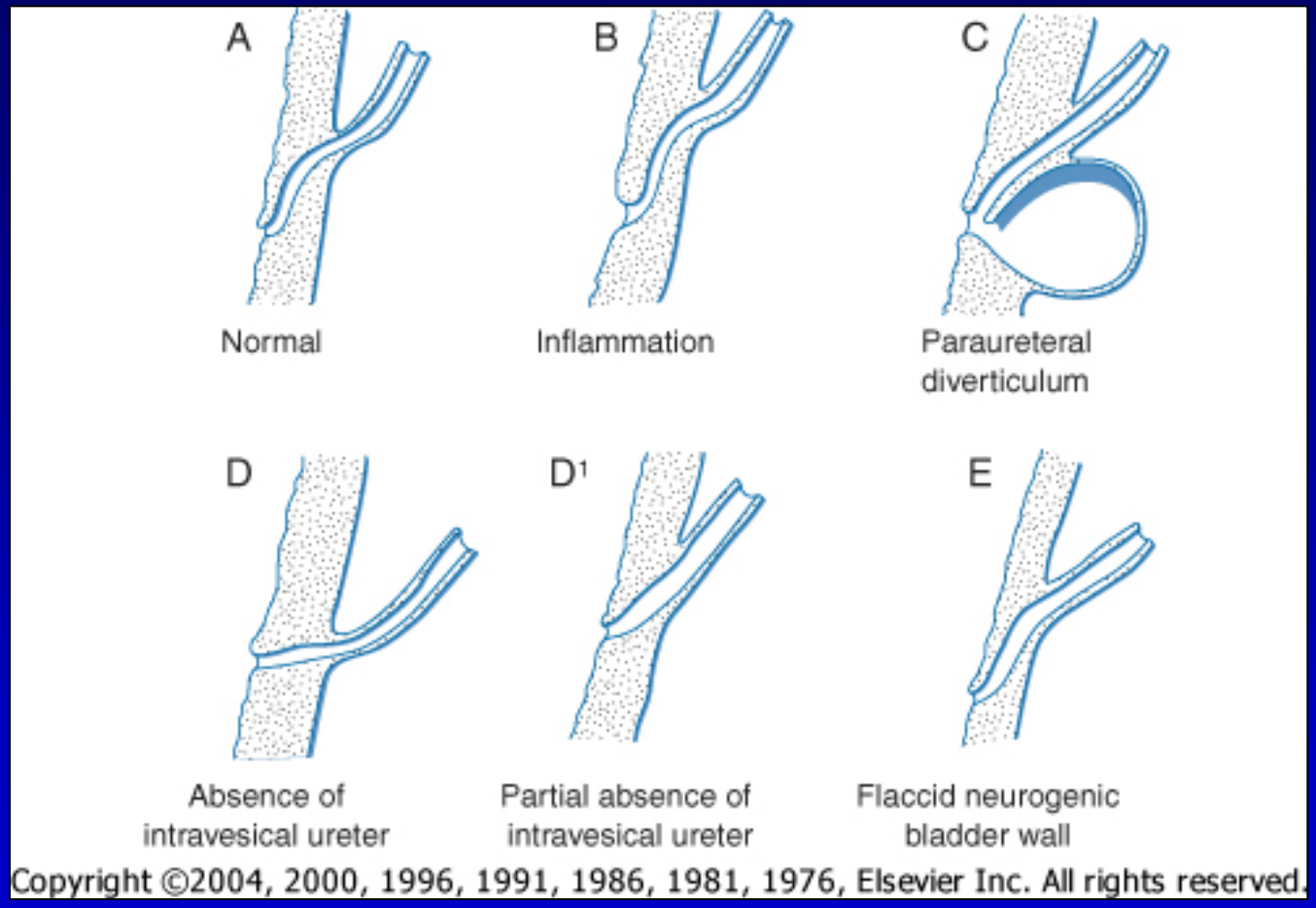
Imaging Protocol: First Non-Febrile UTI

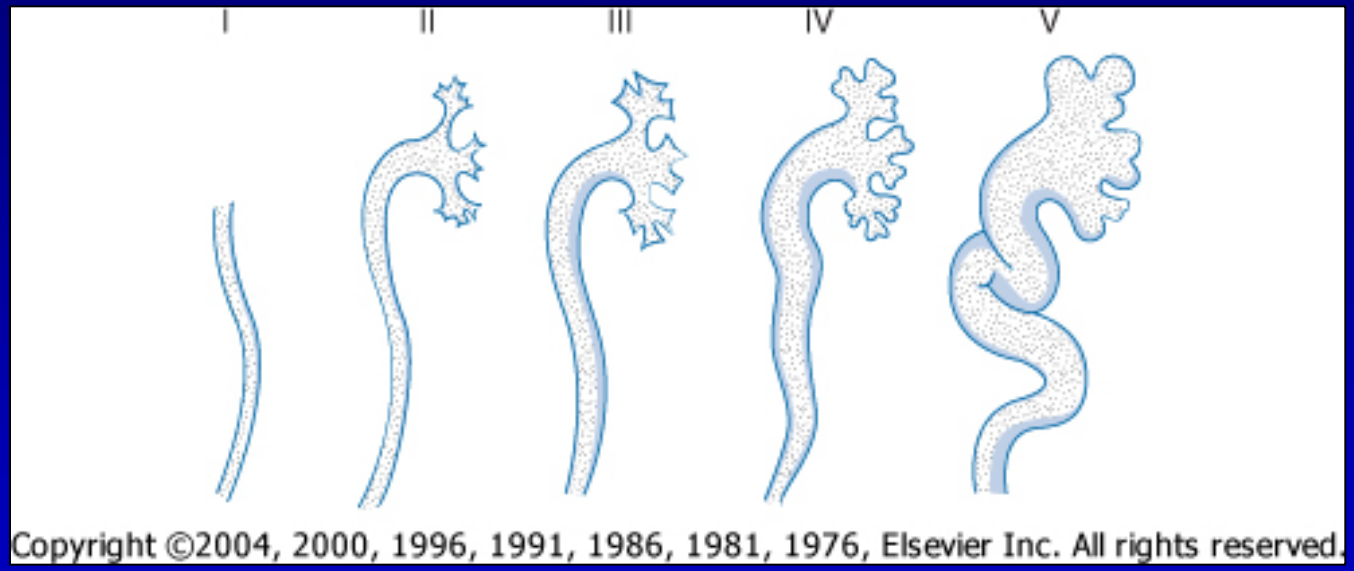
- Under four years of age:
  RBUS

- Over four years of age:
  RBUS, VCUG: only if RBUS abnormal or frequent UTI

Important to Identify Children With Vesicoureteral Reflux Without Delay

- The children with reflux are at risk for recurrent pyelonephritis
- Delay may increase the risk for renal scarring in some children





Primary VUR

- Present at birth
- About 1.5% of healthy children have VUR
- Prevalence is higher
  - After febrile UTI- 8%-50%
  - Antenatal hydronephrosis- 10%
  - Sibling/parent with VUR- 25-30%
  - Congenital renal anomalies- 10-30%

Secondary VUR

Increased bladder pressure affecting the integrity of uretero-vesicular junction. Present at birth or can occur later in life

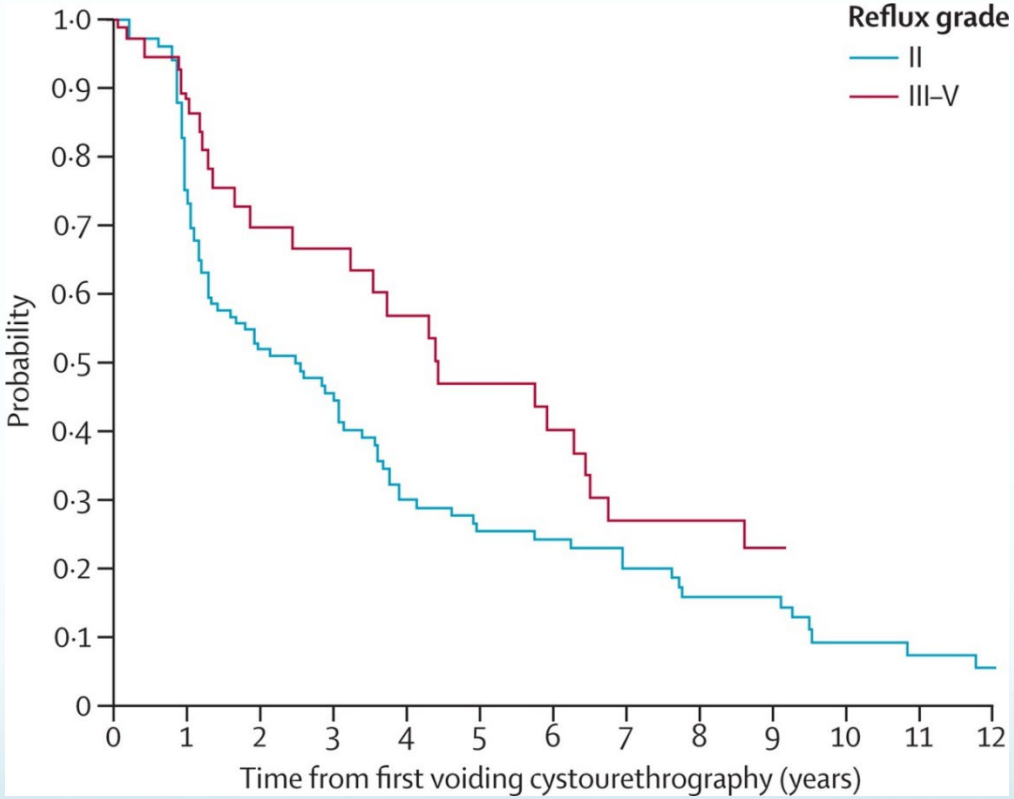
- Anatomical
  - Posterior urethral valves
  - Urethral or meatal stenosis
- Functional
  - Neurogenic bladder
  - Non-neurogenic neurogenic bladder
  - Bladder bowel dysfunction
  - Bladder infection (Transient)

Following surgical procedures

- Renal transplant
- Decompression or a ureterocele
- Correction of VUJ obstruction

Pregnancy and prostate hypertrophy are other risk factors in adults

Resolution of VUR Over Time



Wennerström et al. Arch Pediatr Adolesc Med. 1998

Complications Associated with VUR

- Urinary tract infection
- Renal scarring
  - Hypertension
  - Proteinuria (FSGS)
  - Progressive CKD
  - Pregnancy related complications
  - Complications in old age unknown?

Risk Factors for Renal Scarring with VUR

- High-grade VUR
- Recurrent acute pyelonephritis
- Delayed treatment
- Organisms other than *E. Coli*
- Gene Polymorphisms
- Patient Age (scarring occurs at all ages, not just younger children)

Problems

- No universally accepted protocol
- Existing literature is confusing
- Surgeons tend to prefer surgical options
- Non-surgeons tend to prefer non-surgical options

Varying Etiologies of Primary Vesicoureteral Reflux

Urinary Tract Infection

Hydronephrosis

Familial Reflux

Voiding Dysfunction

Other Congenital Abnormalities

Confounding Variables

- Age
- Gender
- Pre-existing Renal Abnormalities
- Pre-existing Renal Damage
- Dysfunctional Elimination
- Unilateral vs Bilateral
- Documentation of Follow-up
- Imaging Choices

Intermediate Outcomes

- Reflux resolution (medical or surgical therapy)
- Reflux improvement
- Reflux grade
- Renal scarring
- Renal growth and function
- Antibiotic resistance

Health Outcomes

- Urinary tract infection
  - Cystitis
  - Pyelonephritis
- Daily antibiotic
- Hypertension (medication)
- Uremia
- Somatic growth
- Morbidity during pregnancy
- Renal failure/dialysis
- Absence from school/work
- Anxiety regarding condition
- Follow-up testing

Harms of Medical Management

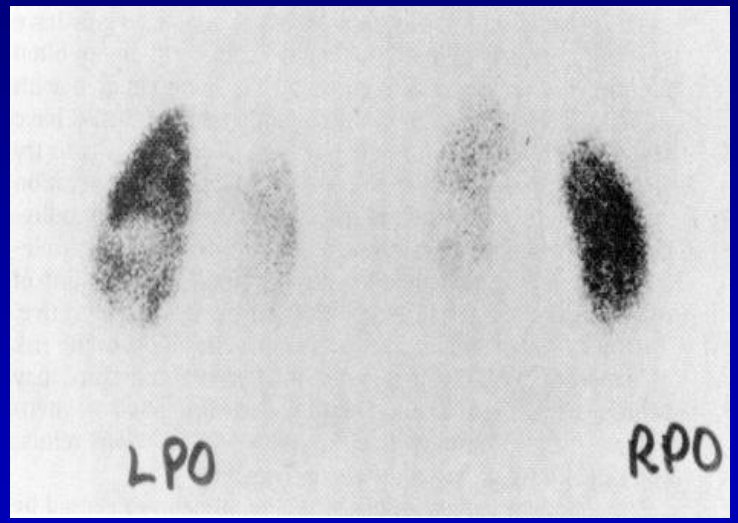
- Adverse drug reactions
- Antibiotic resistance
- Taste of medication
- Need for further testing

Harms of Surgical Management

- Ureteral obstruction
- Contralateral VUR
- Bladder dysfunction
- Scar
- Hospitalization

VUR: One of Many Risk Factors for Pyelonephritis

- Female
- Uncircumcised infant
- Vesicoureteral reflux
- Voiding dysfunction
- P fimbriae
- Host factors (e.g., bacterial colonization)
- Pregnancy/untreated bacteriuria



Goal of Reflux Management

- Reduce renal scarring
- Reduce episodes of pyelonephritis

Reflux Rx:
Low Dose Prophylaxis

- Under 5 years old
- Abnormal Tc-99m DMSA
- High grade/bilateral reflux
- Dysfunctional elimination

Reflux: Consider No Rx

- Over five years of age
- Lower grades of reflux
- Infrequent UTI
- Normal Tc-99m DMSA
- No dysfunctional elimination issues

Medial Versus Surgical Intervention for VUR

No difference in renal outcomes between the two interventions (Birmingham Study 1987, International Reflux Study, 1992).

Very few patients with VUR diagnosed after UTI need surgical correction.

Consider surgical intervention

- High-grade VUR (III – V) that has failed surveillance or antimicrobial prophylaxis
- Non-compliance or intolerance or allergy with antimicrobials
- Breakthrough urinary tract infections on prophylaxis
- Renal scarring- preexisting, new scarring, progressive scarring
- Parental wishes
- Persistence of VUR as puberty approaches in girls (Diamond and Mattoo, NEJM 2012)

Medical Management of VUR

- Surveillance only
- Antimicrobial prophylaxis
- Treatment for constipation/BBD
- Monitoring and management of complications associated with renal scarring

Surveillance only

An ideal child for surveillance only is the one with

- Low-grade VUR with normal renal ultrasound
- Toilet-trained
- Able to communicate symptoms in presence of an infection
- Families who understand and will be compliant in following medical instructions for follow-up.

Adapted from Mattoo and greenfield, UpToDate, May 23, 2023

Post-hoc Analysis of RIVUR data

- **R**ecurrent UTI associated new renal scarring occurred in 5 of 244 (2%) patients on antibiotic prophylaxis and 13 of 245 (5%) on placebo. The study revealed that compared to antibiotic prophylaxis, placebo was associated with a higher risk of recurrent urinary tract infection associated new renal scarring (OR 3.1, 95% CI 1.0-8.8, p=0.04) after adjusting for age, sex, race, index urinary tract infection, bowel bladder dysfunction, duplication, hydronephrosis, VUR grade and baseline renal scarring.

Wang HH et al, J Urol 2019

Antimicrobial Prophylaxis

American Urological Association (AUA) recommendation for UTI and VUR (2017)

- All children less than a year old
- Older children based on-
  - High grade VUR
  - Recurrent UTI
  - Presence of BBD
  - Renal scarring

Other factors that should be considered before initiating long-term antimicrobial prophylaxis

- Status of toilet training
- Risk of antibiotic resistance
- Anticipated compliance with daily medication administration
- Parental choice
- Medication expense

Antimicrobial Prophylaxis

- Long-term antibiotics may reduce the risk of repeat symptomatic UTI in children who have had one or more previous UTIs but the benefit may be small and must be considered together with the increased risk of microbial resistance.

Williams et al, Cochrane Database Syst Rev Review 2019

Summary of evidence

Summary of evidence	LE
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary, however, any colony count of one specimen indicates a high suspicion for UTI	2b
Due to increasing resistance numbers good antibiotic stewardship should guide the choice of antibiotics, taking into account local resistance patterns, old urine cultures (when available) and clinical parameters.	2a
Preventive measures against recurrent UTIs include: chemoprophylaxis (oral and intravesical), cranberries, probiotics and Vitamin A and E.	2a
During acute UTI both DMSA and diffusion-weighted MRI can confirm pyelonephritis or parenchymal damage.	2a

Recommendations

Recommendations	LE	Strength rating
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	Strong
Exclude bladder- and bowel dysfunction in any toilet-trained child with febrile and/or recurrent UTI.	3	Strong
Clean catch urine can be used for screening forUTI. Bladder catheterisation and suprapubic bladder aspiration to collect urine can be used for urine cultures.	2a	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results.	2a	Strong
Midstream urine is an acceptable technique for toilet-trained children.	2a	Strong
The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhea; non-compliance; complicated pyelonephritis.	2a	Strong
Treat febrile UTIs with four to seven day courses of oral or parenteral therapy.	1b	Strong
Treat complicated febrile UTI with broad-spectrum antibiotics	1b	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	1b	Strong
In selected cases consider dietary supplements as an alternative or add-on preventive measure.	2a	Strong
In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract within 24 h	2a	Strong
In infants, exclude VUR after first epidose of febrile UTI with a non-E. Coli infection. In children more than one year of age with an E. Coli infection, exclude VUR after the second febrile UTI.	2a	Strong

Thank You!

Frost Valley YMCA Summer Kidney Camp Program

Voiding Dysfunction in Children

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Disclosures

- Paid consultant to the American Urological Association

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Objectives

- Be able to diagnose the various presentations of voiding dysfunction in children
- Perform an appropriate work-up for voiding dysfunction
- Be able to counsel parents and patients on appropriate voiding/elimination habits
- Know when more invasive work-up is indicated and what the next steps are

Bladder as a Dynamic Organ

Dual Job Description

- Storage
  - High compliance
  - Closed sphincter/ BN
- Voiding
  - Bladder contraction
  - Open Sphincter/ BN

Neurologic Bladder Control

Generalizations

Sympathetic:

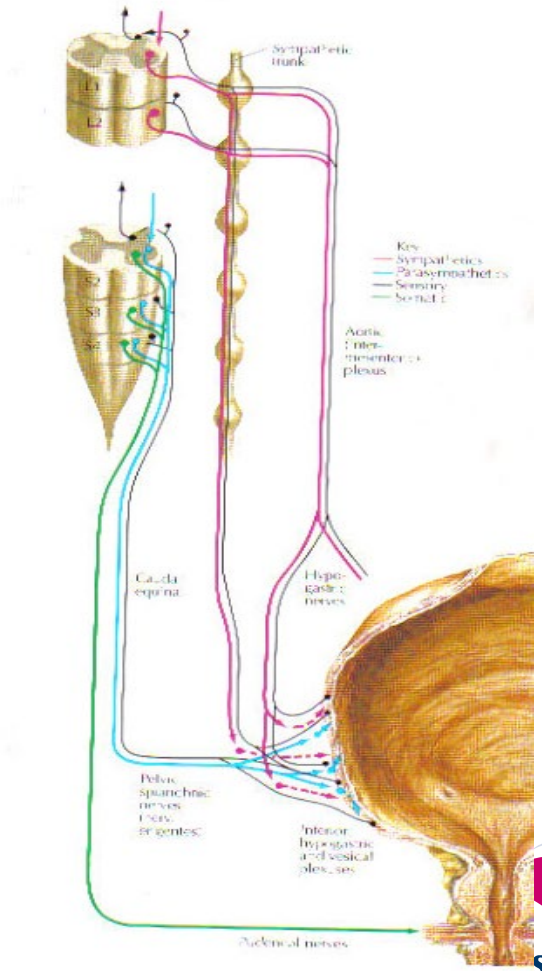
Storage

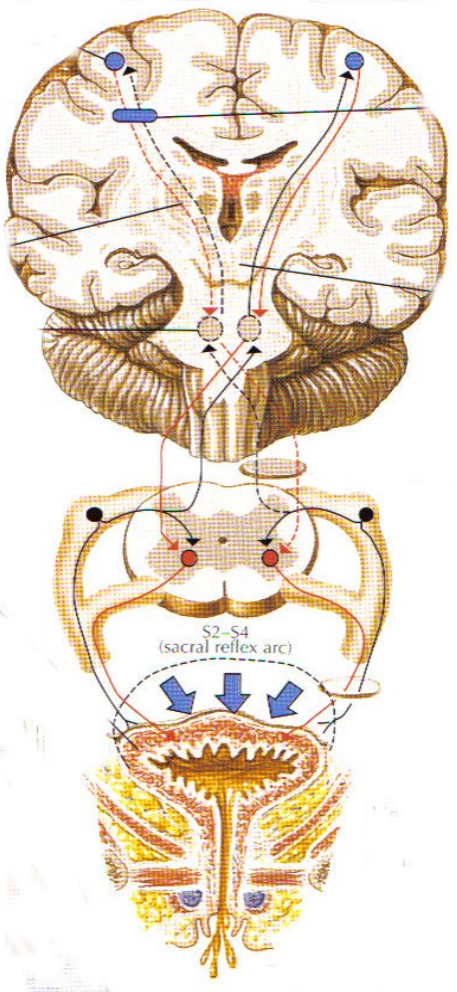
Parasympathetic:

Voiding

Somatic:

External Sphincter Contraction





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Voiding in Infants

- Urine storage
  - Sympathetic and pudendal nerve-mediated inhibition of detrusor contractility
  - Closure of the bladder neck and proximal urethra
  - Increased activity of the external sphincter
- Infant has coordinated reflex voiding
  - 15-20 times/day
- Over time, bladder capacity increases
- Bladder capacity in ml = age (years) + 2 x 30

Voiding in Infants

- Detrusor sphincter dyscoordination is part of normal voiding patterns in 1/3rd of neonates and infants
- Bladder emptying is incomplete in infancy
- Spinal reflex only?
  - Signs of arousal before voiding

Voiding in Infants

- Sex differences
  - Males have higher voiding pressures on average about >100cm H_20
  - Results from DSD and detrusor hypercontractility, which resolves with time

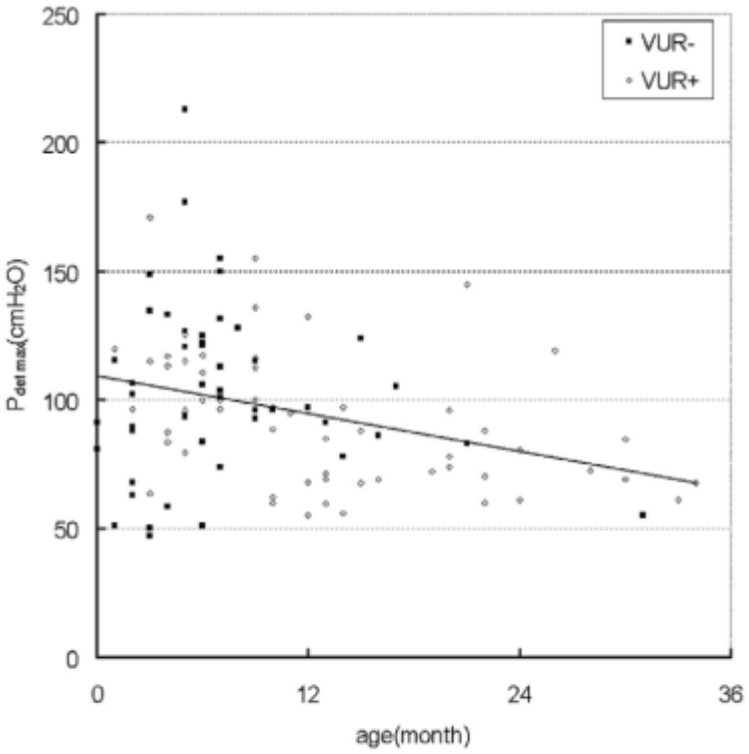


FIG. 1. Relationship between $P_{det\ max}$ and age. $P_{det\ max}$ displays significant negative correlation with age ($r_s = -0.28$, $p = 0.005$). Black and white dots indicate value of $P_{det\ max}$ in infants without and with VUR, respectively.

Acquisition of Bladder Control

- When should children become toilet trained?
  - Most girls between 2-2.5 years
  - Most boys between 2.5-3 years
- Child is developmentally ready at 2-4 yrs of age
- Trend in later age of achieving continence in recent years

Acquisition of Bladder Control

- To achieve conscious bladder control:
  - Awareness of bladder filling
  - Cortical inhibition (suprapontine modulation) of reflex (unstable) bladder contractions
  - Ability to consciously tighten the external sphincter
  - Normal bladder growth
  - Motivation to stay dry
- Bowel control typically is achieved before bladder
- Abnormal defined by DSM-5 as:
  - Failure of bowel control by age 4
  - Failure of bladder control by age 5

Bladder Dysfunction

- **Non-neurogenic**
- Neurogenic
  - Myelomenigocele
  - Spina bifida occulta
  - Sacral agenesis
  - Tethered cord
  - Spinal cord injury/CNS tumors
  - Imperforate anus/Cloacal malformations
  - Posterior urethral valves

Lower Urinary Tract Symptoms

- Daytime Urinary Frequency
  - Voiding more than 8 times per day
- Decreased Daytime Urinary Frequency
  - Voiding fewer than 3 times per day
- Urinary Incontinence
  - Involuntary leakage of urine
- Urinary Urgency
  - Sudden and unexpected experience of immediate and compelling need to void
- Nocturia
  - Need to void during the night

Types of Urinary Incontinence

- Continuous Incontinence
  - Constant urinary leakage
  - Due to anatomic problem
- Intermittent Incontinence
  - Leakage in discrete amounts
  - Daytime incontinence
  - Enuresis

Voiding Symptoms

- Urinary hesitancy
  - Difficulty initiating void
- Weak stream
- Dysuria
- Holding maneuvers
- Feeling of incomplete emptying
- Post-micturition dribble
- Spraying
- Genital pain

Epidemiology

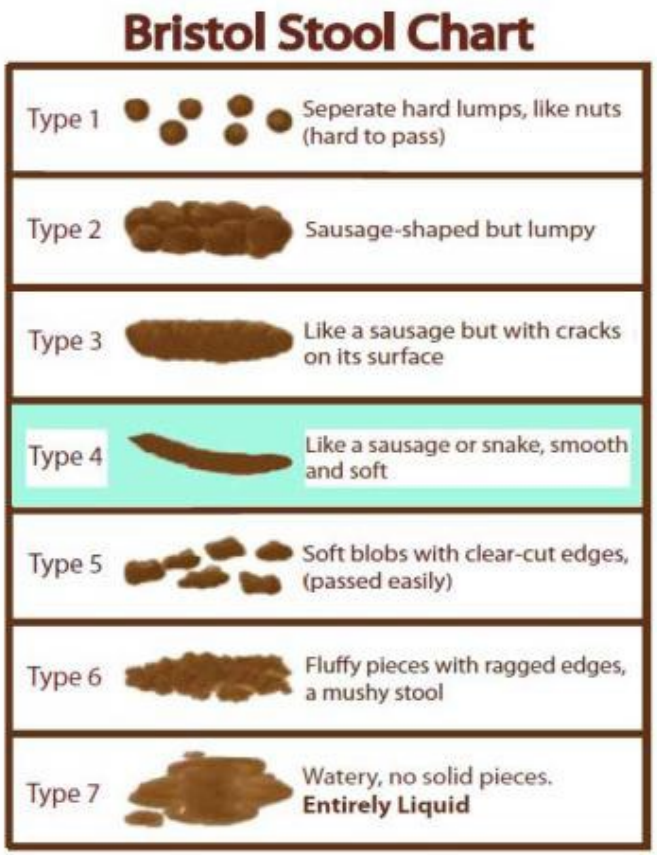
- 25% of healthy 7 year olds have mild to moderate Lower Urinary Tract Symptoms (LUTS)
  - Daytime wetting occurs in:
    - 6% of girls
    - 4% of boys

Co-Morbidities of LUTS

- Urinary Tract Infections
  - Due to stasis of urine and incomplete emptying
- Vesicoureteral Reflux
  - Secondary reflux is due to high voiding pressures
- Psychological Conditions
  - 20-30% association with nocturnal enuresis
  - 20-40% association with daytime urinary incontinence
  - 30-50% association with fecal incontinence
  - ADHD, ODD, anxiety, depression
- Bowel Dysfunction

Evaluation - History

- Age and difficulty of potty training
- Presence of LUTS
  - Nocturnal enuresis vs. diurnal wetting
- Bowel habits
  - Bristol stool scale
- Bladder and bowel diaries
  - Frequency, volume, urgency, accidents, fluid intake, BMs
  - Holding behavior



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Evaluation – Physical Exam

- Abdominal exam
  - Distended bladder
  - Palpable stool
  - Tenderness
- Sacral exam
- Genitalia
  - Phimosis, meatal stenosis
  - Labial adhesions, chronic skin irritation, urinary drainage

Evaluation – Investigative Tools

- Urinalysis
  - Diabetes mellitus or insipidus, hematuria, proteinuria, infection
  - Urine culture as indicated
- Renal/bladder ultrasound with PVR
- KUB to evaluate stool load
- VCUG after 2nd febrile UTI or in setting of abnormal u/s

Diagnoses

- Overactive Bladder
  - Urinary urgency without infection
  - Frequency and nocturia
- Insensate Bladder
  - Usually associated with fecal impaction/distended rectum
- Underactive Bladder
  - Weak slow stream, straining
- Dysfunctional Voiding
  - Contraction of urethral sphincter during voiding
- Stress Incontinence
  - Leakage with physical exertion

Diagnoses

- Vaginal reflux
  - Urine collects in vagina during voiding
- Giggle Incontinence
- Constipation
  - Common cause of urinary frequency, dysuria, feeling of incomplete emptying
  - Causes bladder spasms which can present as pain at tip of penis or in vagina

Treatment – Behavioral Modification

- Strict timed voids
  - Every 2-3 hours while awake
  - Can use reminder alarms
- Proper toilet habits
  - Girls sit with legs apart, leaning forward, hands on knees
  - Deep breathing and relaxation during voiding
- Voiding diaries
- Treat bowel dysfunction!!!

Treatment - Pharmacotherapy

- Anti-cholinergics like Ditropan/oxybutynin
  - Good for treating true over-active bladder
  - Causes constipation
- Antibiotic prophylaxis
  - Prevent recurrent UTIs
- Laxatives and fiber supplements

Nocturnal Enuresis

- Involuntary release of urine while sleeping in child over age 5
- Primary nocturnal enuresis
  - Never been dry for at least 6 months
- Secondary nocturnal enuresis
  - Recurrence of nighttime wetting after dry period of at least 6 months

Pathophysiology

- Nocturnal polyuria
- Arousal disorder
  - "difficult to wake up"
  - Obstructive sleep apnea
- Nocturnal detrusor overactivity

Epidemiology

- 15-20% of children between ages 4-6
- Twice as common in boys
- Likely autosomal dominant inheritance pattern

Treatment of Nocturnal Enuresis

- Bedwetting alarm
  - Most effective treatment
  - Requires HIGHLY MOTIVATED family
  - Takes about 3 months
- Desmopressin
  - Decrease urine production at night
  - Use adequate dose
- Tricyclic antidepressants – imipramine
  - Centrally acting for treating nocturnal enuresis

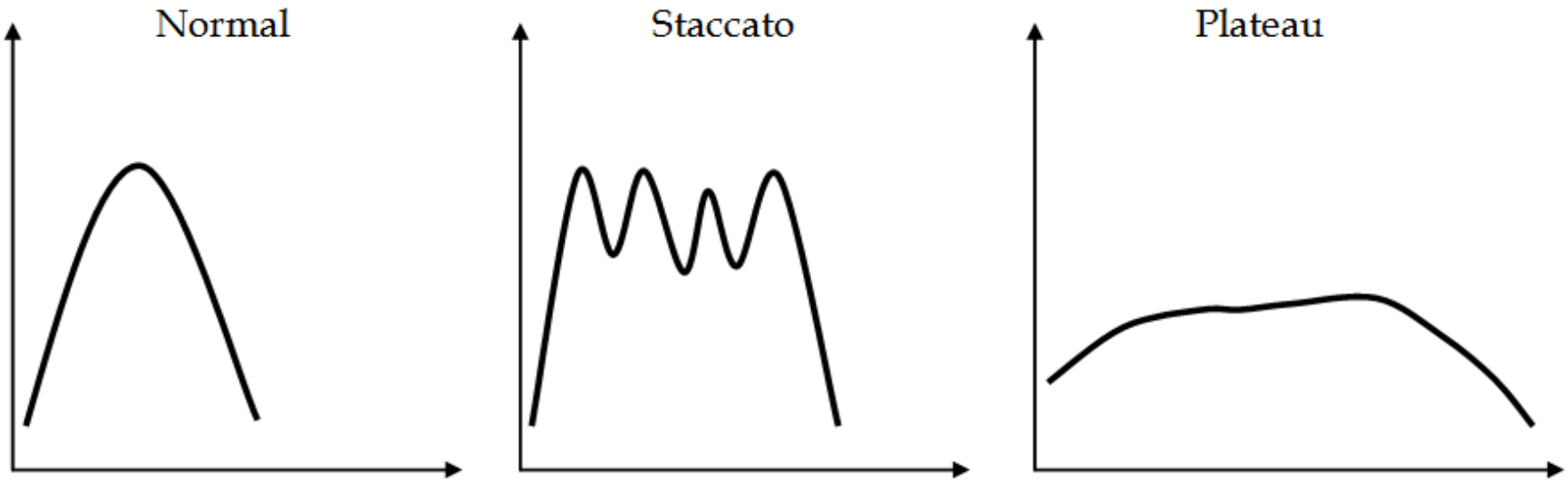
Biofeedback

- Building self-perception on detrusor contractions
- Pelvic floor relaxation
- Highly effective
- 80% improvement in daytime incontinence
- 83% improvement in UTI

Uroflow +/- EMG

- All children should have a bell shaped curve
  - Regardless of age, gender or voided volume
- Qavg > 50% but < 85% of Qmax
- Shape of curve most important
- Adaptations for children
- EMG shows dysfunctional voiding

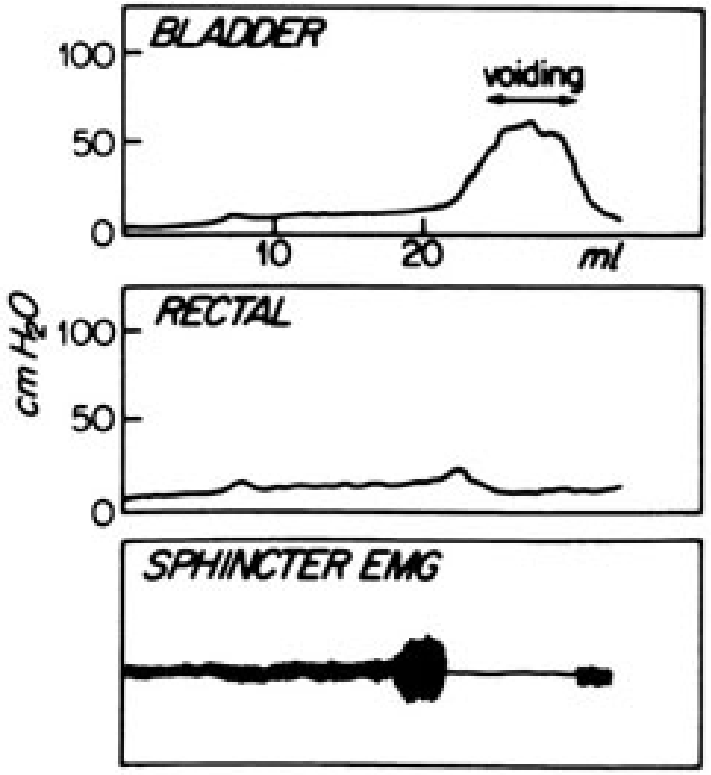
Uroflow



Urodynamics

- Measure
  - Sensation
  - Capacity
  - Storage Parameters
    - Compliance and Hyperreflexia
  - Contractility
  - Sphincter/Urethra
    - Competence & Leak Point Pressure
  - EMG pattern
  - Flow Rate

Synergy


BLADDER
100
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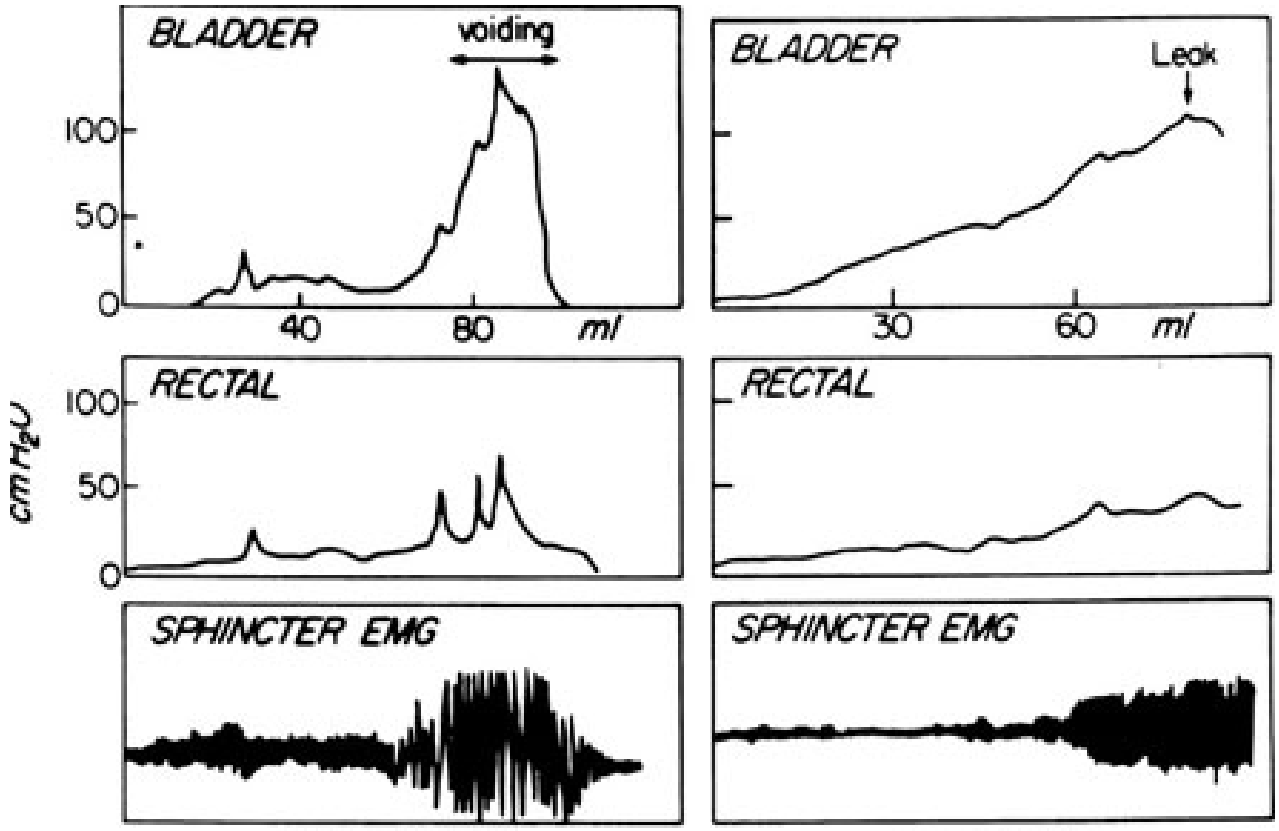
SPHINCTER EMG

Dyssynergic



Conclusion

- Voiding dysfunction is very common
  - Urinary frequency, urgency, incontinence, recurrent UTIs
- Usually associated with bowel dysfunction
  - Must treat constipation or urinary symptoms will not improve
- Nocturnal enuresis can be associated with daytime symptoms or be monosymptomatic
- Treatment of voiding dysfunction requires behavioral modification
  - Cooperation of family