Clinico-pathological Conference: Glomerular disease

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Case 1

6 year old Indian boy
Trisomy 21 with autistic spectrum disorder

Recurrent syndromic gross haematuria

1 Aug 23 — 11 Aug — 19 Aug — 20 Aug — 25 Aug

- Painless specks of blood in urine with resolution
- Fever with cough
- Presented in clinic
- Gross haematuria, abdominal discomfort during urination (non-verbal) and fever
- No urinary symptoms
- No symptoms of hypertension or oliguria
- No autoimmune symptoms
- No family history of renal disease or hearing loss

On examination:
BP 105/68
Abdomen soft, non-tender and no masses
No signs of fluid overload

- Resolution of gross haematuria

Investigations

Haematuria and proteinuria
Urine RBCs 9/hpf (25% dysmorphic)
Urine protein/cr ratio 80mg/mmol
Urine albumin/cr ratio 42.5mg/mmol
Normal albumin

Raised creatinine
Creatinine 54umol/L (eGFR: 78ml/min/1.73m2)

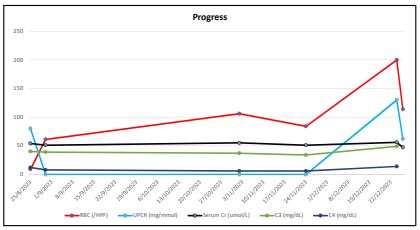
No anemia or cytopenias
Low C3 40mg/dL
Low C4 12mg/dL
Raised IgA 4.4g/L
ASOT 200 IU/ml
ANA 1:80 (nucleolar)
Anti-ds DNA and ANCA normal
Hepatitis B and C screen negative

KUB X-ray: No radio-opaque calculi
US kidneys: Right kidney 7.3cm and left kidney 6.8cm, normal

Whole exome sequencing: negative

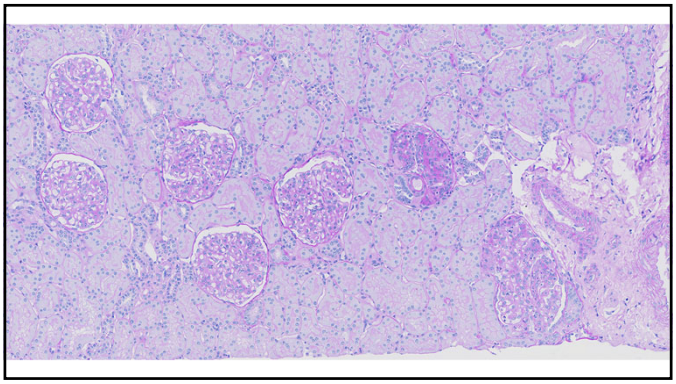
Subsequent progress

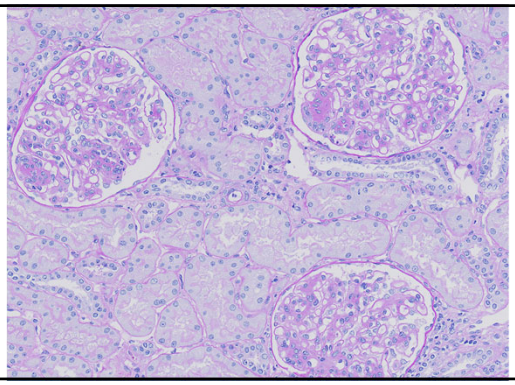
- Parents were not keen for renal biopsy initially
- Had synpharyngitic gross haematuria in Dec 23
- Persistent mild renal impairment (Cr 50s), microscopic haematuria, proteinuria, low C3 and C4

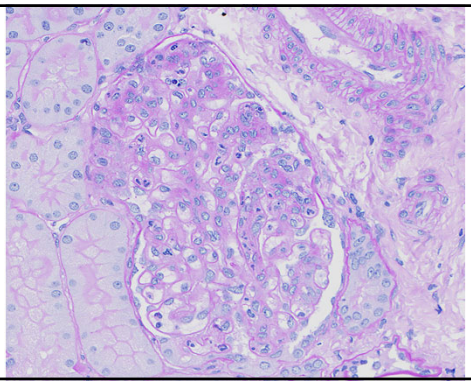


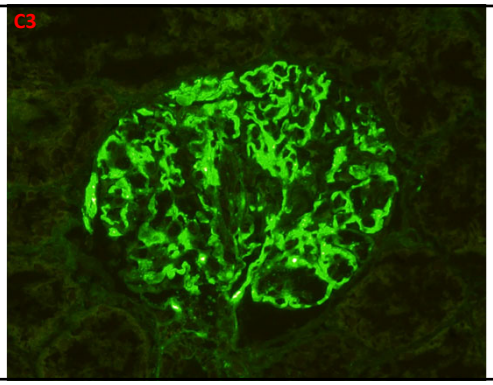
Renal biopsy in Feb 2024

RBC
UPCR
Cr
C3
C4





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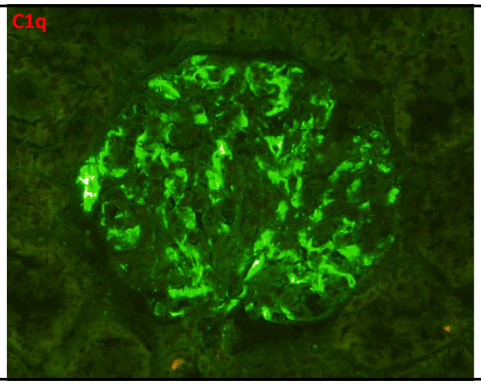
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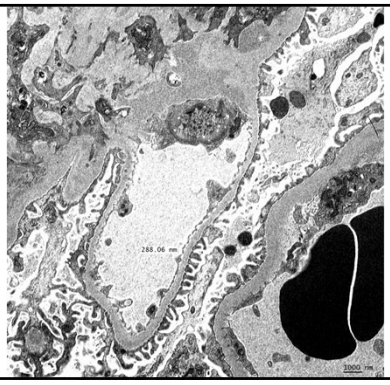
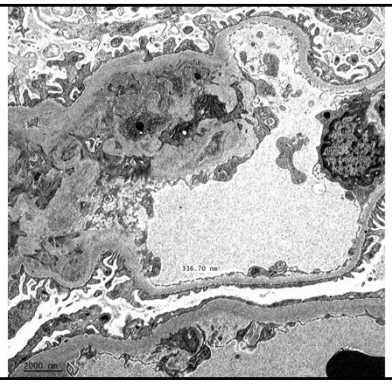


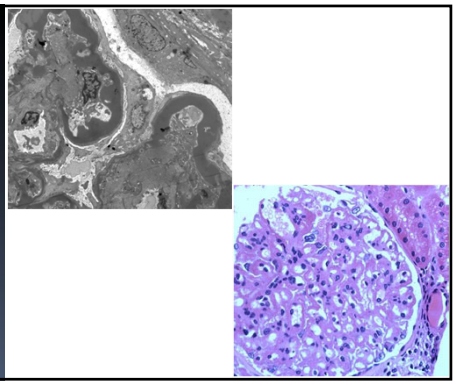


Diagnosis: C3 dominant mesangial and focal endocapillary proliferative glomerulonephritis

Subsequent progress

- Given 2 courses of IV pulse methylprednisolone
- Maintained on mycophenolate mofetil and oral prednisolone
- Had normalisation of creatinine and hypocomplementemia
- Had improvement in microscopic haematuria and resolution of proteinuria
- Subsequently defaulted follow-up appointments

1. The renal biopsy from a child shows dominant glomerular C3 staining on immunofluorescence. Light and electron microscopic images are as shown. What is your diagnosis?



1. The renal biopsy from a child shows dominant glomerular C3 staining on immunofluorescence. Light and electron microscopic images are as shown. What is your diagnosis?

A. C3 glomerulonephritis
B. Post-infectious glomerulonephritis
C. Dense deposit disease
D. Membranoproliferative glomerulonephritis
E. Lupus nephritis

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Glomerulonephritis with dominant C3

- C3 GN
- Infection-related GN
- Atypical infection-related GN
- MPGN with immune complex deposits
- Dense deposit disease
- Membranous-like glomerulopathy with masked IgG-kappa deposits
- FSGS with entrapped C3 in insudates

Case 2

17 year old Malay girl
Previously well

Acute nephritic syndrome with rapidly progressive glomerulonephritis

- Presented in May 24 with gross haematuria, oliguria, vomiting and intermittent headaches
- Systems review was unremarkable
- No family history of renal disease
- Had hypertensive urgency requiring IV labetalol and glyceryl trinitrate (GTN)

On examination:
BP: 180/116 mmHg
Well thrived
Raised JVP
Hepatomegaly 2cm
Bilateral pedal edema up to shins
No rashes, lymphadenopathy or arthropathy

Haematuria and nephrotic-range proteinuria
Urine RBC 29/hpf (33% dysmorphic)
Urine protein/cr ratio: 756mg/mmol
Urine albumin/cr ratio: out of detection limit
Albumin normal

Renal impairment
Urea 17.0mg/dL
Creatinine 729 umol/L
iPTH 44.1pmol/L

Investigations

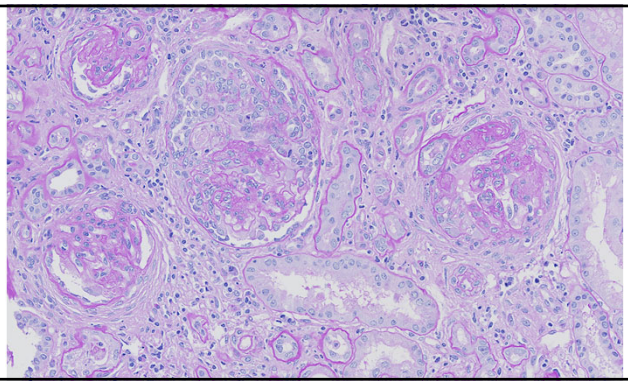
Hb 10.2 and no cytopenias
ESR 66

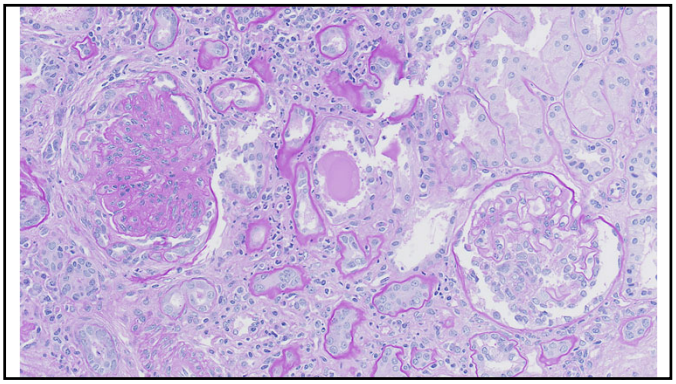
C3 and C4 normal
ANA and anti-ds DNA normal
ANCA negative
ASOT negative
Raised IgA: 4.6 g/L
Anti-GBM antibodies positive
Hepatitis B and C screen negative

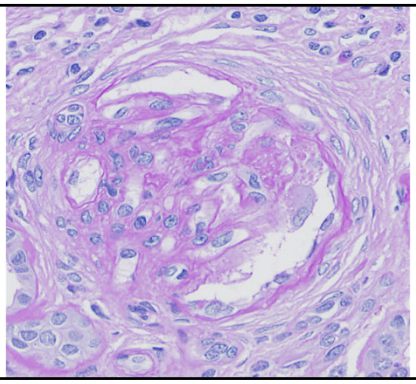
CXR: normal
US kidneys: Right kidney 9.8cm and left kidney 10cm, increased echogenicity with loss of cortico-medullary differentiation

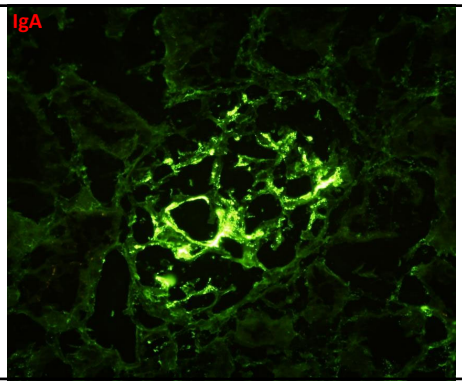
Underwent urgent diagnostic renal biopsy

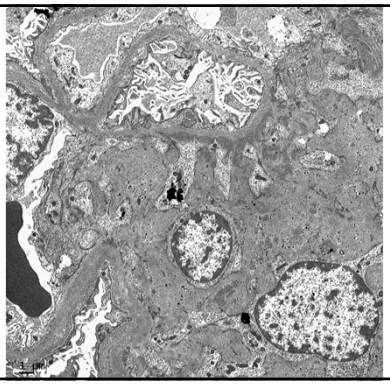
IV pulse methylprednisolone
Rituximab
Plasmapheresis
IVIG

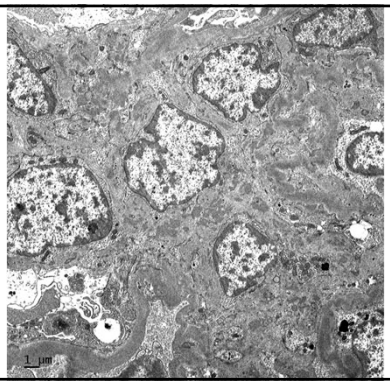


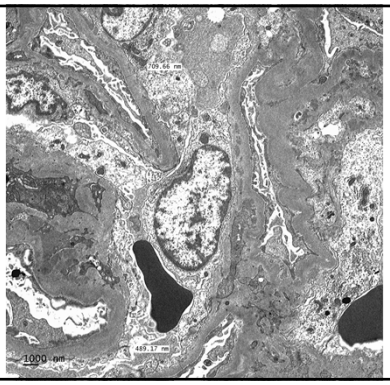








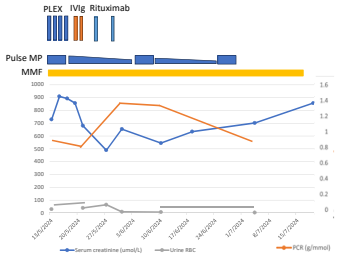




Diagnosis: IgA nephropathy

Focal proliferative glomerulonephritis with 30% cellular/fibrocellular crescents and focal segmental glomerulosclerosis

Subsequent progress



- Received 3 doses of IV pulse methylprednisolone, 2 doses of IV rituximab and IVIG
- Received 6 sessions of plasmapheresis
- Maintained on mycophenolate mofetil and oral steroids
- Minimal improvement in serum creatinine ~700umol/L to and proteinuria ~700mg/mmol
- Anti-GBM subsequently negative
- Progressive renal failure with worsening fluid overload
- Initiated on intermittent haemodialysis in July 24

2. Which of the following is associated with dominant or co-dominant IgA immune deposits?

A. Primary IgA nephropathy
B. IgA vasculitis
C. Infection-related glomerulonephritis
D. Hepatic glomerulosclerosis
E. All of the above

2. Which of the following is associated with dominant or co-dominant IgA immune deposits?

A. Primary IgA nephropathy
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C. Infection-related glomerulonephritis
D. Hepatic glomerulosclerosis
E. All of the above

meeting report www.kidney-international.org

Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group

Hernán Trimarchi[1], Jonathan Barratt[2], Daniel C. Cattran[3], H. Terence Cook[4], Rosanna Coppo[5], Mark Haas[6], Zhi-Hong Liu[7], Ian S.D. Roberts[8], Yukio Yuzawa[9], Hong Zhang[10] and John Feehally[2] on behalf of the IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society[1]; for Conference Participants[11]

[1]Hospital Británico de Buenos Aires, Argentina; [2]Department of Infection, Immunity, and Inflammation, University of Leicester, Leicester, United Kingdom; [3]Department of Medicine, Toronto General Research Institute, University Health Network, Toronto General Hospital, Toronto, Ontario, Canada; [4]Centre for Complement and Inflammation Research, Department of Medicine, Imperial College, London, United Kingdom; [5]Fondazione Ricerca Molinette, Nephrology, Dialysis, and Transplantation, Regina Margherita Hospital, Turin, Italy; [6]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA; [7]Department of Nephrology, National Clinical Center of Kidney Disease, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; [8]Department of Cellular Pathology, Oxford University Hospitals, Oxford, United Kingdom; [9]Department of Nephrology, Fujita Health University School of Medicine, Toyoake Aichi, Japan; and [10]Renal Division, Peking University First Hospital, Beijing, China

Table 3 | Recommendations for the renal biopsy report in IgA nephropathy (updated from refs. 1, 2, and 32)

Detailed description of the features present on:
Light microscopy
Immunohistochemistry or immunofluorescence
Electron microscopy
Summary of 5 key pathologic features
Mesangial score <0.5 (M0) or >0.5 (M1)
Endocapillary hypercellularity absent (E0) or present (E1)
Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy/tip lesions in biopsy specimens with S1
Tubular atrophy/interstitial fibrosis ≤25% (T0), 26%–50% (T1), or >50% (T2)
Cellular/fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in >25% of glomeruli (C2)
Quantitative data
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, necrosis, extracapillary hypercellularity (cellular/fibrocellular crescents), global glomerulosclerosis, and segmental glomerulosclerosis

www.kidney-international.org clinical investigation

Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy

Shubha S. Bellur[1], Fanny Lepeytre[2], Olga Vorobyeva[1], Stéphan Troyanov[2], H. Terence Cook[3] and Ian S.D. Roberts[1]; on behalf of the International IgA Nephropathy Working Group

[1]Department of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom; [2]Division of Nephrology, Hôpital du Sacré-Coeur de Montréal, Montreal, Quebec, Canada; and [3]Department of Medicine, Imperial College, London, United Kingdom

Focal segmental glomerulosclerosis (FSGS) is a common finding in IgA nephropathy (IgAN). Here we assessed FSGS lesions in the Oxford Classification patient cohort and correlated histology with clinical presentation and outcome to determine whether subclassification of the S score in IgAN is reproducible and of clinical value. Our subclassification of lesions in 137 individuals with segmental glomerulosclerosis or adhesion (S1) identified 38% with podocyte hypertrophy, 10% with hyalinosis, 9% with resorption droplets within podocytes, 7% with tip ...

The first pictorial illustration of focal segmental glomerulosclerosis (FSGS) by Fahr[1] was published in an atlas of human pathology as early as 1925. Since its recognition as a clinical entity distinct from minimal change disease in 1979,[2] it has caught the attention of nephrologists and pathologists alike in a continued attempt to obtain a clear understanding of this disease process. Segmental glomerulosclerosis is characterized by a segmental increase in the glomerular matrix with obliteration of capillary lumens and is a common morphologic feature of biopsy specimen, either as ...

Evidence from the large VALIGA cohort validates the subclassification of focal segmental glomerulosclerosis in IgA nephropathy

see commentary on page 1165

Shubha S. Bellur[1], Stéphan Troyanov[2], Olga Vorobyeva[3], Rosanna Coppo[4] and Ian S.D. Roberts[5]; for the Validation in IgA Nephropathy study group[6]

[1]William Osler Health Systems Brampton & Queen's University, Kingston, Ontario, Canada; [2]Hôpital du Sacré-Coeur de Montréal, University of Montreal, Montreal, Quebec, Canada; [3]National Center of Clinical Morphological Diagnostics, Saint Petersburg, Russia; [4]Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy; and [5]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Evidence from the Oxford IgA nephropathy (IgAN) cohort supports the clinical value of subclassifying focal segmental glomerulosclerosis lesions (S1). Using the larger Validation in IgA (VALIGA) study cohort, we investigated the association between podocytopathic changes and higher proteinuria, kidney outcome and response to immunosuppressive therapy. All biopsies were evaluated for glomeruli with segmental capillary occlusion by matrix ("not otherwise specified", NOS lesion), simple capsular adhesion without capillary occlusion (Adh), tip lesions, and ... associated with a response to corticosteroids, while other S1 lesions defined chronicity. Thus, our findings support subclassifying S1 lesions in IgAN.

Kidney International (2024) 105, 1279–1290; https://doi.org/10.1016/j.kint.2024.03.011

KEYWORDS: IgA nephropathy; podocytopathy; segmental sclerosis; subclassification

Lay Summary

Factors associated with more aggressive disease or progressive renal injury

- MESTC
- Subendothelial deposits
- Positive glomerular IgG (co-localisation with kappa associated with E1 & C1/2 lesions)
- Glomerular positivity for C4d
- Dysregulation of alternative complement pathway
- Podocyte injury
- Hyperfiltration injury with glomerulomegaly
- Tubulointerstitial inflammation

Case 3

13 year old Malay boy

Post-renal transplant with end stage renal failure secondary to collapsing focal segmental glomerulosclerosis

Rising creatinine 4 years post-transplant

2yrs old
- Diagnosed with nephrotic syndrome with late steroid resistance
- Progressive renal failure despite immunosuppression (cyclosporine, mycophenolate mofetil and prednisolone)

4yrs old
- End-stage renal failure
- Commenced on peritoneal dialysis

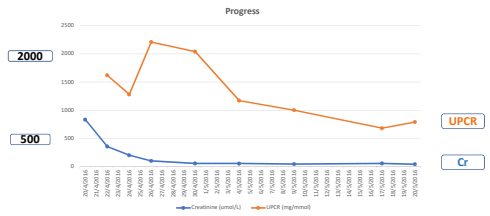
6yrs old
- Underwent cadaveric renal transplant in April 2016
- CMV positive to negative
- EBV positive to positive

Highly sensitised pre-transplant:
- 2 antigen matches
- Weakly positive B cell crossmatch
- 3 DSAs with MFIs ranging from 700 to 1800
- Given IV rituximab, IVIG 2g/kg and 10 cycles of plasmapheresis

Post-transplant complications

1. Acute tubular necrosis from reperfusion injury
2. Recurrence of FSGS: severe proteinuria and hypoalbuminemia immediately post-transplant
3. Antibody-mediated injury

Post-transplant progress



Normalisation of creatinine: 57umol/L (eGFR: 72ml/min/1.73m²) by POD 9

Initial proteinuria beyond detection limit > 24h UTP 0.34g/day/1.73m² on POD 46

Rising creatinine 4 years post-transplant

7yrs old
- 1 DSA (DR4 MFI 1800): received 3 doses of IVIG 2g/kg from Jun to Oct 16

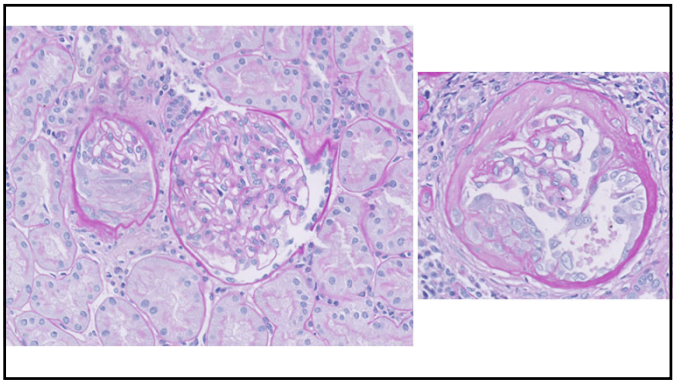
8yrs old
- 2 DSAs (DR4 and CW1: MFI 1500-3600): received 3 doses of IVIG and IV rituximab from Aug to Sep 17

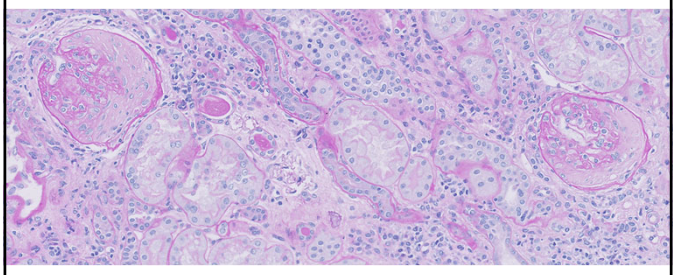
11yrs old
- Rising creatinine from baseline of 60 to 85umol/L with no proteinuria
- Poor height velocity: plans to wean prednisolone to EOD

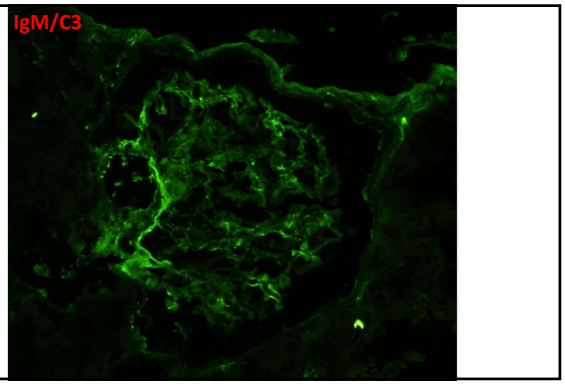
Antibody-mediated injury

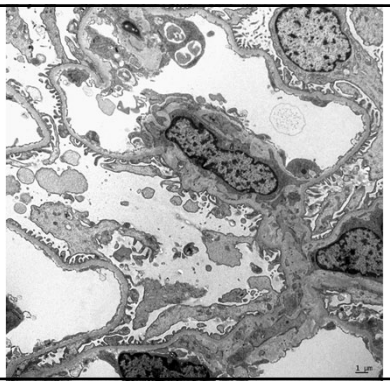
Concerns of chronic allograft rejection

Renal biopsy in Dec 2020









Diagnosis: De novo pauci-immune glomerulonephritis

Subsequent progress

- Given 6 courses of IV pulse methylprednisolone and IV rituximab
- Subsequent normalization of creatinine

3. Which of the following is most likely to produce lesion(s) that mimic a cellular crescent?

A. Polyomavirus nephropathy
B. Focal segmental glomerulosclerosis, tip variant
C. Focal segmental glomerulosclerosis, cellular variant
D. Collapsing glomerulopathy
E. Diabetic nephropathy

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Crescents in the renal biopsy

- Rare or few isolated crescents are fairly common
- Extracapillary proliferation of cells (parietal epithelial cells, podocytes, macrophages, fibroblasts) defines a crescent
- The 2003 ISN/RPS classification of lupus nephritis requires a cellular crescent to be 3 or more cell layers occupying 25% or more of the Bowman capsular circumference
- The 2016 revision of ISN/RPS lupus classification: extracapillary hypercellularity involving 10% or more of Bowman capsular circumference
  - Cellular crescent: more than 75% cells and fibrin, less than 25% fibrous matrix
  - Fibrocellular crescent: 25 to 75% cells and fibrin, remainder fibrous matrix
  - Fibrous crescent: more than 75% fibrous matrix, less than 25% cells and fibrin

Crescents in the renal biopsy

- Crescentic glomerulonephritis defined as presence of crescents in ≥50% of glomeruli in a biopsy sample; constitutes an "urgent or significant unexpected diagnosis"
- Pauci-immune GN
  - Most frequent cause in all age groups
- Anti-GBM disease
  - Most number of crescents which tend to be cellular and of similar age
- Immune complex mediated
  - Almost any immune complex mediated glomerulopathy can have crescents but glomeruli tend to be focally involved
  - Lupus nephritis, IgA nephropathy/IgA vasculitis, post-infectious GN, MPGN are common examples

Case 4

12 year old Chinese girl

Previously well

Microscopic haematuria and proteinuria with microangiopathic haemolytic anemia

- Presented in Jul 24 with fever, abdominal pain, vomiting, diarrhea, jaundice, dark-coloured urine and gum bleeding
- Decrease in effort tolerance and lethargic
- No rashes, alopecia, joint pains
- No family history of renal, autoimmune or haematological conditions

On examination:

BP 120/70

Mild periorbital edema and facial swelling

Pale

Abdomen – soft, tender over peri-umbilical area and no masses

Mild bilateral pedal edema

Haematuria and nephrotic-range proteinuria
Urine RBCs 700 cells/Ul (36% dysmorphic)
Urine protein/cr ratio 320mg/mmol
Albumin 31g/L

Normal renal function

Investigations

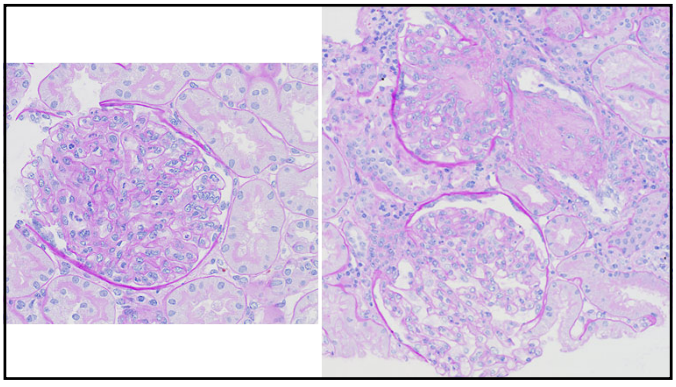
Haemolytic anemia and thrombocytopenia
Anemia Hb 7.7g/Dl and thrombocytopenia 8 x10^9/L
DCT 1+, raised LDH and low haptoglobin

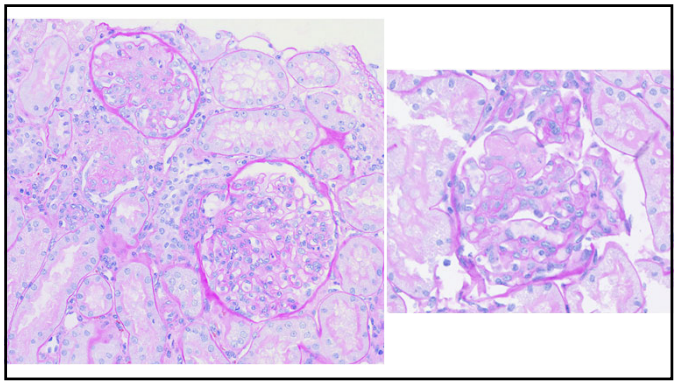
ESR 85mm/hr
Low C3 34mg/dL
Low C4 4mg/dL
ANA >= 640 (homogeneous)
Anti-ds DNA 70.0IU/ml
Anti-Ro, anti-La and anti-Crithidia antibody positive

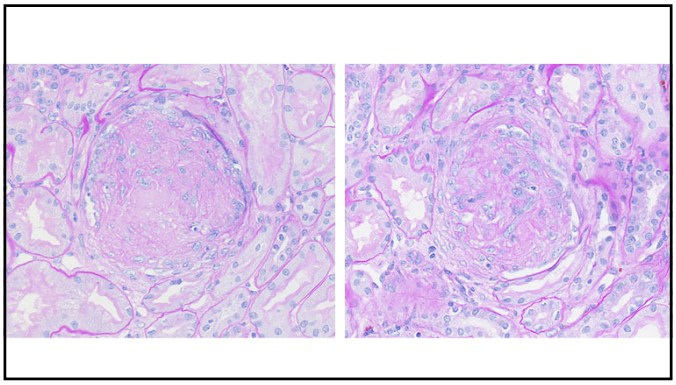
Immune-mediated thrombotic thrombocytopenic purpura

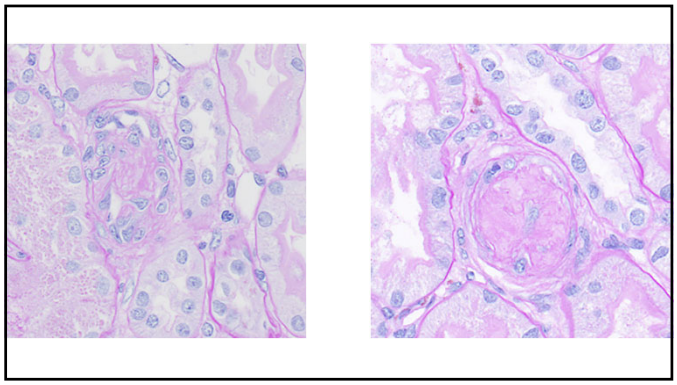
Low ADAMTS13 activity >2%
High antibodies to ADAMTS13 69

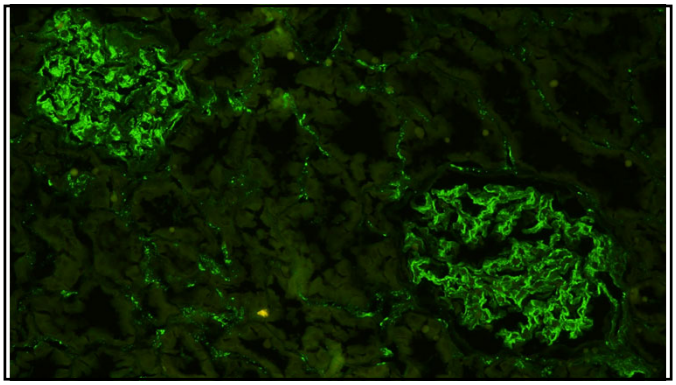
Renal biopsy in Jul 2024

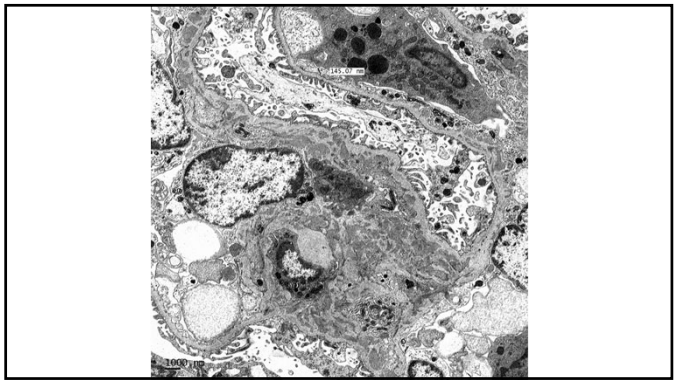


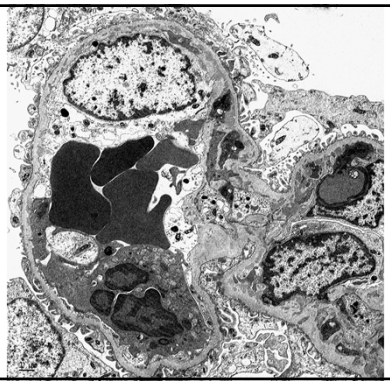


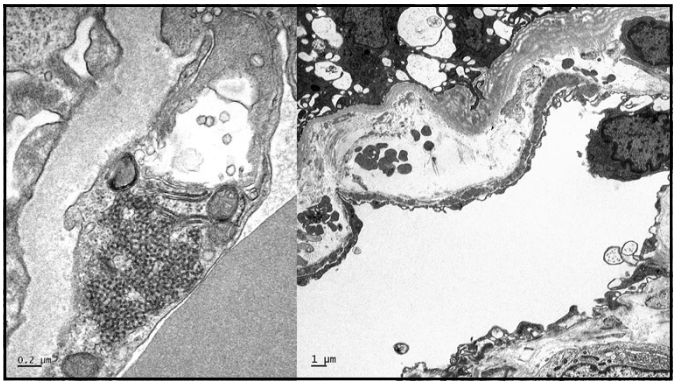








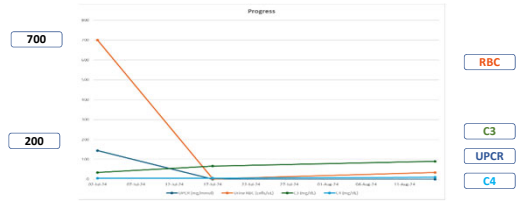




Diagnosis: Diffuse proliferative glomerulonephritis consistent with diffuse (class IV) lupus nephritis. Acute-on-chronic (organising) thrombotic microangiopathy.

Subsequent progress

- Given 6 doses of IV pulse methylprednisolone, 5 sessions of plasmapheresis and 2 cycles of cyclophosphamide
- Maintained on hydroxychloroquine and oral prednisolone
- Normal C3 and improvement in C4 (10mg/L) with resolution of proteinuria



4. Injury to which cell type is the most common cause of thrombotic microangiopathy?

A. Endothelial cell
B. Podocyte
C. Parietal epithelial cell
D. Mesangial cell
E. Smooth muscle cell

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A. Endothelial cell
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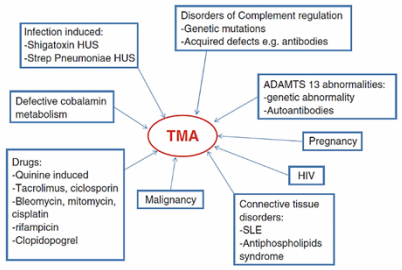
Pathophysiological approach to thrombotic microangiopathies

- Complement-mediated
- Coagulation-mediated
- Autoimmune-mediated and transplant rejection-related
- Metabolism-associated
- Drug-induced & radiation-associated
- Shiga toxin-associated



Pediatr Nephrol 26: 523–533, 2011

Challenges in transplanting the young child: anaesthetic considerations

Dr Andrea Yap
Consultant Anesthesiologist
Al Jalila Children's Hospital, Dubai

Content

- Case summary
- Management of intra-operative issues
- MCQs

What makes this case so interesting?

1) Young child

2) Aortic cross clamping

3) Significant blood loss (>1 circulating blood volume) and dilutional coagulopathy

Case summary

Case summary

- **5 year old** chinese female for **living donor renal transplant** (Donor characteristics: mother, weight 56.5kg, height 162cm)

- Weight: **13.5 kg** (<3rd centile)
- Height: **98 cm** (<3rd centile)

- Born at KKH at 34+1 weeks , BW 1910g
- Congenital nephrotic syndrome due to **Denys-Drash syndrome**

Medical background

- Renal replacement therapy:
- Started on CRRT via right femoral line on D12 of life
- TK catheter insertion at 6 wks, initiated on PD 8 wks of life

- Developed peritoneal failure with initiation of **haemodialysis** by age 4

- **Prophylactic bilateral nephrectomy at 1 year with PEG insertion**

Medical background

- **Complications of CKD**:
- Anaemia, on injectable erythropoietin and oral iron
- Mineral bone disease, on phosphate binders and oral calcijex
- Hypertension with early LVH, normal biventricular function
- Short stature, on growth hormone therapy

Investigations

- Hb **9.7** TW 9.6 Plt 226
- Na 136 K 4.0 Ur 14.2 Cr 549
- PT 9.9 PTT 22.7 INR 0.93
- Alb 33

- ECG: NSR
- CXR- no consolidation

ECHO

- LVEF 65%
- Stable mild LVH
- Dilated aortic root
- Stable mild aortic and mitral regurgitation

Ultrasound abdominal vessels

- The infrarenal abdominal aorta measures 0.6 x 0.6 cm in axial dimension.
- The **right CIA measures 0.5 x 0.4 cm** in axial dimension.

- The abdominal aorta segment from inferior mesenteric artery (IMA) to aortoiliac bifurcation measures 7.6 x 6.7 mm in maximal axial dimension.

- The visualised infrarenal abdominal aorta, inferior vena cava, right common iliac artery and veins demonstrate normal Doppler waveforms.

Ultrasound peripheral vessels

- Features suggestive of partial / non-occlusive thrombus around the vascular catheter in the right brachiocephalic vein.

- **Right IJV is not visualised, probably occluded**, with multiple venous collaterals noted in the vicinity, suggesting chronicity to the occlusion.

- **Left IJV is small in calibre** but grossly patent.

Intra-op

Anaesthesia

- Induced with propofol and fentanyl
- Paralysed with atracurium
- Maintenance anaesthesia with Propofol TCI and remifentanil

Airway and breathing

- Grade 1 intubation, size 5 cuffed ETT, cuff not inflated
- Secured at 14.5cm at lips
- Nil issues with ventilation intra-op

Circulation

- Arterial and central line inserted
- BP 135mmHg at max (required vasopressors and vasodilators to support swings in BP)
- CVP maintained between 15-20mmHg

Intra-operative issues and management

1) Young child

2) Aortic cross clamping

3) Significant blood loss (>1 circulating blood volume) and dilutional coagulopathy

Summary of the surgical procedure done

- Living related renal transplant, retroperitoneal approach.
- Vascular anastomosis - The transplanted kidney was placed in the retroperitoneal space towards the empty right renal fossa. Graft renal vein (single) was anastomosed to the recipient common iliac vein with continuous sutures. The aorta below the takeoff of the inferior mesenteric artery and proximal to the bifurcation was utilised for the arterial anastomosis. **Arterial anastomosis was performed end-to-side between the graft renal artery (single) to the recipient aorta with continuous sutures.**
- Ureteric anastomosis – The bladder was very small sized. Non tunnelled ureteric re-implantation was performed full thickness ureter to full thickness bladder over a 4F DJ stent as there was no room on the bladder wall to tunnel the ureter. There was urine leak noted from the ureteric anastomosis and ureteric re-implantation was re-done immediately with no further leak. The transversus abdominus was not closed, only external and internal obliques were closed.
- On table USG doppler showed good flow and waveforms in the renal vessels (main, upper and lower pole vessels).
- Ischemic times:
  - Cold ischemic time: 110 min
  - Warm ischemic time: 64 min
- Patient demonstrated urine output on table.

Aortic cross-clamping

Cross clamp on → increased afterload → hypertension → vasodilators (e.g GTN)

Cross clamp release → decreased afterload → hypotension, lactic acidaemia, myocardial ischaemia → vasoconstrictors (e.g. Dopamine)

Intra-operative issues and management

1) Young child

2) Aortic cross clamping

3) Significant blood loss (>1 circulating blood volume) and dilutional coagulopathy

Massive blood loss

- Bleeding from veins in the perinephric fat of the graft kidney at the time of reperfusion and subsequently from another vein on the graft
- Bleeding controlled surgically

- Hb drop to 7
- PRBC and 5% albumin given to maintain haemodynamics → Hb 9

Massive blood loss

- Later in the operation, there was diffuse oozing noted by surgeons
- ROTEM was done → Fibrinogen deficiency
- Total blood loss was estimated at around 1.7L

Fluids

- **Total input 6.3L**
- **Output: blood loss 1.7L, urine output 1.5L**
- **Total intra-op fluid balance +3.1L**

What is a massive transfusion?

- Defined as replacement of >1 total circulating blood volume in 24 hours, or
- >50% of total circulating blood volume in 4 hours

Treatment goals intra-op

- **Communication**
- Know your thresholds (Hb drop targets, total blood volume)
- Early recognition of blood loss and intervention
- Use of different blood products to correct coagulopathy

Treatment goals

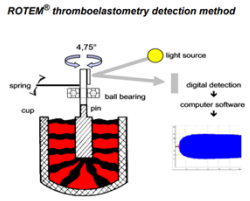
- **Keep them warm**
- Monitor acid-base status
- Calcium (>1.1)
- Point of care testing

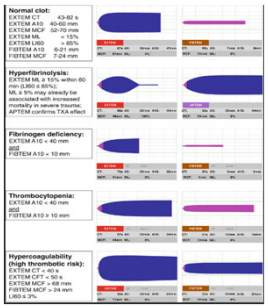
Rotational thromboelastometry

ROTEM® *delta* ROTEM® *sigma*

Calatzis, A et al. Rotem® Analysis Target Treatment of Acute Haemostatic Disorders

How it works





Görlinger, K et al. Rotational Thromboelastometry (ROTEM®). P267-298. Apr 2016

Post-operative course

Post-operative course

- Kept intubated post-op (extubated on POD1)
- Borderline BP on arrival to PICU → 190 ml 5% albumin given
- Hb drop 7.8> 4.9, APTT 104.5, PT 19.3 PLT 52
→Transfused 230ml FFP and 230ml platelet and 15ml/kg blood
- Post transfusion labs: Hb 7.5, PT 11.9, APTT 29.6, Plt 196

Issues in PICU

- Post transplant ATN and tubulopathy (hypokalaemia, hypophosphataemia, hypomagnesaemia)
- Brisk urine output requiring large volume urine replacement
- Required IV GTN infusion on POD2 and labetalol on POD4, weaned off by POD 7
- Duration of stay in PICU: 10 days

Post-operative course

- Underwent bladder cycling followed by urinary catheter removal 4 weeks later, no urine leak on US kidneys after catheter removal
- MAG3 scan 6 weeks post-op showed well perfused, functioning kidney

Summary

1) Young child

2) Aortic cross clamping

3) Significant blood loss (>1 circulating blood volume) and dilutional coagulopathy

MCQs

MCQs

1. Which of the options below is <u>not</u> a physiological response to aortic cross-clamp release?

a) profound hypotension
b) lactic acidaemia
c) myocardial ischaemia
d) an increase in mean arterial pressure

MCQs

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MCQs

2. What is the definition of a massive transfusion?

a) replacement of >50% total blood volume in 24 hours, or >50% of total blood volume in 4 hours

b) replacement of >100% total blood volume in 24 hours, or >50% of total blood volume in 4 hours

c) replacement of >50% total blood volume in 24 hours, or >25% of total blood volume in 4 hours

d) replacement of >100% total blood volume in 24 hours, or >25% of total blood volume in 4 hours

CHILDREN COME FIRST

MCQs

2. What is the definition of a massive transfusion?

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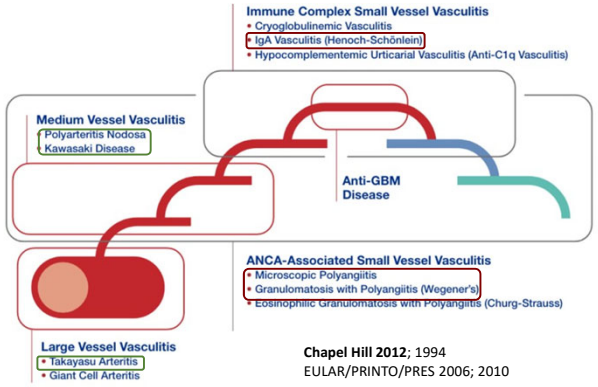
CHILDREN COME FIRST

Management of Vasculitis



Chapel Hill 2012; 1994
EULAR/PRINTO/PRES 2006; 2010

Suspecting vasculitis

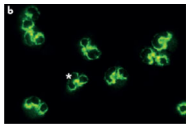
- Fever, weight loss, fatigue
- Palpable purpura, fixed urticaria, livedo, nodules, ulcers
- Headache, mononeuritis multiplex, focal lesions
- Arthralgia/arthritis, myalgia, serositis
- Hypertension, hematuria, AKI
- Pulmonary infiltrate, hemorrhage
- Myocardial ischemia, arrhythmias

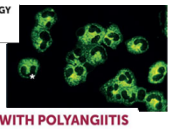
- High ESR, C-RP
- Leukocytosis, anemia, thrombocytosis
- Eosinophilia
- Hematuria, proteinuria
- Antineutrophil cytoplasmic antibodies
- High F-VIII antigen (vWF)
- Cryoglobulinemia
- Circulating immune complexes

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY
CLASSIFICATION CRITERIA FOR **MICROSCOPIC POLYANGIITIS**

Clinical	Nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect /perforation	-3
Diagnostic Tests	pANCA or anti-MPO ANCA positive	+6
	Fibrosis or interstitial lung disease on chest imaging	+3
	Pauci-immune glomerulonephritis on biopsy	+3
	cANCA or anti-PR3 ANCA positive	-1
	Serum eosinophil count ≥ 1 ($x10^9$/L)	-4

Sum scores for 6 items. A score of ≥ 5 is needed for classification of MPA





GRANULOMATOSIS WITH POLYANGIITIS

Clinical Criteria	Nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect /perforation	+3
	Cartilaginous involvement (cartilage inflammation of the ear or nose, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
	Conductive or sensorineural hearing loss	+1
Diagnostic Testing Criteria	cANCA or anti-PR3 ANCA positive	+5
	Pulmonary nodules, mass, or cavitation on chest imaging	+2
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
	Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
	Pauci-immune glomerulonephritis on biopsy	+1
	pANCA or anti-MPO ANCA positive	-1
	Serum eosinophil count ≥ 1 ($x10^9$/L)	-4

Sum scores for 10 items, if present. A score of ≥ 5 is needed for classification of granulomatosis with polyangiitis.

#1. 11-yr boy; fever 20 d, cola-colored urine 5 days

Oliguria, anasarca 3 days
No sore throat; pyoderma; arthralgia
Cough 4 d; no hemoptysis; dyspnea

48 kg (1.4 SDS); 153 cm (1.2 SDS)
30 breaths/min; **136/84** mm Hg
Mammary, axillary crepitations
Soft liver 4 cm; span 12 cm

C3; C4; **ANA:** 135; 38 mg/dL; **negative**
Viral serologies, SARS-CoV2: **Negative**
c-ANCA Positive; PR3-ANCA 233 IU/mL
P-ANCA negative; MPO-ANCA negative

Hemoglobin **7 g/dl**; **no schistocytes**; retics 4%	
White cells; platelets	12,000; 436,000/mm^3
Urea; creatinine	142; **4.1-5.3** mg/dL
Na^+; K^+	127; 4.9 mEq/L
Protein; albumin	5.1-5.5; 2.7-2.9 g/dL
Urinalysis	4+ protein; RBC; casts
Urine PCR	5.8-6.8 mg/mg

Next most appropriate management?

Initiate hemodialysis, kidney biopsy &
1. IV methylprednisolone
2. IV cyclophosphamide
3. Plasma exchanges
4. Await biopsy results, decide

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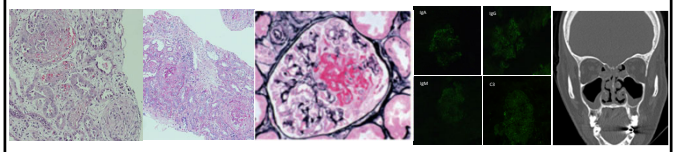
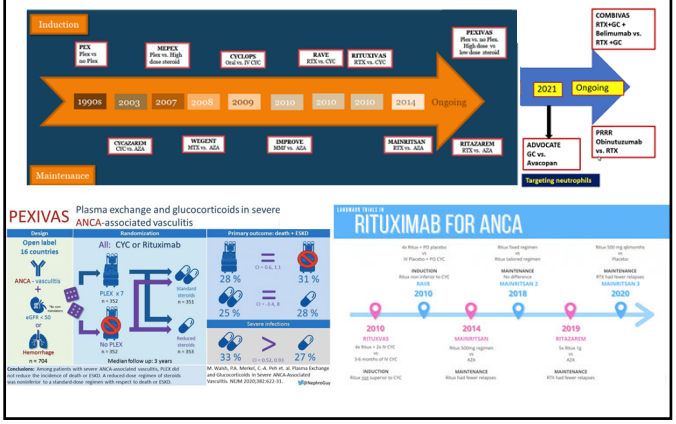
Pauci-immune necrotizing crescentic glomerulonephritis



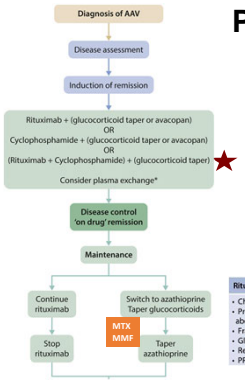
Granulomatosis with polyangiitis

IV Methylprednisolone 30 mg/kg for 6 d; prednisone 1 mg/kg/d
IV Cyclophosphamide 500 mg/m^2 q 3-4 wk x 6
PEX 1-1.5 volumes; daily then alternate days (total 7)
Low dose **prednisone** x 6-12 months
Mycophenolate mofetil (1000 mg/m^2) x 3-4 years

Trials in AAV



Principles of therapy



- Prompt diagnosis
- Induction: Steroids & CP/RTX
- Low dose steroids are effective
- Avacopan: Steroid sparing; low eGFR
- PEX: Creatinine >3.4 mg/dL, rapidly rising; dialysis need; alveolar h'age with hypoxemia; anti-GBM-ANCA overlap
- Maintenance: RTX/AZA + low dose steroids; 18-48 months

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3-ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered

Relapse: Reinduction with RTX
Discontinue if dialysis ≥3 months & no extrarenal features
Transplant: Delay ≥6 months after remission, irrespective of ANCA

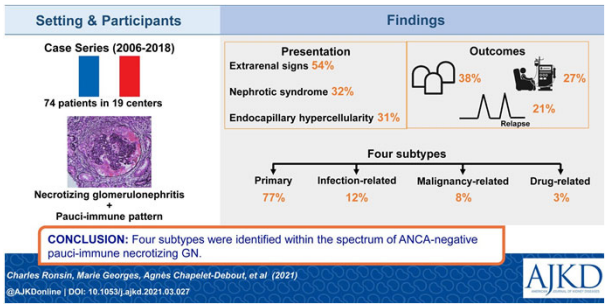
Medications for induction therapy

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF	Avacopan
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m²/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m²/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with i.v. cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response	30 mg twice daily as alternative to glucocorticoids, in combination with rituximab or cyclophosphamide induction

Plasma exchange: Creatinine >3.4 mg/dl; requires dialysis; diffuse alveolar hemorrhage with hypoxemia; overlap AAV & anti-GBM

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

ANCA-negative pauci-immune crescentic GN (25%): Proteinuria, less extrarenal involvement, unsatisfactory outcome KI Reports 2023



Meta-analysis (n=301; 14 studies): **Similar data**
UK. Kidney360 2023;4:69-77

Pediatric AAV: Induction, maintenance

		SHARE 2019	CARRA CTP 2021
Induction			
Steroids		Prednisone	IV pulses; oral std. dose
Other therapies		IV > oral cyclophosphamide (CYC)	IV > oral CYC RTX (refractory AAV, CYC toxicity); do not combine
PEX		Yes	Physician discretion
Maintenance	1st line 2nd line	**AZA**/MTX/**MMF**/RTX **MMF/RTX**/IVIG/TCZ/TNF block	**AZA**/MTX; **RTX** for 24-48 months; discretion

Rheumatol 2019;58:656-71
Arthritis Care Res 2022;74:1550-58

IgA vasculitis: 14-20/100,000 school children

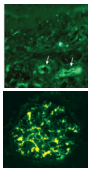
Palpable purpura 100%, arthritis 68%, abdomen pain 53%, nephritis **30**-50%; recurrences 30-40%

Peak incidence 4-6 yrs (M:F 1.5:1)

Renal involvement in 6 months of onset ~95%; mild in most

Hematuria & proteinuria; nephritic, nephrotic syndrome <20%; ESKD 1-2%

Screen urine for 6-12 months



The EULAR/PReS/PRINTO classification criteria for childhood IgA vasculitis.

Validated (N=872 <18-yr): 100% sensitivity & 87% specificity

Criterion	Description
Mandatory	Purpura or petechia with lower limb predominance
At least 1 out of 4	(1) Acute onset diffuse abdominal colicky pain (may include intussusception and gastrointestinal bleeding) (2) Histology showing leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposition. (3) Acute onset arthralgia or arthritis (4) Either proteinuria or haematuria

Management

Supportive…. analgesics

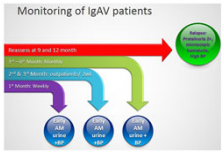
Corticosteroids: not indicated for mild cases

Indications for corticosteroids

- Severe GI disease, hemorrhage; orchitis
- Pulmonary hemorrhage, cerebral vasculitis

Prednisone 1-2 mg/kg/day for 2 weeks; taper 2 weeks

Prophylactic steroids do not prevent nephritis

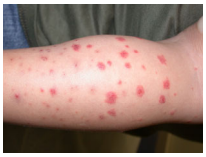


Kidney biopsy
Significant proteinuria
Impaired GFR

#2. 6-yr-old girl; abdominal pain, melena 7-d; rash 3 d

No hematuria, oliguria, arthralgia, rash
Heart rate 96/min; 126/84 mm Hg
Mild pallor; pedal edema

Hemoglobin	10 g/dl; normocytic
Platelets	538,000 /mm^3
Urea, **creatinine**	16; **0.4** mg/dL
Na^+, K^+	130; 4 mEq/L
Protein, albumin	5.5; 3.0 g/dL
Urinalysis	1-2+ protein; 5-8 RBC
Urine PCR	0.6-0.7 mg/mg
24-hr protein	450-500 mg/day
C3; C4	168; 19 mg/dL
ANA, HBsAg, anti-HCV	Negative



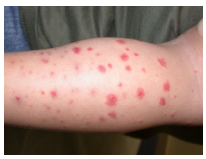
Most appropriate next step?

1. Paracetamol; urinalysis q 2-wk
2. Oral prednisolone x 2 weeks
3. Oral prednisone, ACEi
4. Kidney biopsy

#2. 6-yr-old girl; abdominal pain, melena 7-d; rash 3 d

No hematuria, oliguria, arthralgia, rash
Heart rate 96/min; 126/84 mm Hg
Mild pallor; pedal edema

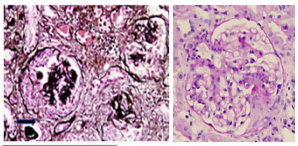
Hemoglobin	10 g/dl; normocytic
Platelets	538,000 /mm^3
Urea, **creatinine**	16; **0.4** mg/dL
Na^+, K^+	130; 4 mEq/L
Protein, albumin	5.5; 3.0 g/dL
Urinalysis	1-2+ protein; 5-8 RBC
Urine PCR	0.6-0.7 mg/mg
24-hr protein	450-500 mg/day
C3; C4	168; 19 mg/dL
ANA, HBsAg, anti-HCV	Negative



Most appropriate next step?

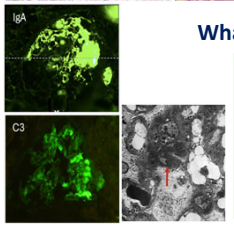
1. Paracetamol; urinalysis q 2-wk
2. Oral prednisolone x 2 weeks
3. Oral prednisone, ACEi
4. **Kidney biopsy**

#3. 6-yr-old girl; IgA vasculitis



ISKDC Class IIIa focal mesangial proliferation with crescents, sclerosis

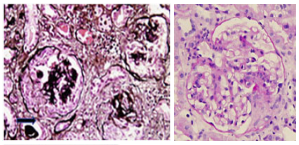
M1E1C1S1T0



What is the most appropriate management?

1. Prednisolone, taper over 6-months
2. Prednisolone + PO cyclophosphamide x 12-wk
3. Prednisolone + cyclophosphamide; then azathioprine/MMF
4. IV methylprednisolone + rituximab (2 doses); then azathioprine/MMF

#3. 6-yr-old girl; IgA vasculitis



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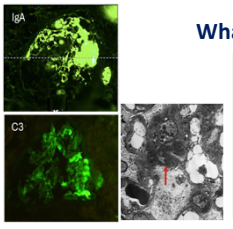

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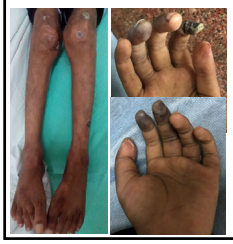
IgA vasculitis with nephritis: Comparing guidelines

Severity	Definition	SHARE 2019	KDIGO 2024
Mild IgAVN	Normal eGFR, UPCr <2.5; minimal change, mesangial proliferation	**1st** Prednisone **2nd** AZA/MMF/CsA if proteinuria >4-wk	Up >0.5 g: ACEi/ARB Proteinuria persists: Consider prednisone
Moderate IgAVN	<50% crescents; eGFR <80, or UPCr >2.5 (>4 weeks)	**1st** Prednisone, IV MP **2nd** AZA/MMF/CP (ISKDC class III, more)	Proteinuria: Steroids Crescents & no RPGN: No more therapy
Severe IgAVN	>50% crescents; eGFR <80 or UPCr >2.5 (>4 weeks)	**Induction** IV CP, IV MP **Maintenance** AZA/MMF, prednisone	Treat similar to ANCA associated vasculitis

IPNA guidelines 2024

#4. 12-yr; fever, pain abdomen, weight loss 3 months

Myalgia, large joint arthralgia; blood pressure 130/86 mm Hg
Hb 11 g/dl, TLC 27000, platelets 620000/cu mm, ESR 50 mm
Urine: 1+ protein; hyaline casts
Creatinine 0.7 mg/dl; albumin 4 g/dl, SGOT, SGPT normal
Antinuclear factor, ANCA negative; C3 100 mg/dl



What diagnostic test would you perform?

1. Kidney biopsy
2. Standard skin punch biopsy
3. CT angiography
4. Sequencing *ADA2, MEFV, SAVI*

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Myalgia, large joint arthralgia; blood pressure 130/86 mm Hg
Hb 11 g/dl, TLC 27000, platelets 620000/cu mm, ESR 50 mm
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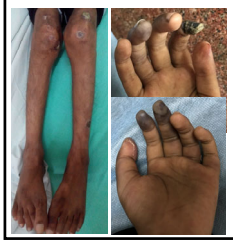

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3. **CT angiography**
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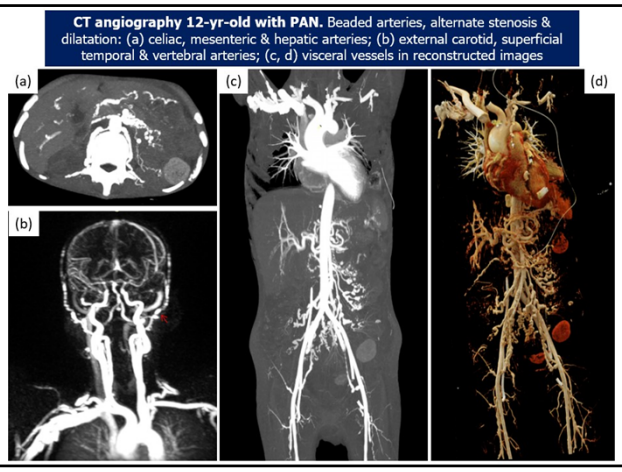
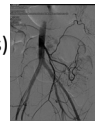


CT angiography 12-yr-old with PAN. Beaded arteries, alternate stenosis & dilatation: (a) celiac, mesenteric & hepatic arteries; (b) external carotid, superficial temporal & vertebral arteries; (c, d) visceral vessels in reconstructed images

Classification criteria for childhood polyarteritis nodosa

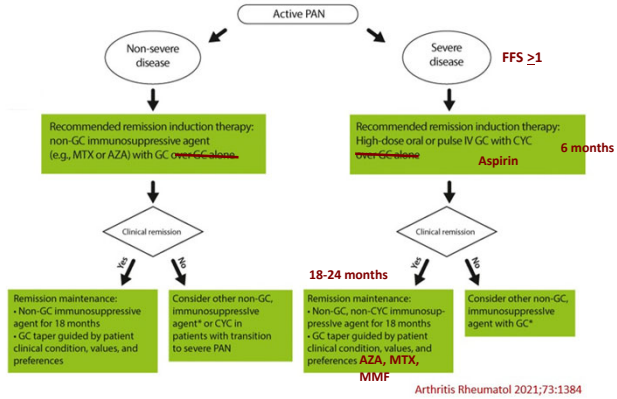


Necrotizing vasculitis in medium/small arteries, OR angiographic abnormalities (aneurysm, occlusion, stenosis) plus one of the following:

- Skin involvement (livedo reticularis, nodules, infarcts)
- Myalgia or muscle tenderness
- Systemic hypertension
- Peripheral neuropathy (sensory, motor)
- Kidney involvement (proteinuria, hematuria, eGFR <50%)

***ADA2* associated PAN:** Young age; family history; livedo +++; **ischemic stroke**; leukopenia, thrombocytopenia; low IgA, IgM, IgG
TNF-α inhibitors, thalidomide, early HSCT, gene therapy

Polyarteritis nodosa : 2021 ACR Guideline



Arthritis Rheumatol 2021;73:1384

Adequate therapy of PAN: Satisfactory outcomes

Permanent cure can be anticipated in children

PVAS (pediatric vasculitis activity score) disease activity

Five factor score (FFS) predicts 5-yr mortality [severe GI involvement, creatinine >1.6 mg/dl, proteinuria >1 g/d, heart disease, CNS disease]
0=12%; **1**=26%; **2**=46%

Steroid & cytotoxic therapy: **5-yr survival ~90%**

Refractory disease: **TNF-α, IL-6 blockers;** tofacitinib, IVIG

EULAR/PRES 2005

Mandatory

Abnormalities (conventional, CT, MR angiogram)

One of 5 criteria

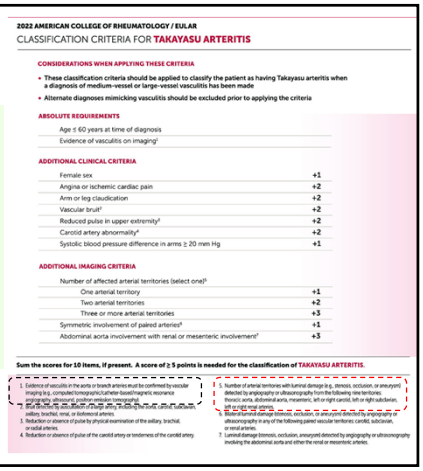
Pulse deficit, claudication extremities

Blood pressure discrepancy limbs >10 mm Hg

Bruit aorta, major branches

Systolic/diastolic hypertension

Elevated ESR or CRP



2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR

CLASSIFICATION CRITERIA FOR **TAKAYASU ARTERITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify the patient as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

ABSOLUTE REQUIREMENTS

Age ≤ 60 years at time of diagnosis	
Evidence of vasculitis on imaging[1]	

ADDITIONAL CLINICAL CRITERIA

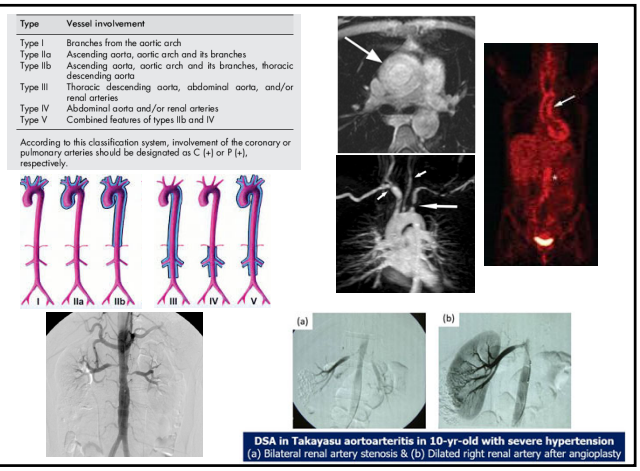
Female sex	+1
Angina or ischemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit[2]	+2
Reduced pulse in upper extremity[3]	+2
Carotid artery abnormality[4]	+2
Systolic blood pressure difference in arms ≥ 20 mm Hg	+1

ADDITIONAL IMAGING CRITERIA

Number of affected arterial territories (select one)[5]	
One arterial territory	+1
Two arterial territories	+2
Three or more arterial territories	+3
Symmetric involvement of paired arteries[6]	+1
Abdominal aorta involvement with renal or mesenteric involvement[7]	+3

Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of TAKAYASU ARTERITIS.

1. Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (e.g., computed tomographic/catheter-based/magnetic resonance angiography, ultrasound, positron emission tomography).
2. Bruit over the aorta, through one or both subclavian, axillary, brachial, renal, or ilio-femoral arteries.
3. Reduction or absence of pulse by physical examination of the axillary, brachial, or radial arteries.
4. Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery.
5. Number of arterial territories with luminal damage (e.g., stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography from the following nine territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal artery.
6. Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography in any of the following paired vascular territories: carotid, subclavian, or renal arteries.
7. Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries.



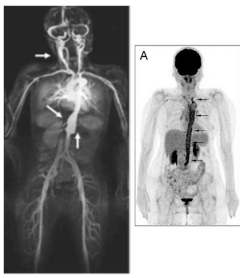
Type	Vessel involvement
Type I	Branches from the aortic arch
Type IIa	Ascending aorta, aortic arch and its branches
Type IIb	Ascending aorta, aortic arch and its branches, thoracic descending aorta
Type III	Thoracic descending aorta, abdominal aorta, and/or renal arteries
Type IV	Abdominal aorta and/or renal arteries
Type V	Combined features of types IIb and IV

According to this classification system, involvement of the coronary or pulmonary arteries should be designated as C (+) or P (+), respectively.

DSA in Takayasu aortoarteritis in 10-yr-old with severe hypertension
(a) Bilateral renal artery stenosis & (b) Dilated right renal artery after angioplasty

#5. 14-yr-old girl Takayasu arteritis; stage II hypertension, left ventricular hypertrophy

CBC, creatinine normal
Na 125-126; K 3.1-3.3 mEq/L
Tuberculin 18 mm
Urinalysis 1+ protein



Apart from antihypertensives, the most appropriate initial therapy is:

1. Prednisone & antitubercular agents
2. High dose prednisone & MMF/AZA/MTX
3. Low dose prednisone & tocilizumab
4. Low dose prednisone & TNF inhibitors

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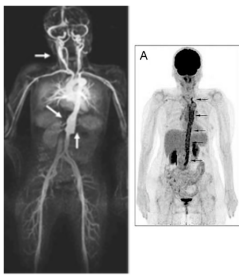

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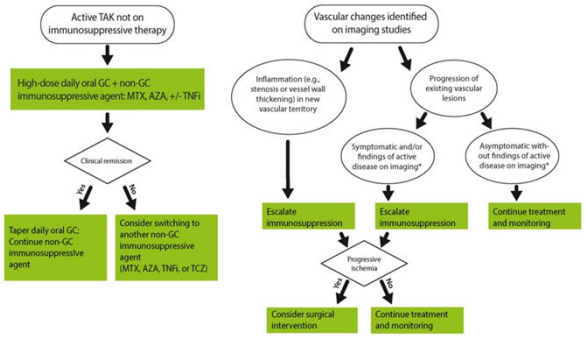
Takayasu arteritis : 2021 ACR Guideline

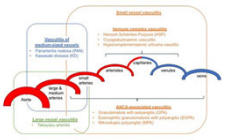


* Can be suggested by vascular edema, contrast enhancement, and/or increased wall thickness on MR or CT angiography, or supra-physiologic FDG uptake in the arterial wall on PET imaging

Arthritis Rheumatol 2021;73:1349

Managing childhood vasculitides

- Classification criteria, serology enable accurate diagnosis
- Therapies extrapolated from large studies in adults
- Recognition & appropriate therapy: Satisfactory outcomes
- IgA vasculitis, Kawasaki disease, PAN: Focused studies in children



Difficult-to-Treat Nephrotic Syndrome

Apollo Children's HOSPITALS

#1. 2-yr girl, onset of nephrotic syndrome

Oliguria, pedal edema, ascites
Pulse 94/minute; breaths 22/min; 90/70 mm Hg
Urine protein 3-4+; no red cells or leukocytes; few hyaline casts
Urea 40, creatinine 0.34 mg/dl; albumin 1.9 g/dl; Na^+ 134, K^+ 3.8 mEq/L
Hb 13.0 g/dl, PCV 40; TLC 11800/cu mm, platelets 170000/cu mm
Further evaluation, include all **EXCEPT:**

1. Urine protein to creatinine ratio
2. Tuberculin test
3. Vaccination status, serology (if possible)
4. Ultrasound abdomen

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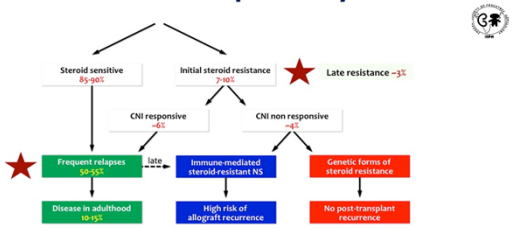
Difficult to treat nephrotic syndrome



Steroid sensitive	Complete remission within 4-6-weeks' prednisone treatment
Frequent relapses	Relapses ≥2 in ***first*** 6-months, ≥***3*** in any 12-months
Dependence	≥2 consecutive relapses on/in <2-wk of discontinuing prednisone

Significant toxicity Hyperglycemia; obesity; stunted; glaucoma, cataract; myopathy; psychosis

Difficult-to-treat **Frequent relapses *or* significant toxicity & failing ≥2 strategies**

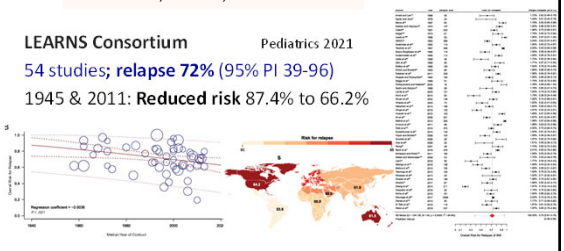
Relapses in 72%; frequent in 50%

Prednisone 60 mg/m²/d till remission; 40 mg/m²/alt. d for 4 wk

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

CJASN 2020; KI 2020; Pediatr Nephrol 2021

LEARNS Consortium Pediatrics 2021
54 studies; **relapse 72%** (95% PI 39-96)
1945 & 2011: **Reduced risk** 87.4% to 66.2%



Frequent relapses: Alternate-day prednisone

Concern in developed countries

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

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

Risk of corticosteroid toxicity

Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial
Pediatr Nephrol 2019;34:829-35

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

CTRI/2019/01/017091

Daily prednisone during infections

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

Prednisolone 15 mg/m² x 6 d during URTI *Adjusted risk difference: -0.024, 95% CI -0.14 to 0.095; *P*=0.7

Alkylating agents reduce relapses by ~56%

Cochrane 2020: RR 0.44; 0.32-0.60

Review 38 studies (n=1504) **Better in FR & children >5-8 yr**

Relapse free survival	2 yr	5 yr
Frequent relapses	72%	36%
Dependence	40%	24%

Pediatr Nephrol 2001; **CRD42021241332**

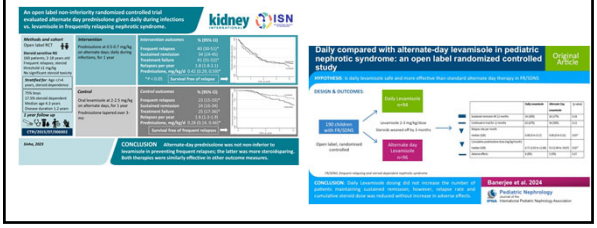
Levamisole: Steroid sparing; safe

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

A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome **N=99; Kidney Int** 2018

Sustained remission & reduced relapses

Better in frequent relapsers



Levamisole ADR with long term use

Psychiatric (OR 1.4); hepatobiliary (2); vasculitis (7); encephalopathy (22); hematological, rashes VigiBase. Br J Clin Pharmacol 2022

Cocaine-levamisole associated vasculitis Rheumatol Int 2019

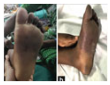
Serological features: ANCA +, PR3 + and MPO +, ANA +, complement levels ↓, APS-Abs +

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

J Clin Med 2019

N = 117	%
ANCA (IFA, ELISA)	**17%** (11-25)
ANCA (IFA)	13% (8-20)
ANCA (ELISA)	13% (8-20)
MPO; PR3; both	9%; 1%; 3%
HNE	6%
ANA (IFA)	**16%** (11-24)
ACL IgM >> IgG	7% (4-13)

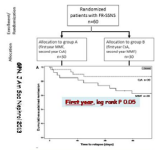
Leukopenia (4); transaminitis (1); flu (2)
ANCA positive: Females; duration of therapy; prednisone use



Limb ischemia, gangrene; toe autoamputation
Indian J Rheumatol 2021

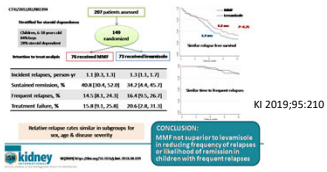
MMF: Steroid sparing; use right dose

MMF inferior to CsA



CsA sustained remission 85%
MMF-remission 64% (P=0.06)
High MPA levels better eGFR better with MMF

MMF not superior to levamisole



KI 2019;95:210

MMF more effective in young

Pediatr Nephrol (2016) 31:2095–2101

N=96; MMF 1063-1100 mg/m²/day

Better: Young; short disease course

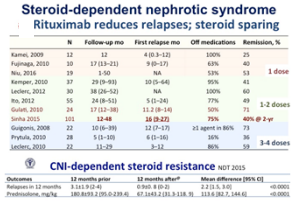
MMF: Target higher AUC

	Relapses/yr
AIIMS (2019) MMF group 750-1000 mg/m²	**1.05**
Gellerman (2013) MMF group	**0.75**
Low MPA exposure (AUC_{0-12} <50 µg.h/ml)	**1.40**
High MPA exposure (AUC_{0-12} >50 µg.h/ml)	**0.27**
Hackl (2016)	
Low MPA exposure (AUC_{0-12} <45 µg.h/ml)	**1.06**
High MPA exposure (AUC_{0-12} >45 µg.h/ml)	**0.17**

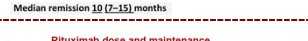
KI 2019; JASN 2013; IPNA 2023

Steroid-dependent nephrotic syndrome

Rituximab reduces relapses; steroid sparing



CNI-dependent steroid resistance NDT 2015



Median remission 10 (7–15) months

Larkins et al, 2020

6 RCTs; 269 participants

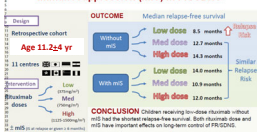
Moderate certainty evidence

Reduced risk of relapse

@ 6-months: **RR 0.23** (0.1-0.4)

@ 12-months: **RR 0.63** (0.4-0.9)

Rituximab dose and maintenance immunosuppression (mIS) in FR/SDNS



Two doses ~ optimal KI 2020:97:393

Rituximab : Most favored for FR/SD

Front Immunol 2024 15 studies; 1053; systematic review May'23

Rituximab @ 1-yr

- Most likely (92%) fewest relapses
- Most likely (99.9%) low exposure to steroids
- Most likely (46%) not to show failure

Relapse free: CsA; tacrolimus; RTX

RTX : High likelihood of relapse at 6-24 months

I. Add MMF: JSKDC07; RITURNS II; RITUXIVIG

II. Repeat @ CD19 recovery; ***sequential***

III. Re-dose @ relapse

Sequential Therapy

RTX 375 mg/m² x 2 doses

SDNS *q* 12-month

CNI dependence *q* 6-month

Data from Korea; Multicenter survey
Pediatr Nephrol 2024; JASN 2022

Steroid and/or CNI-dependent nephrotic syndrome 2015-19 **NDT 2022**

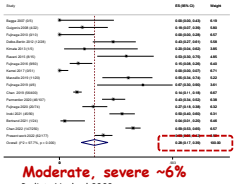
Steroid sensitive disease: Failed ≥2 alternative therapies [n=127]

Steroid resistance: Prolonged CNI therapy; CNI toxicity [n=123]

~3-yr in steroid sensitive
~2-yr in steroid resistant

~10% at 2-yr; 25% at 5-yr
More if steroid resistant (P=0.08)

RTX associated low IgG 25-35%; persistent 10-15%



Moderate, severe ~6%
Pediatr Nephrol 2023

8633 adults: **19**% low IgG
JAMA Netw Open 2018

ESPN 2022; n=1328
47-61% had low IgG; 33 severe infections
Pediatr Nephrol 2023;38:3035

Low IgG 62/177 **(35%)**	n	% (95% CI)
Moderate (100-300 mg/dL)	11	**6.2 (4-11)**
Severe (<100 mg/dL)	4	**2.3 (1-6)**

Important risk factors

- Pre-existing low IgG; low IgM, low IgA
- Steroid resistance; autoimmune CNS disease; GPA; stem cell Tx
- Younger age @ administering rituximab; <6-**10** yr
- Prior cyclophosphamide & high steroids; later MMF, purine analogs
- Multiple RTX courses (>8 infusions)

Pediatr Nephrol 2019; Pediatr Nephrol 2022; Pediatr Nephrol 2023; Ann Allergy Asthma Immunol 2023; JASN 2022; Sinha. NDT 2022

ISPN 2021

Frequently relapsing nephrotic syndrome

Prednisone alternate day; daily during infections

Frequent relapses, steroid dependence

Relapse threshold >1 mg/kg AD
Significant steroid toxicity
>1 severe relapse

No → Levamisole, Mycophenolate mofetil
Yes → MMF, Cyclophosphamide*

Frequent relapses

Difficult-to-treat disease → Cyclosporine, tacrolimus ★ → Rituximab*

Choice: Severity, AE, age, cost, parent preference
***Avoid cyclophosphamide:** <5-7 yr; peri-pubertal boys
***Avoid RTX in the young**

Attention to adverse effect monitoring

#2. 4-yr boy; nephrotic syndrome @ 2-yr of age

Frequent relapses (3 in 12 months); recent relapse; now **remission**
Compliance erratic; relapses @ 0.6-0.8 mg/kg alt. day
92 cm (**-2.5**); 16 kg (-0.03); BMI 19 (**2.2**); Cushingoid; 108/68 mm Hg
No cataract; creatinine 0.33 mg/dl; albumin 2.5 g/dl
What is the next most appropriate therapy?

Counsel regarding compliance….
Taper corticosteroids; therapy with

1. Cyclophosphamide for 12 weeks
2. Levamisole for 1-2 yr
3. Mycophenolate mofetil for 1-2 yr
4. Tacrolimus for 1-2 yr

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2. Levamisole for 1-2 yr
3. **Mycophenolate mofetil for 1-2 yr**
4. Tacrolimus for 1-2 yr

#3. 5-yr; mycophenolate mofetil 1100 mg/m^2/d

Prednisone off at 5-months; **2 relapses in last 6-months**
Hospitalizations: Hypovolemia, peritonitis
95 cm (**-3.03**); 20 kg (0.62); BMI 22.2 (**3.48**); subcapsular cataract
Creatinine 0.43 mg/dl; albumin 3.0 g/dl; glucose 88; IgG 188 mg/dl
MMF failure; difficult-to-treat nephrotic syndrome; dependence
What is the next most appropriate therapy?

1. Cyclophosphamide for 12 weeks
2. Daily therapy with levamisole
3. Tacrolimus for 2-yr
4. Sequential rituximab doses

#3. 5-yr; mycophenolate mofetil 1100 mg/m^2/d

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What is the next most appropriate therapy?

1. Cyclophosphamide for 12 weeks
2. Daily therapy with levamisole
3. **Tacrolimus for 2-yr**
4. Sequential rituximab doses

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

Genetic basis ~25%

Trautmann '15	Sadowski '15	Bierzynska '17	Wang '17	Warejko '18	Nagano '20	Cheong '20
277/1174	526/1783	49/187	34/120	85/300	69/230	127/291
24%	**30%**	**26%**	**28%**	**28%**	**30%**	**43%**
NPHS2 50%	*NPHS2* 34%	*NPHS1* 29%	*COQ8B* 24%	*NPHS1* 15%	*WT1* 25%	*WT1* 24%
WT1 17%	*NPHS1* 25%	*NPHS2* 25%	*NPHS1* 21%	*PLCE1* 13%	*NPHS1* 12%	*COQ6* 9%
NPHS1 15%	*WT1* 16%	*WT1* 8%	*WT1* 21%	*NPHS2* 9%	*INF2* 12%	*NPHS1* 9%
SMARCAL 4%	*PLCE1* 7%	*NUP107* 8%	*NPHS2* 12%	*SMARCAL* 9%	*TRPC6* 10%	*NUP107* 7%
PLCE1 4%	*LAMB2* 4%	*TRPC6* 6%	*LMX1B* 6%	*LAMB2* 7%	*LAMB2* 9%	*COQ8* 6%

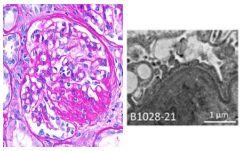
DRAGoN Network Clin Genet 2022
183 patients
Pathogenic variants **14%**
COL4A4, COL4A5 **5%**

Nanjing Univ Kidney Dis 2024
114 patients; 2018-22
Causative variants in 31%
WT1, NPHS1, ADCK4, ANLN

Pediatric Renal Biology Program
Monogenic cause [90/355] **25%** (21, 30)
NPHS2, COL4A5-A4, WT1, *PLCE1, NPHS1,* others

#4. 4-yr girl; onset @ 3-yr; initial steroid resistance

Anasarca, oliguria; 110/76 mm Hg
Developmental delay; no hematuria
Urinalysis: 3+ protein, 3-5 red cells
Urine PC 4.8 mg/mg; 24-hr 2.1 g
Blood counts normal
Creatinine 0.5 mg/dl; albumin 2.4 g/dl
TSH 8 mU/L; LDL 170 mg/dl



Most appropriate therapy?

Alt. day prednisone, ACEi &
1. Rituximab 2-4 doses
2. Tacrolimus orally
3. IV cyclophosphamide pulses
4. Mycophenolate mofetil

#4. 4-yr girl; onset @ 3-yr; initial steroid resistance

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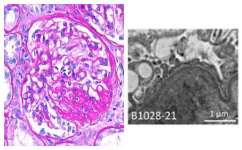

Most appropriate therapy?

Alt. day prednisone, ACEi &
1. Rituximab 2-4 doses
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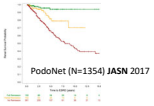
3. IV cyclophosphamide pulses
4. Mycophenolate mofetil

CNI: 50-70% complete, partial remission

Response by **8-12** weeks
Relapses ~70% on stopping therapy



Interventions for FSGS Cochrane 2022: CD003233
CsA ± Prednisone: Complete remission (RR 2.3; 1.1, 4.7); remission (RR 1.6; 1.1, 2.4) [4 studies; n=231]
Efficacy CsA ~ tacrolimus

KDIGO: Assess response @ 6-months; stop if **no response**
Minimum 12-months if response; usually 2-3 years

Referred back for no response @ 3, 6 months

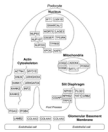
Compliance checked
Trough levels fine

Persistent proteinuria
Non-response

Steroid & CNI resistance

102 cm (-2.8); 13.5 kg (-2.7); BMI 13.5 (-1.1)
Heart rate 94/min; 100/63 mmHg
Increased intercanthal distance, flat nasal bridge

Gene	Location	Variant	Classification	ACMG
OSGEP Galloway-Mowat syndrome	Exon 2	c.157 A>T p.Ile53Phe	Likely pathogenic	**PM1** mutational hotspot; **PM2** absent in population database; **PP2** missense variant in a gene with low rate of benign variation; **PP3** disease causing variant by computational analysis; **PP5** previously reported in clinical database
	Exon 1	c.65G>T p.Gly22Val	Likely pathogenic	**PM1, PM2, PP2, PP3**



Parental segregation was confirmed [exon 2 mum; exon 1 dad]

Modest efficacy of RTX in CNI resistance

Rituximab ~35-40% partial, complete remission
Initial resistance 54/123 (44%); late 45/78 (58%)
FSGS 54/130 (42%); minimal change 49/77 (64%)

Author (publication year)	Number of patients	Patients of remission[a]	Patients of CR	Patients of PR
Case reports[b] [17–29]	13	10 (76.9%)	10 (76.9%)	0 (0.0%)
Bagga et al. (2007) [30]	33	16 (48.5%)	9 (27.3%)	7 (21.2%)
Gulati et al. (2010) [31]				
Prytula et al. (2010) [32]	27	18 (66.7%)	6 (22.2%)	12 (44.4%)
Kari et al. (2011) [33]	4	1 (25.0%)	1 (25.0%)	0 (0.0%)
Ito et al. (2013) [34]	19	12 (63.2%)	6 (31.6%)	6 (31.6%)
Kamei et al. (2014) [35]	10	8 (80.0%)	7 (70.0%)	10 (10.0%)
Sinha et al. (2015) [36]	58	17 (29.3%)	7 (12.1%)	10 (17.2%)
Basu et al. (2015) [37]	24	16 (66.7%)	5 (20.8%)	11 (45.8%)
Hoseini et al. (2018) [38]	30	17 (56.7%)	14 (46.7%)	3 (10.0%)
Magnano et al. (2019) [39]	16	3 (18.8%)	NA	NA
Total	234	118 (50.4%)	65 (29.8%)[c]	50 (22.9%)[c]

N=146; retrospective; 78 initial resistance; FSGS 57%
RTX: **CR/PR 35% over 6-12 months** Ped Nephrol 2020; Chan & Tullus 2024

RTX in FSGS & MCD (adults) BMC Nephrol 2020
16 studies (221); **remission FSGS 54%; MCD 80%**

Not promising yet, ….

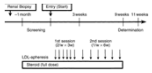
ACTH For membranous nephropathy, FSGS
ATLANTIS (NCT02132195) CJASN 2018; 13 (12): 1859-65
RCT (China, NCT02972346); 3-12 yr for SDNS/SRNS

Abatacept (CTLA-4-Ig) Binds to CD80; inhibits T cell activation
Remission (Yu 2013); not replicated 24/25; NCT02592798

Adalimumab FONT I & II BMC Nephrol 2015

LDL apheresis POLARIS benefit; needs confirmation

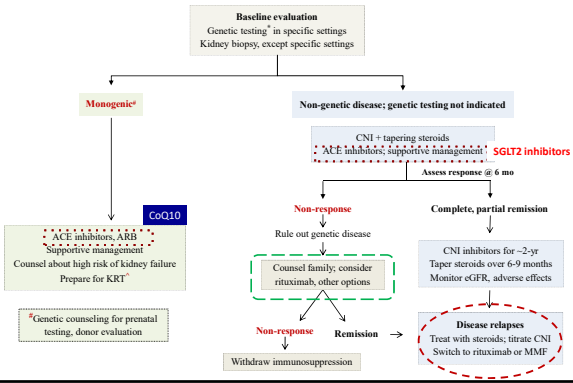
NCT02235857 Drug resistant, recurrent FSGS



Dapagliflozin [CTRI/2022/04/042032] Limited efficacy in reducing proteinuria in adolescents with proteinuric CKD receiving ACEI

Indian Pediatrics 2021

Steroid resistant nephrotic syndrome



Beyond treatment plans……

Ms Cheng Peizhi, Senior Medical Social Worker
Ms Suraya Ya'akub, Senior Child Life Therapist

Content

- Introduction to the Patient Support Team
- Role & Intervention Models
- Case Study 1 - Alfred
- Case Study 2 - Nikki

Medical Social Work

Role:

- Provision of ongoing and holistic case assessment and intervention
- Mitigate impact of end-stage kidney disease and treatment upon patient and family
- Support treatment maintenance
- Empower patient in the pursuit of life's goals and milestones

Models:

- Bio-psycho-social-spiritual model
- Systems Theory
- Ecological Model
- Life Development Theory
- Family Centered Approach
- Strengths-based Approach

Child Life Therapy

Goal: To help paediatric patients cope by reducing stress, fear and anxiety that they may face during the medical experiences at the hospital

- Prepare them for procedures and surgery
- Equip them with pain/anxiety coping skills
- Normalizing their environment
- Providing opportunities for self-expression

Visual example of step-by-step blood taking

01
Purple strap wrapped around your preferred arm.

It feels like a squash and a squeeze!

EMLA or pain numbing cream is applied on different parts of your arms.

Let's wait for 30 minutes to let the cream work!

Reference : www.emla.co.nz

02
Time's up!

The cream is removed with alcohol wet wipes.

Euuugghhh… It smells…

The nurse pats on the arms to find a good vein.

Step by step blood taking

03
Ah ha! We found a good vein.

Keep your arm still while your mother hugs you.

Going to feel some pain but it's going to be a short while!

Are we ready?

Go watch videos on the phone.

Let's count together, 1 ..2…3!

04
Hold your arm still!

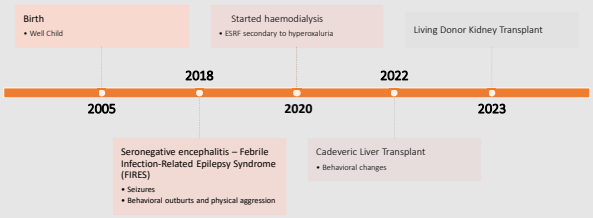
Sleepy medicine will be given with a syringe into the straw.

Thank you for being cooperative Jake!

Case Study 01 : Alfred

Towards Living Donor Kidney Transplant

Diagnosis/Procedure Time Line



Challenges

- Acquired cognitive impairment
  - Assessed cognitive abilities around 7 years old
  - Somewhat intact long-term memory
- Aphasia (receptive and expressive)
  - Frequent misunderstanding
  - Difficulty expressing thoughts and ideas
- Grief and Loss (Unprocessed)
  - Close family members
  - Friends
  - Life-stage and milestones
- Emotion dysregulation / behavioral disruptions
  - Difficulty recognizing and acknowledging emotions
  - Fixation and demands (especially to familiar persons)
- Trauma
  - Procedures
  - Behavioral
- Parenting Difficulties / Caregiver burnout

Preparation: Overall transplant plans

- Drawing out a visual estimated timeline and expectation of both transplants (liver & kidney)
- Includes phone call anytime (for cadevaric liver transplant)
- Patient will continue to require dialysis after liver transplant, until kidney transplant

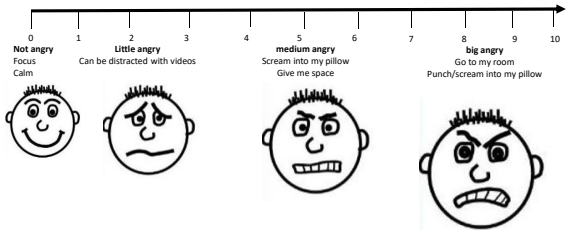
Alfred's Daily Time Table

Day/Time	Mon	Tue	Wed	Thu	Fri	Sat	Sun
5am	Wake Up -Shower -Brush teeth -Breakfast	Wake Up -Shower -Brush teeth -Breakfast	Wake Up -Shower -Brush teeth -Breakfast	Wake Up -Shower -Brush teeth -Breakfast	Wake Up -Shower -Brush teeth -Breakfast	Sleep (Wake up before 12pm)	Sleep (Wake up before 12pm)
8.15am	School		School		School		
11.30am	School ends		School ends		School ends		
12pm	Dialysis @ CKC	School	Dialysis @ CKC	School	Dialysis @ CKC	Wake Up -Shower -Brush teeth -Breakfast	Wake Up -Shower -Brush teeth -Breakfast
3.30pm		School ends		School ends		- Rest - Study time(1 hr)	- Rest - Study time(1 hr)
5pm		Home & Shower		Home & Shower			
6pm	Home & Shower	- Rest - Dinner	Home & Shower	- Rest - Dinner	Home & Shower	- Dinner - Walk / play / ipad (max 2 hrs)	- Dinner - Walk / play / ipad (max 2 hrs)
7pm	- Rest - Dinner - Free Activity -ipad(max 2hr)	- Free Activity - ipad(max 2hr)	- Rest - Dinner - Free Activity -ipad(max 2hr)	- Free Activity -ipad(max 2hr)	- Rest - Dinner - Free Activity -ipad(max 2hr)		
10pm	Sleep	Sleep	Sleep	Sleep	Sleep	Sleep	Sleep

Alfred's Daily To-Do Checklist

Day	Sat	Sun	Mon	Tue	Wed	Thu	Fri
Date							
Shower							
Brush Teeth							
3 meals a day							
Medicine							
Dialysis (only Mon / Wed / Fri)							
Gadget (only 2 hours everyday)							
Study							

Anger Score Chart : I am angry so what can I do?



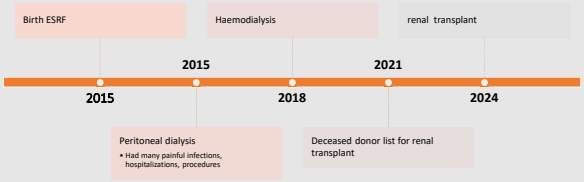
Family Discussions with parents

- Understanding the perspective from both parents, and helping them hear each other's hopes and concerns
- Facilitate a post-transplant care plan:
  - If mother is unable to cope with patient's behavior, father agreeable to take over
  - If both are unable to cope with patient's behavior, an external placement (eg. Disability home) will be considered

Case Study 02 : Nikki

Post Cadaveric Kidney Transplant Coping

Diagnosis/Procedure Time Line



Challenges

Caregiver Issues:

- Nikki's main caregivers : maternal grandparents
- Main reason : parents' young age, many children, incarceration
  - Challenged with frequent medical appointments, hospitalizations
- Nikki's main medical team caregivers :
  - Medical team i.e doctors, dialysis nurses aka 'god sisters, god aunts'
  - Patient support team i.e MSW, CLT aka 'god mothers'
  - Art therapist
  - Transport volunteer (temporary)
  - School : school counsellor

Coping Style:

- sensitizer, avoidant, **comfort food**
- Well known for fretful++ behavior during hospitalization, procedures. **Medical PTSD?**

De-escalation Protocol : The Angry Bird

Establishing healthy food relationship

- Ward team to show physical food menu (pictures) to Nikki
- Use of phone app to monitor water, food and medicine intake
- Medical team to show and explain how her food intake affects her blood test results

Key Takeaways

- Expect the unexpected
- Supporting patients in renal replacement therapy is a multi-disciplinary team effort
- Every patient and family are different with unique ways of coping and challenges. It is thus important to get to know them and involve them in designing the treatment plans

Thank you

Renal Primer 2024
MSW Cheng Peizhi
CLT Suraya Ya'akub

SickKids

aHUS & C3G

Christoph Licht
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Toronto, ON
21.8.2024

Disclosures

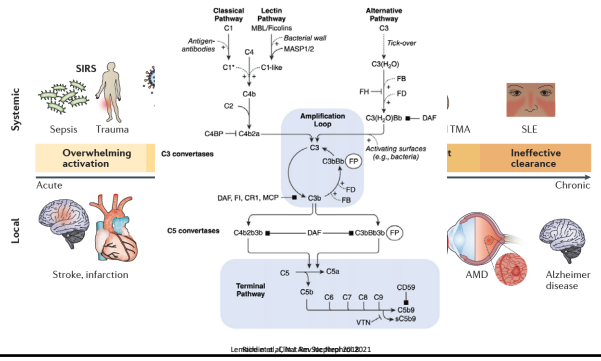
- **Scientific advisor and/or speaker**
  - Alexion, AstraZeneca Rare Disease
  - Apellis Pharmaceuticals, Inc.
  - Catalyst Biosciences
  - Eleva GmbH
  - Novartis
  - Oak Bay Biosciences
  - Otsuka Pharmaceuticals, Inc.
  - Pfizer Inc.
  - Samsung Bioepis Co, Ltd.
- **DSMB member**
  - Argenx – Axio Research
  - Early Protect Alport / Double Protect Alport / EMPA Alport
  - OPKO Health, Inc.

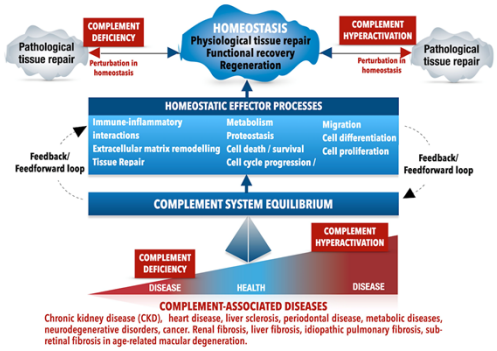
Overview

- Complement-mediated diseases
- Pathogenesis
- Diagnosis
- Treatment

SickKids

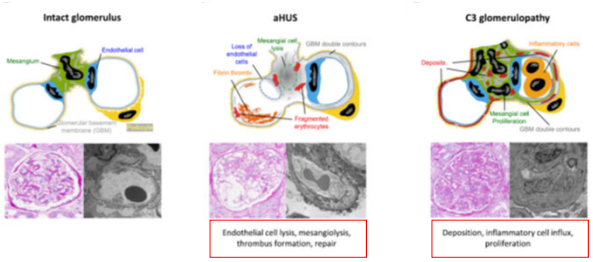
Complement-mediated diseases





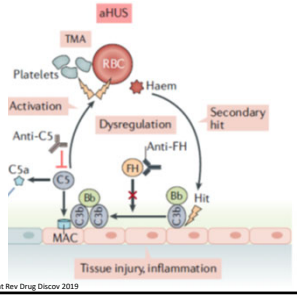
Licht et al: UofT CFREF MbD Grand Question Program Competition (2020)

Disease specific complement dysregulation



Zipfel et al, J Am Soc Nephrol 2020

Disease specific complement dysregulation



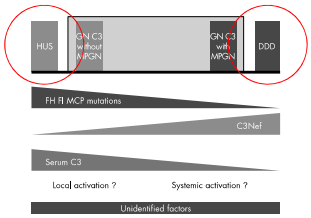
Mastellos et al, Nat Rev Drug Discov 2019

ORIGINAL ARTICLE

Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome

Aude Servais, Véronique Frémeaux-Bacchi, Magkie Lequintrec, Rémi Salomon, Jacques Blouin, Bertrand Knebelmann, Jean-Pierre Grünfeld, Philippe Lesavre, Laure-Hélène Noël, Fadi Fakhouri

J Med Genet 2007;44:193–199. doi: 10.1136/jmg.2006.043328



Servais et al, J Med Genet 2007

Question 1: Which answer is correct?

A. Complement-mediated disease are always caused by genetic mutations or autoantibodies.

B. aHUS is caused by systemic complement dysregulation.

C. C3G is characterized by surface complement dysregulation.

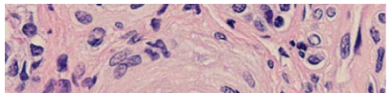
D. Dysregulation of the alternative pathway is key in the pathogenesis of aHUS and C3G.

SickKids

Pathogenesis

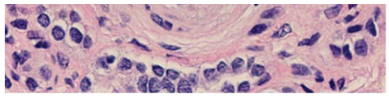
5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

Thrombotic microangiopathy



TMA defines a histological lesion in arterioles and capillaries characterized by:

- thickening and inflammation of the vascular wall
- detachment of the endothelial cells
- subendothelial widening due to accumulation of proteins and cellular debris
- platelet thrombi occluding the vascular lumen



George and Nester, N Engl J Med 2014

TMA is characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ damage / dysfunction

Thrombocytopenia
Platelet count <150 000/mm³ or >25% decrease from baseline

and

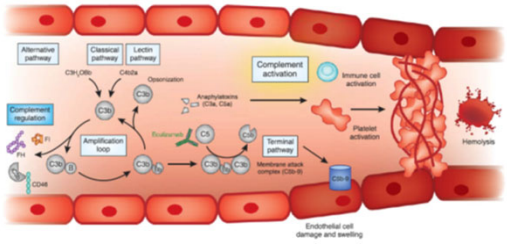
Microangiopathic haemolysis
Schistocytes and/or
Elevated LDH level and/or
Decreased haptoglobin level and/or
Decreased haemoglobin level

Plus 1 or more of the following:

Neurological symptoms **Confusion** and/or **Seizures** and/or **Stroke** and/or **Other cerebral abnormalities**	**Renal impairment** **Elevated creatinine level** and/or **Decreased eGFR** and/or **Elevated blood pressure** and/or **Abnormal urinalysis results**	**GI symptoms** **Diarrhoea ± blood** and/or **Nausea/vomiting** and/or **Abdominal pain** and/or **Gastroenteritis/pancreatitis**
CV symptoms **Myocardial infarction** and/or **Hypertension** and/or **Arterial stenosis** and/or **Peripheral gangrene**	**Pulmonary symptoms** **Dyspnoea** and/or **Pulmonary haemorrhage** and/or **Pulmonary oedema**	**Visual symptoms** **Pain and blurred vision** and/or **Retinal vessel occlusion** and/or **Ocular haemorrhage**

Azoulay et al, Chest 2017; Laurence et al, Clin Adv Hematol Oncol 2016; Fremeaux-Bacchi et al, Clin J Am Soc Nephrol 2013; Jamme et al, PLoS One 2017

aHUS – a complement-mediated TMA



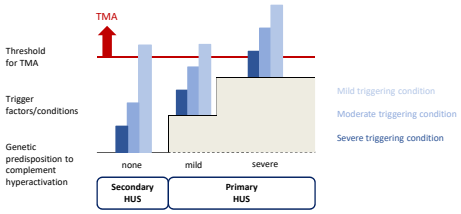
Brocklebank et al, Clin J Am Soc Nephrol 2018

Complement defects in aHUS

		Function in complement system	Frequency in aHUS (%)	ESRD after 5 years (%)	Recurrence (%)	Recurrence after kidney transplantation (%)
FH	Factor H	Co-factor for factor I	21–25	70–80	30–50	68–90
MCP/CD46	Membrane co-factor protein	Membrane-bound complement regulator	5–22.8	10–50	58–90	11–20
FI	Factor I	Inactivation of C3b and C4b	6–16.6	45–60	10–30	70–80
FB	Factor B	Allows the formation of C3 and C5 convertases	1.9–4	70	Rare	Rare
C3	Complement C3	Necessary for complement cascade activation	6–9	45–65	50	40–50
FHRs	Factor H-related proteins	Circulating proteins similar to factor H associated with autoantibodies against FH	4.5–35	30–63	23–60	20
FHR hybrid genes	Factor H, Factor H-related proteins	See function FH and FHRs	1–5	–	–	–
THBD/CD141	Thrombomodulin	Degradation C3b	2–5	53–60	23–30	Rare

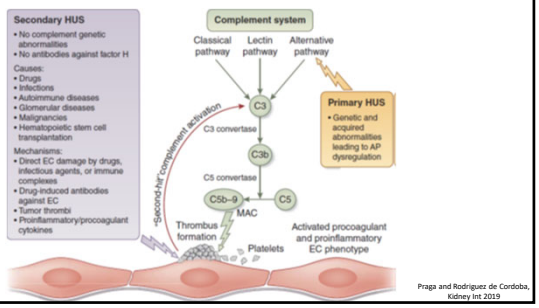
Reiz et al, Medizinische Genetik 2018

Two (multiple) hit hypothesis of TMA manifestation



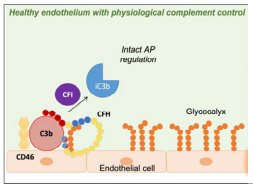
Modified from Riedl et al, Semin Thromb Hemost 2014

The role of complement in TMA pathogenesis



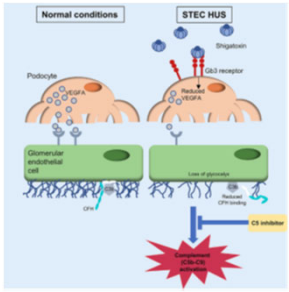
Praga and Rodriguez de Cordoba, Kidney Int 2019

The role of complement in the pathogenesis of 2nd TMA



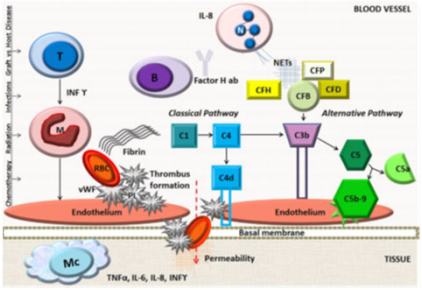
Teoh et al, Front Med 2023

Epithelial (podocyte) VEGF determines endothelial homeostasis via glycocalyx dependent CFH deposition and complement control



Bowen et al, Med 2023

Complement is *likely* involved in HSCT related TMA



Jodele,
Seminars in Hematology 2018

Question 2: Which answer is incorrect?

A. Only 50-60% of aHUS patients are positive for genetic mutations or autoantibodies.

B. CFH autoantibodies can be found in up to 50% of aHUS patients.

C. Secondary TMA can involve complement dysregulation.

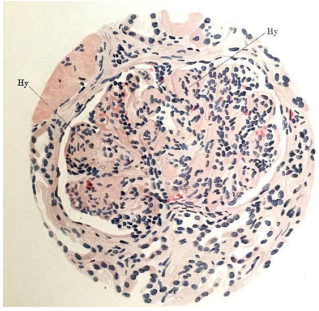
D. aHUS is always preceded by a detectable trigger event.

Historical background

- Volhard and Fahr (1914): Die Brightsche Nierenkrankheit
  "Camera lucida" drawing of lobular glomerulonephritis
- Habib and Hamburger (1960):
  At the first worldwide Renal Biopsy Meeting, MPGN is first defined via a variety of findings made in patients with Bright's disease; MPGN becomes a formally named sub-type of glomerulonephritis ("a disease").
- Clinical phenotype (1960's):
  - Mean age 10 (range 2-17)
  - Nephrotic syndrome (70%)
  - Hematuria (90%)
  - Renal function "low" (33%)
- Clark West (1965):
  - Describes hypocomplementemia in MPGN
  - Complement defects (classical pathway) suspected

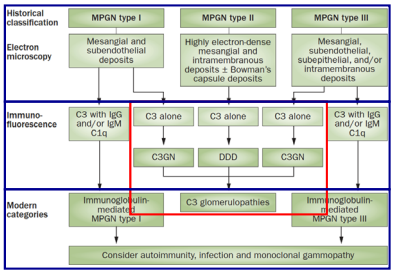
Wolstenholme and Cameron, Editors (1961). CIBA Foundation Symposium on Renal Biopsy: Clinical and Pathological Significance.
West, J Pediatr 1965

Bright's disease

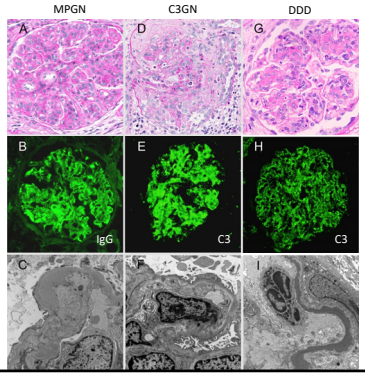


Volhard and Fahr (1914). Die Brightsche Nierenkrankheit

Historical vs. current classification of *MPGN*

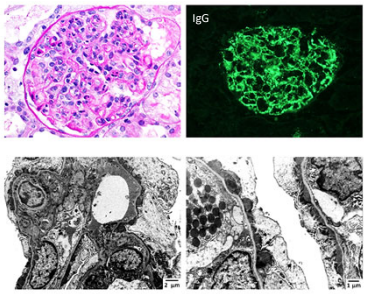


Cook and Pickering, Nat Rev Nephrol 2015



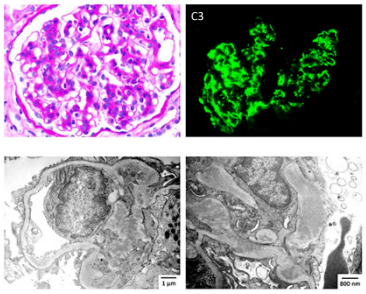
Riedl et al, Pediatr Nephrol 2017

First biopsy: IC-MPGN



Courtesy of Patrick Walker, Arkana Laboratories, Little Rock, AR

Second biopsy (+6 months): C3GN



Courtesy of Patrick Walker, Arkana Laboratories, Little Rock, AR

Glomerular complement profile in C3G

Sethi et al, Kidney Int 2009; Sethi et al, Nephrol Dial Transplant 2017

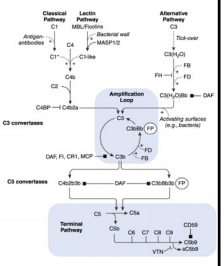
Causes of secondary MPGN

Condition	Diagnosis
Infections (bacterial / viral / protozoal)	Hepatitis B / C EBV HIV Malaria Mycoplasma Tuberculosis
Systemic immune disease	Cryoglobulinemia Systemic lupus erythematosus Sjögren's syndrome Rheumatoid arthritis
Neoplasmas / dysproteinemias	Plasma cell dyscrasia Light / heavy chain disease Leukemia / lymphoma / other malignancies Waldenstrom macroglobulinemia
Chronic liver disease	Hepatitis / cirrhosis Alpha-1-antitrypsin deficiency
Miscellaneous (null C3 + null IgG)	TMA (aHUS / TTP) Radiation nephropathy Antiphospholipid syndrome Sickle cell disease Transplant glomerulopathy

Riedl et al, Pediatr Nephrol 2017 (modified)

Autoimmune causes for C3G

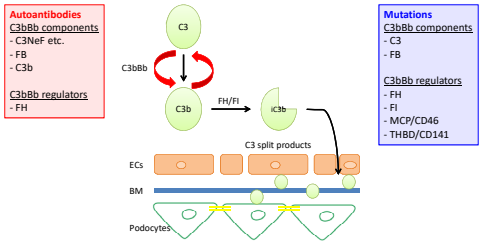
	Incidence	Co-existing with C3NeF?	Effect on complement
C3NeF	Common	-	Stabilizes AP C3 convertase
C4NeF	Rare	Yes	Stabilizes CP C3 & C5 convertases
C5NeF	Rare	Yes	Stabilizes AP C5 convertase
Anti-FB Ab	Rare	No	Stabilizes AP C3 convertase
Anti-C3b Ab	Rare	No	Stabilizes AP C3 convertase
Anti-FH Ab	Rare	Yes	Fluid phase regulation



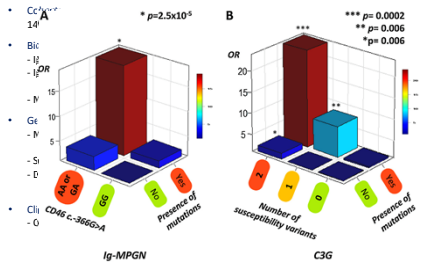
Genetic causes for C3G

Gene/Protein	Mutation/SNP	Function	Phenotype
FH	Homo-/compound heterozygous SCRs 1–4 (regulatory domain)	Intact surface binding Reduced C3b binding Loss of FH cofactor and decay-accelerating activity	C3G IC-MPGN
FI	Homozygous Heterozygous	Decreased FI mediated C3b degradation	C3G IC-MPGN
C3	Heterozygous	C3mut – resistant to cleavage by C3bBb C3mut convertase – resistant to FH inactivation C3 binding with FI or FH	C3GN IC-MPGN
FB	Heterozygous/ homozygous	Alters C3-FB interaction	C3G IC-MPGN
THBD	Homozygous	Not tested	DDD
DGKE	Homozygous Heterozygous – unclear impact	Not complement mediated	MPGN

C3G Pathogenesis - Summary

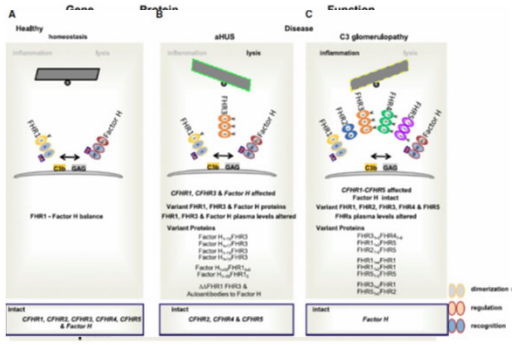


Genetic causes for C3G – *Susceptibility variants*



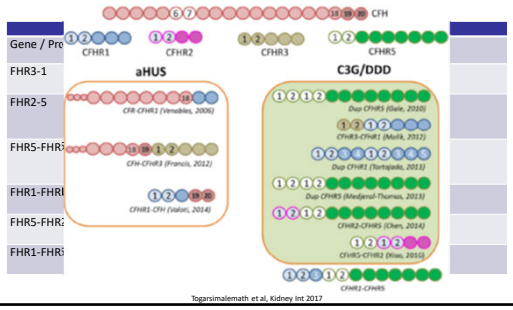
Iatropoulos et al, Mol Immunol 2016

FH related proteins (FHRs)



Zipfel et al, J Am Soc Nephrol 2020

Genetic causes for C3G – *FH deregulation*



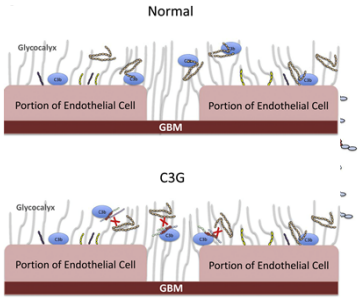
Togarsimalemath et al, Kidney Int 2017

Genetic causes for C3G – *FH deregulation*

Protein name	Protein structure	Phenotype	Comments
Normal proteins			
FHR1	1 2 3 4 5	NA	Homodimerizes and heterodimerizes with FHR2; competitive antagonist of factor H; C5 convertase inhibitor and terminal complement cascade blocker
FHR2	1 2 3 4	NA	Homodimerizes and heterodimerizes with FHR1; competitive antagonist of factor H; C3 convertase inhibitor
FHR3	1 2 3 4 5	NA	Exact function unknown
FHR5	1 2 3 4 5 6 7 8 9	NA	Homodimerizes; competitive antagonist of factor H; binds to extracellular matrix; complement amplifier and surface anchor for properdin
Fusion proteins			
$FHR2_{1/2}$–$FHR5_{3-9}$	1 2 1 2 3 4 5 6 7 8 9	DDD	Normal gene copies present in variant allele: *CFHR3*, *CFHR1* and *CFHR4*
$FHR5_{1/2}$–$FHR5_{3-9}$	1 2 1 2 3 4 5 6 7 8 9	C3GN	Normal gene copies present in variant allele: *CFHR3*, *CFHR1*, *CFHR4*, *CFHR2* and *CFHR5*
$FHR3_{1-4}$–$FHR1_{3-5}$	1 2 1 2 3 4 5	C3GN	Normal gene copies present in variant allele: *CFHR3*, *CFHR1*, *CFHR4*, *CFHR2* and *CFHR5*
$FHR1_{1/2}$–$FHR5_{3-9}$	1 2 1 2 3 4 5 6 7 8 9	C3GN and/or DDD	Normal gene copies present in variant allele: *CFHR3* and *CFHR5*
$FHR1_{1-4}$–$FHR1_{3-5}$	1 2 3 4 1 2 3 4 5	C3GN	Normal gene copies present in variant allele: *CFHR3*, *CFHR4*, *CFHR2* and *CFHR5*
$FHR5_{1/2}$–$FHR2_{3-4}$	1 2 1 2 3 4	C3GN	Normal gene copies present in variant allele: *CFHR3*, *CFHR1*, *CFHR4*, *CFHR2* and *CFHR5*

Smith et al, Nat Rev Nephrol 2019

FH deregulation in C3G via FHR multimers



Xiao et al, Mol Immunol 2016

SickKids

Diagnosis

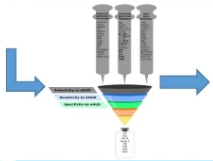
5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

Systematic review of atypical hemolytic uremic syndrome biomarkers

Graphical Abstract

Objective: Observing biomarkers that affect alternative pathway dysregulation components may be effective in obtaining a new and more rapid diagnostic portrayal of atypical hemolytic uremic syndrome.

Method:
A literature search was conducted for aHUS patient population plasma/serum, collected/reported at the onset of diagnosis.



Biomarker	Unit	aHUS values: Sample size	No. of studies	Mean (SD)	Median (IQR)	Range (Min - Max)	Reference range*
CFP	mg/dl	783	34	25.41 (15.84)	78.5 (52 - 94.78)	1.1 - 221.3	79 - 179
CFP	mg/dl	363	14	7.041 (9.56)	30.3 (16 - 38)	2 - 65	16 - 40
CFD	pg/ml	808	5	7.2 (6 -09)	2.75 (2.56 - 8.35)	1.1 - 35.8	≤9.8
CFB	mg/dl	817	6	54.49 (12.56)	48.8 (34.98 - 64.53)	4.96 - 168.7	10.4 - 36.5
C5b-9	ng/ml	474	14	466.89 (481.13)	317 (136 - 549.77)	4.6 - 10.68	2,700
CH50	U/ml	63	9	26.25 (12.89)	24.25 (5.5 - 93.25)	3 - 154	30-75
AH50	%	19	2	17.64 % (24.24 %)	10% (10% - 30.9%)	10% - 91%	2.98%
Bb	pg/ml	77	4	0.63 (2.1)	0.9 (0.36 - 3.25)	0.7 - 7.346	13.4
C3b	mg/dl	19	4	13.68 (6.96)	12.41 (3.69 - 30.75)	5 - 26.4	19.2 - 43.3
CFH	mg/dl	113	7	40.3 (132.36)	26.45 (9.65 - 68.8)	10.2 - 607	37.6 - 43.3
CFI	mg/dl	38	6	8.05 (5.16)	6.55 (5.93 - 6.88)	4.4 - 18.1	N/A
D-Dimer	ng/ml	2	2	2.66 (69.09)	266 (223 - 309)	240 - 292	<2.3

Results:
Lower levels: C3, CH50, AH50, CFB
Normal levels: C4d, CFH, CFI
Elevated levels: C5a, C5b-9, Bb, D-Dimer

Conclusion: If a comprehensive complement profile were built using our data, aHUS would be identified by low levels of C3, CH50, AH50, and CFB along with increased levels of C5a, C5b-9, Bb, anti-CFH autoantibodies, and D-Dimer.

Raina, Sethi et al. 2022

IPNA Pediatric Nephrology Journal of the International Pediatric Nephrology Association

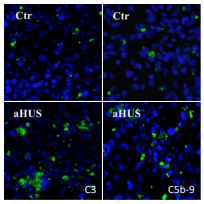
Table 1 | Suggested indications for complement tests and gene screening in TMA

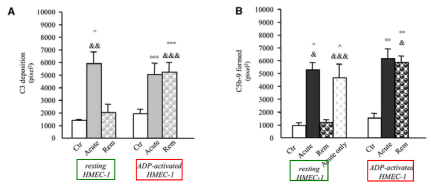
Test	Indication	Notes
Measurement of C3, C4, FH, FI and CH50 and in plasma and CD46 expression on granulocytes	Primary aHUS	Clinical relevance in the initial work-up of other forms of TMA remains to be fully assessed
Anti-CFH antibodies	Primary aHUS	Valuable for the diagnosis of anti-CFH autoantibody-associated HUS, which potentially requires immunosuppressive treatment
Measurement of sC5b-9 in plasma	Primary aHUS	Potentially useful to aid decisions on whether to discontinue eculizumab
Complement deposition in vitro	TMA	Clinical relevance not yet clear
Complement gene testing (screening for variants and hybrid genes in CFH, CFI, MCP, C3, CFB, THMD and DGKE using next-generation sequencing and multiplex ligation-dependent probe amplification)*	Primary aHUS	Recommended for all patients. The results can potentially enable discontinuation of complement blockade, individualized prophylactic use of complement blockade in kidney graft recipients and retrospective confirmation of complement-mediated aHUS. Genetic results are not required for urgent diagnosis
	STEC-HUS	To be discussed on a case-by-case basis. Complement gene testing is indicated for children with severe forms leading to kidney failure within 3 years of diagnosis
	Post-transplant de novo TMA	To be discussed on a case-by-case basis following the exclusion of alternative causes of TMA in the kidney graft (such as drugs and humoral rejection)
	TTP	Not currently recommended
	Cobalamin deficiency HUS (resulting from mutations in MMACHC)	Not currently recommended
	Preeclampsia, eclampsia or HELLP syndrome	Not currently recommended
	Delivery haemorrhage	Not currently recommended
	Secondary TMA	Not currently recommended

Fakhouri and Fremeaux-Bacchi, Nature Reviews Nephrology 2021
McFarlane et al, Canadian Journal of Kidney Health and Disease 2021

Ex vivo demonstration of complement activation

EC C3 and C5b-9 deposition correlates with aHUS activity





Noris et al, Blood 2014; Galbusera et al, Am J Kidney Dis 2019; Palomo et al, Clin J Am Soc Nephrol 2019

Diagnostic workup for C3G patients

Global complement function	CH50, APH50
Complement activation	C3, C4, C3d
Terminal pathway activation	SC5b-9
Complement protein levels	CFH, CFI, CFB
Autoimmune forms	C3 Nephritic factor (C3NeF) CFH/CFB/C3b autoantibodies
Genetic forms	Mutations/CNVs in CFH, CFI, CFB, MCP/CD46, C3 CFHR–5 (MLPA)

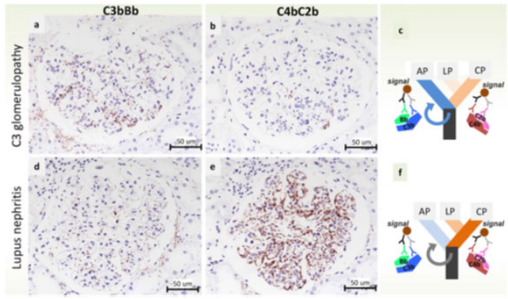
Other Nephritic factors

Genetic variants in FHR locus

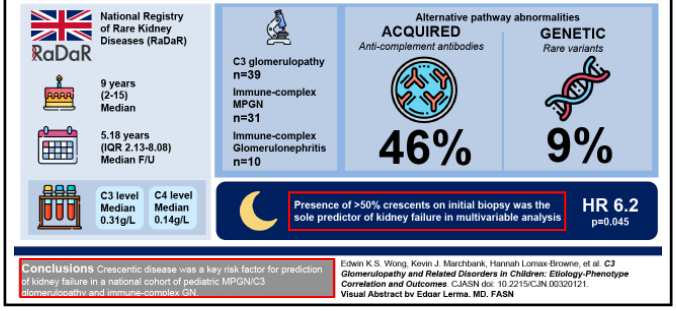
Riedl et al, Pediatr Nephrol 2017
Goodship et al, Kidney Int 2017 & Rovin et al, Kidney Int 2021 (modified)

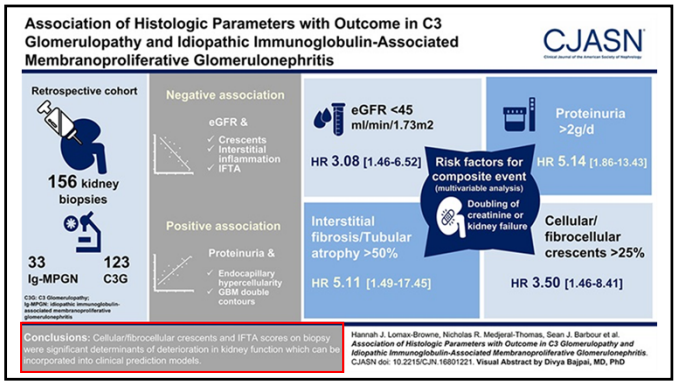
Differential histopathology

Staining for AP vs. CP C3 convertase identifies active pathway



Zipfel et al, Cell and Tissue Research 2021

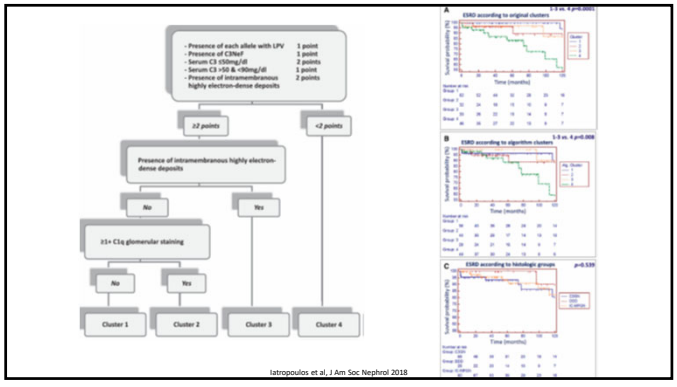




Cluster analysis identifies pathogenic patterns in C3G / IC-MPGN

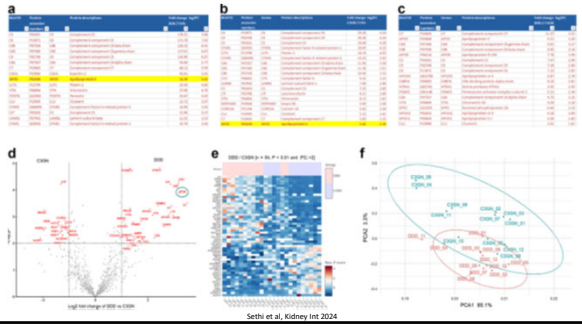
Cluster 1	Cluster 2	Cluster 3	Cluster 4
N=62	N=32	N=33	N=46
High prevalence of LPVs and/or C3NeF Low serum C3 Very high plasma SC5b-9 Few crescents Mesangial deposits (EM)	High prevalence of LPVs and/or C3NeF Low serum C3 Very high plasma SC5b-9 High prevalence of subendothelial deposits Strong glomerular IgG / IgA / C1q staining Nephrotic syndrome at disease onset	High prevalence of LPVs and/or C3NeF Low serum C3 Significantly lower SC5b-9 levels Higher prevalence of crescents, intra-membranous electron dense deposits, fewer subendothelial deposits	Lower prevalence of LPVs and/or C3NeF Higher serum C3 Lower prevalence of microhematuria More sclerotic glomeruli and arteriolar sclerosis, less endocapillary proliferation
C3GN & IC-MPGN	DDD & IC-MPGN	DDD & IC-MPGN	C3GN & IC-MPGN

Iatropoulos et al, J Am Soc Nephrol 2018



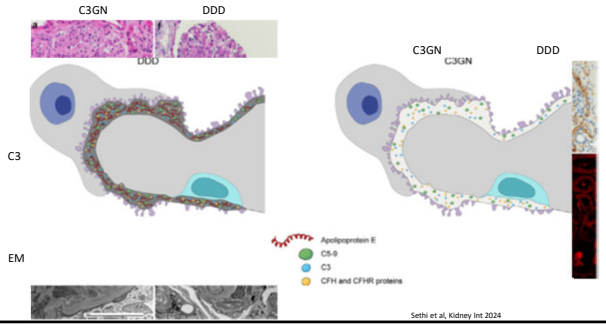
Iatropoulos et al, J Am Soc Nephrol 2018

Apolipoprotein E (ApoE) in DDD vs. C3GN



Sethi et al, Kidney Int 2024

Apolipoprotein E (ApoE) in DDD vs. C3GN



Sethi et al, Kidney Int 2024

Question 3: Which answer is correct?

A. aHUS and C3G are completely distinct diagnoses.

B. Autoimmune causes are more frequent in C3G than in aHUS.

C. CFHR mutations do not play a role in the pathogenesis of C3G.

D. Complement dysregulation is only involved in C3G but not in IC-MPGN.

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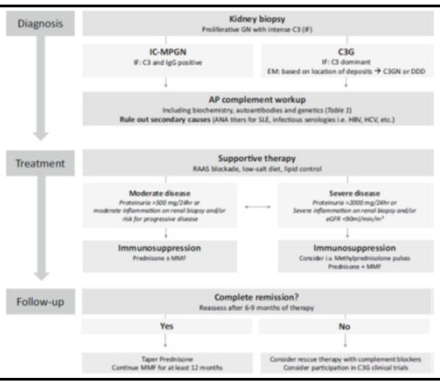
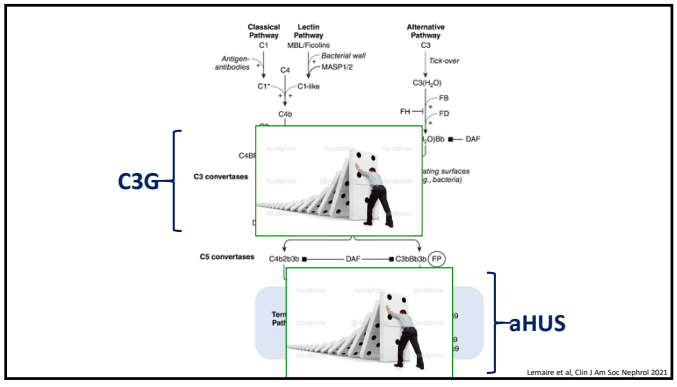
Treatment

5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

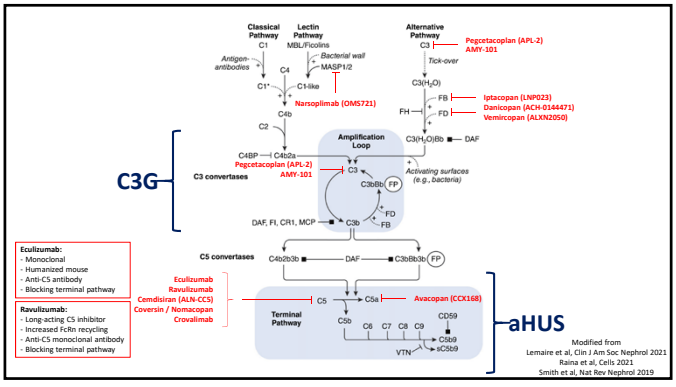
Current treatment recommendation for C3G



Vivarelli et al, Pediatr Nephrol 2022



Lemaire et al, Clin J Am Soc Nephrol 2021



Modified from
Lemaire et al, Clin J Am Soc Nephrol 2021
Raina et al, Cells 2021
Smith et al, Nat Rev Nephrol 2019

Drug	Target	Mechanism	Clinical trial number
Atypical hemolytic uremic syndrome			
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	**NCT04889430 Phase III, adults**
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT05148299 Phase II postBMT-TMA
Crovalimab (i.v. then monthly s.c.)	C5	Prevents formation of C5 convertase	**NCT04558265** **NCT04861259**
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02464891 Phase II, pts on dialysis
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	**NCT03205995**
C3 glomerulopathy and immune-complex glomerulonephritis			
Danicopan oral	Factor D	Prevents formation of C3 and C5 convertases	NCT03124368 NCT03369236 Phase II NCT03459443
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	NCT03832114, NCT03955445 **NCT04817618 C3G Phase III adults** Ext 12-18 years **NCT05755386 IC-MPGN Phase III**
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT03453619 Basket Phase II NCT04572854 C3G – IC-MPGN Phase II **NCT05067127 C3G – IC-MPGN Phase III**
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	**NCT03301467 (completed)**
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, terminated/discontinued for BCX10013 once daily
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN

Antonucci et al, Pediatr Nephrol 2024

Licht Lab 2024

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Transition: difficulties and successes

Christoph Licht
Division of Nephrology and RI Cell Biology Program
The Hospital for Sick Children
Toronto, ON
22.8.2024

5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

Disclosures

- **Scientific advisor and/or speaker**
  - Alexion, AstraZeneca Rare Disease
  - Apellis Pharmaceuticals, Inc.
  - Catalyst Biosciences
  - Eleva GmbH
  - Novartis
  - Oak Bay Biosciences
  - Otsuka Pharmaceuticals, Inc.
  - Pfizer Inc.
  - Samsung Bioepis Co, Ltd.
- **DSMB member**
  - Argenx – Axio Research
  - Early Protect Alport / Double Protect Alport / EMPA Alport
  - OPKO Health, Inc.

Case

- A 19-year-old female patient was referred to the Nephrology Department during late 2020 for transition of care.
- She was newly diagnosed with SLE three years prior to transition. Due to significant proteinuria and microscopic hematuria a kidney biopsy was performed, which revealed crescentic focal segmental glomerulonephritis (class III lupus nephritis with crescents according to WHO classification).
- She was initially managed with a combination of cyclophosphamide, corticosteroids and azathioprine, which was – due to poor response – modified to MMF and rituximab.

Case kindly provided by Dr. Rupesh Raina

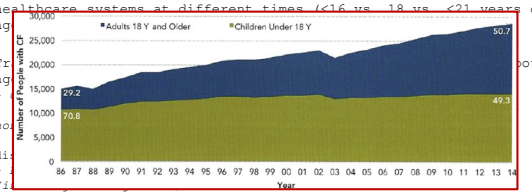
Case (continued)

- However, despite the absence of extra-renal manifestations of lupus, kidney function gradually deteriorated, and patient reached ESKD about 2 years after initiation of immunosuppression.
- Renal replacement therapy via peritoneal dialysis was initiated with the concomitant administration of hydroxychloroquine and low dose methylprednisolone.
- *One year prior to transition, she received an LRD kidney transplant.*
- Patient had poor medication compliance:
  - Increase in creatinine (up to 250 µmol/l)
  - Proteinuria (2 g)
  - ? Rejection

Case kindly provided by Dr. Rupesh Raina

The challenge

- Transition from pediatric to adult care occurs in different healthcare systems at different times (<16 vs. 18 vs. <21 years of ag
- Tr… both ag…
  - …
  - *Re-establishing medical care working with less experienced providers:*
    Medical progress introduces rare pediatric diagnoses to adult healthcare providers
    who lack expertise (irregular Pap, loss of…, etc.)



Frederick, Pediatr Clin North Am 2016

Learning objectives

- To recognize the need for structured transition of care in childhood-onset chronic illness
- To identify the key elements of a successful transition program
- To discuss strategies to operationalize a transition program
- Take home message

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The need for structured transition of care in childhood-onset chronic illness

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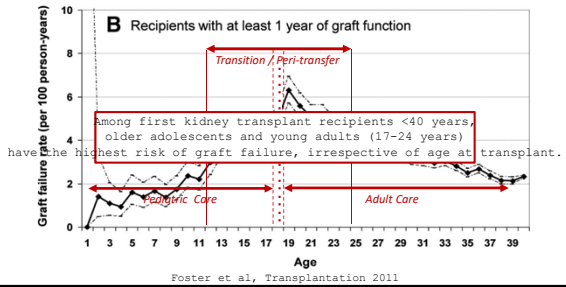
Association between age and graft failure rate



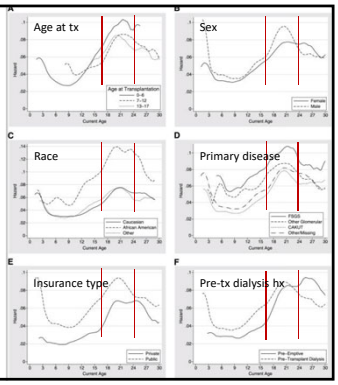
Foster et al, Transplantation 2011

"High-risk window" of 17-24 years

N = 16,266 (SRTR 1987-2010)

Graft loss risk:
3-17 yrs < 17-24 yrs < above 24 yrs

No recipient subgroup is exempt from the "high-risk age window" for graft loss.



van Arendonk et al, Clin J Am Soc Nephrol 2013

Question 1:
Which factor is most important to define the risk of kidney graft loss during transition of care?

A. Age at TX
B. Type of TX (DD vs. LRD)
C. HLA-match
D. Health care coverage
E. Transition of care (age window 17-24 years)

Question 1:
Which factor is most important to define the risk of kidney graft loss during transition of care?

A. Age at TX
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Key elements of a successful transition program

5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

Poor adherence

Risk factors:

- Patient-related factors
  - Adolescence, gender, race, immigrant status
- Condition-related factors
  - CKD / ESKD / Tx
- Treatment-related factors
- Socio-economic factors
  - Health literacy
- Health care system / team
  - Insurance

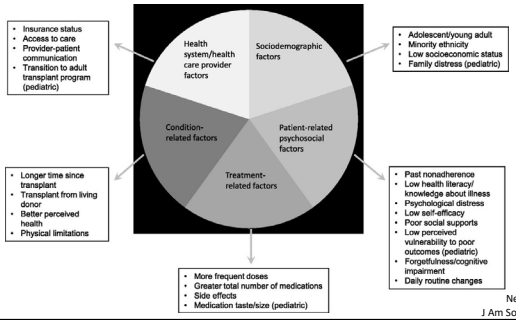
Patient

Provider

Health system

World Health Organization 2003; Raina et al, Ann Transplant 2018

Major categories of risk factors for nonadherence in chronic kidney disease based on reviews of the empirical literature and the WHO



Nevins et al, J Am Soc Nephrol 2017

Question 2:
According to the WHO, which of the following factors contribute to non-adherence at time of transition of care?

1 Patient-related factors
2 Condition/diagnosis-related factors
3 Treatment-related factors
4 Socio-economic factors
5 Healthcare system-related factors

A. 1
B. 1-3
C. 2+4
D. 5
E. All of the above

Poor adherence

Risk factors:

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- Condition-related factors
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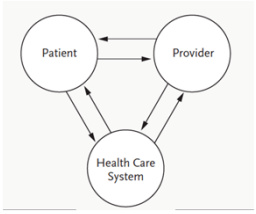
- Treatment-related factors
- Socio-economic factors
  - Health literacy
- Health care system / team
  - Insurance

Patient

Provider

Health system



World Health Organization 2003; Raina et al, Ann Transplant 2018

Osterberg and Blaschke, N Engl J Med 2005

Poor adherence

Risk factors:

- Patient-related factors
  - Adolescence, gender, race, immigrant status
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- Socio-economic factors
  - Health literacy
- Health care system / team
  - Insurance

Patient

Provider

Health system

World Health Organization 2003; Raina et al, Ann Transplant 2018

Neurocognitive and emotional maturation

- Physical development antedates emotional maturity.
- Most girls are physically mature by mid-adolescence, although boys are often not fully grown until the older teenage years.
- Cognitive abilities are also well established by the mid-teenage years.
- However, the development of emotional regulation, reflective judgment, and thus social maturity lag behind achievement of physical maturity and cognitive skills.
- Emotional and social factors may override more rational cognitive functions, leading to inconsistent choices and potentially dangerous risk taking. These influences continue at least into the mid-20s.
- On tests of risk perception, sensation seeking, impulsivity, resistance to peer influence, and future orientation, scores are similar at 10 and 15 years of age; differences begin to emerge at age 16 to 17 years, with a progressively increasing level of function up to at least the age of 30 years.
- The complex interrelated skills of logical reasoning, reflective judgment, and emotional regulation evolve into adulthood.

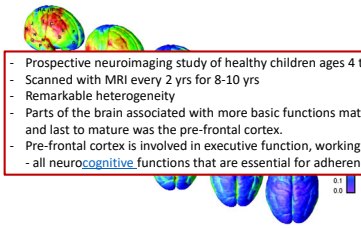
Gogtay et al, PNAS 2004

Neurocognitive and emotional maturation

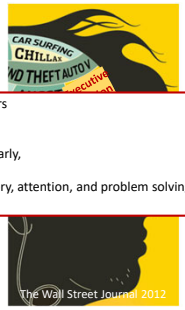
- Developmental changes in brain structure continue into the third decade of life.
- The subcortical limbic regions, such as the amygdala and the nucleus accumbens in the basal ganglia, important for emotion and reward seeking, mature early.
- In contrast, the prefrontal cortex and associated areas, responsible for executive brain functions such as foresight, planning, evaluation of risk and reward, and the capacity to dissociate decision making and strong emotion, are among the last to reach adult levels; moreover, functional connectivity between these two regions is delayed.
- The combination of heightened responsiveness to rewards and immaturity in brain areas for behavioral control may result in adolescents investing more in activities with immediate rather than long-term gains and help explain their increase in risky decision making and emotional reactivity.
- **Thus, there is some biologic basis for the emotional extremes and lack of mature executive planning that can be seen during adolescence and early adulthood.**

Gogtay et al, PNAS 2004

Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface



- Prospective neuroimaging study of healthy children ages 4 to 21 yrs
- Scanned with MRI every 2 yrs for 8-10 yrs
- Remarkable heterogeneity
- Parts of the brain associated with more basic functions matured early, and last to mature was the pre-frontal cortex.
- Pre-frontal cortex is involved in executive function, working memory, attention, and problem solving - all neurocognitive functions that are essential for adherence.



The Wall Street Journal 2012

Gogtay et al, PNAS 2004

Question 3:
Which statement is correct?

A. Boys mature faster than girls

B. Our brain is in all aspects fully developed at age 18.

C. Development of physical maturity and cognitive skills lag behind development of emotional regulation and reflective judgment ("social maturity").

D. Different from the limbic system ("emotions"), which matures early, the pre-frontal cortex ("executive functions") is last to mature.

E. There is no biologic basis for the emotional extremes and lack of mature executive planning that can be seen during adolescence and early adulthood.

Poor adherence

Risk factors:

- Patient-related factors
  - Adolescence, gender, race, immigrant status
- Condition-related factors
  - CKD / ESKD / Tx
- Treatment-related factors
- Socio-economic factors
  - Health literacy
- Health care system / team
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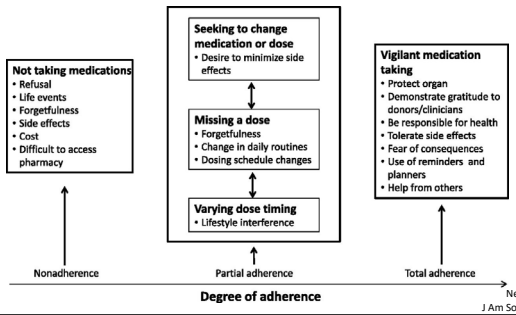
Provider

Health system

World Health Organization 2003; Raina et al, Ann Transplant 2018

Themes reflecting challenges and decisions about medication taking after kidney transplantation



Nevins et al, J Am Soc Nephrol 2017

Cognitive deficits in CKD

N=368, ages 6-16 yrs, median GFR 43 ml/minx1.73m^2, median CKD 8 yrs

Chronic Kidney Disease in Children

Tests:
- WASI Intelligence
- WIAT-II-A Academic achievement
- CPT-II Continuous performance
- BRIEF-P Executive function

Key finding:
- Neurocognitive function within average
- Children with mild-moderate CKD scored in up to 40% at least 1 SD below the average of their healthy peers for tests above
- Results showed positive correlation with degree of CKD
- Deficits are often subclinical and can be missed

Consequences:
- Poor understanding of disease & treatment
- Suboptimal adherence

Hooper et al, Clin J Am Soc Nephrol 2011

"Drugs don't work in patients who don't take them"

C. Everett Koop, M.D.

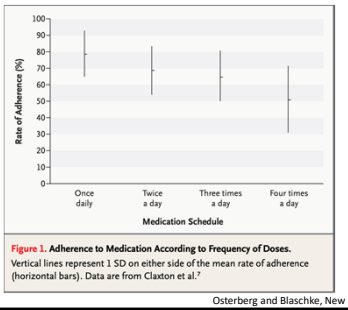


Figure 1. Adherence to Medication According to Frequency of Doses.
Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars). Data are from Claxton et al.[7]

- Patient (& family) education
- Improve dosing schedules
  - Simplify frequency of dosing as much as possible
  - Provide cues to remind patients to take medication
  - Simplify administration of medication (e.g., via pillboxes, blister packs etc.)

Osterberg and Blaschke, New Engl J Med 2005

Successfully Promoting Medication Adherence in Kidney Transplantation

TAKE-IT!

Teen Adherence in Kidney Transplant, Effectiveness of Intervention Trial (TAKE-IT)

169 Kidney Transplant Recipients

Age: 11-24 years

Visits q3 months with electronic medication monitoring

TAKE IT TOO
- Implementation to real life
- Adapted intervention with E-pillbox
- Companion adherence website

Control N = 88
- Non-specific social support

Outcomes

	Taking Medication	Taking Medication On Time
	OR = 1.66 (CI, 1.15-2.39)	OR = 1.74 (CI, 1.21-2.50)
	Reference Group	

Article Reference: A Randomized Trial of a Multicomponent Intervention to Promote Medication Adherence: The TAKE-IT Trial
Bethany J. Foster, Ahna L.H. Pai, Nataliya Zelikovsky, et al
Am J Kidney Dis (ePub Mar 27, 2018 | DOI: 10.1053/j.ajkd.2017.12.012)
© National Kidney Foundation

AJKD

Poor adherence

Risk factors:
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Patient

Provider

Health system

World Health Organization 2003; Raina et al, Ann Transplant 2018

Care processes & structures affecting adherence

POSITIVE

Canadian National TRANSPLANT Research Program

- 14 pediatric / 14 adult tx programs across Canada
- 270 kidney, liver and heart tx recipients, 14-25 yrs old, >3 mths post-tx
- Median age 20.3 yrs, median time since tx 5 years
- Program-level factors associated with adherence
- Adherence measured at 0, 3, and 6 months using BAASIS©

Dabirzadeh et al, Pediatr Transplant 2021

Care processes & structures affecting adherence

POSITIVE

Canadian National TRANSPLANT Research Program

Table 3: Factors associations with Adherence

Model 1: Program-level factors	
Factor	**OR [95% CI] for Adherence (vs. non-adherence)**
Program Level Factors	
Minimum number of routine blood tests per year (per 1 additional)	**1.12 (1.00, 1.26); p=0.047**
Clinical pharmacist on team	1.29 (0.21, 7.91); p=0.78
Same nurse at each visit	1.96 (0.78, 4.96); p=0.15
Average time nurse spends with patient (per 5 min.)	**1.15 (1.03, 1.29); p=0.017**
Self-management interventions offered	1.88 (0.89, 3.98); p=0.098

Program-level factors associated with better adherence:

- *Greater frequency of routine blood testing / visits (+12%)*
- *More nurse time with patients (+15% for each 5-min increment)*

Dabirzadeh et al, Pediatr Transplant 2021

Care processes & structures affecting adherence

+POSITIVE
Canadian National TRANSPLANT Research Program

Factor	OR [95% CI] for adherence (vs. non-adherence)
Program-level factors	
Minimum prescribed number of routine blood draws per year (per 1 additional prescribed blood draw per year)	**1.12 (1.00, 1.26); p = .047**
Clinical pharmacist on team	1.29 (0.21, 7.91); p = .78
Same nurse at each visit	1.96 (0.78, 4.96); p = .15
Average time nurse spends with patient at clinic visits (per 5 min.)	**1.15 (1.03, 1.29); p = .017**
Self-management interventions offered	1.88 (0.89, 3.98); p = .098
Non-modifiable patient-level factors	
Age at Baseline (per year)	1.04 (0.96, 1.13); p = .31
Male sex (vs. female)	0.74 (0.52, 1.06); p = .099
Living donor (vs. deceased donor)	**1.64 (1.12, 2.40); p = .012**
Time since transplant (per year)	**0.95 (0.92, 0.98); p = .0015**
Parent is primary caregiver (vs. self or other)	**1.90 (1.23, 2.95); p = .0041**
Number of Medications (per additional medication)	**1.10 (1.03, 1.18); p = .0067**

Dabirzadeh et al, Pediatr Transplant 2021

Question 4:
Which factors impact medication adherence in kidney TX patients?

A. Support for CKD patients with cognitive impairment

B. Improved dosing schedules – less doses

C. Increased visit / blood draw frequency

D. Increased nurse time

E. All of the above

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Strategies to operationalize a transition program

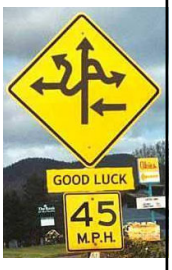
5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

What is the solution?

Structured Multidisciplinary Transition Programs

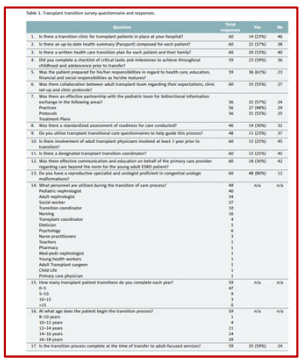
Goals of a transition program

- Building and supporting self management
  - Neurocognitively appropriate education / skill development
- Engaging the receiver team
  - Identify an adult champion
  - Adaptation of adult care to YA / specialized YA TX clinic
- Providing check-list driven guide
- Guiding patients & families through transition

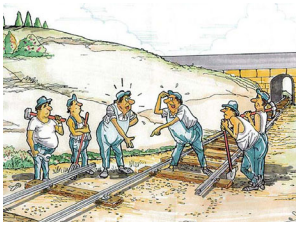


Vaks et al, Healthcare 2016

Pediatric Renal Transplantation: Focus on Current Transition Care and Proposal of the "RISE to Transition" Protocol

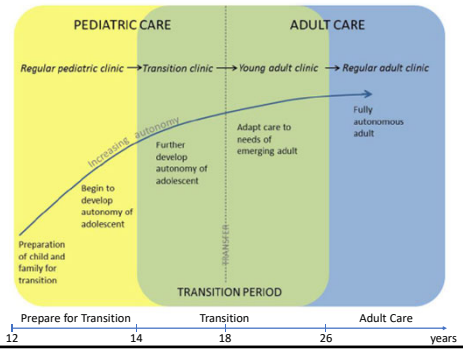


Transition team



- Pediatric nephrology nurse
- Pediatric nephrologist
- Adolescent medicine
- Renal pharmacist
- Renal dietician
- Social worker
- Adult nephrology team
  - Transplant nurse and MD

Structured Transition

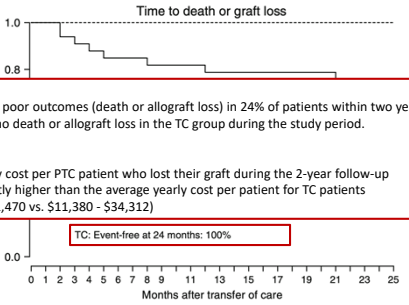


Foster and Bell, 2015

Operationalizing a transition program

- Challenges
  - Funding
  - Access to resources
  - Absence of shared access to same EMR
- Solutions
  - Data to support the necessity of transition, and presenting the data to stakeholders (knowledge mobilization)
  - Advocacy for resources with data in hand
  - Identifying transition "champions", both pediatric and adult, in a joint clinic

Does transition clinic make a difference?



Outcome:
Before the TC, poor outcomes (death or allograft loss) in 24% of patients within two years of transfer, compared to no death or allograft loss in the TC group during the study period.

Cost:
Average yearly cost per PTC patient who lost their graft during the 2-year follow-up was significantly higher than the average yearly cost per patient for TC patients ($40,956 - $61,470 vs. $11,380 - $34,312)

Prestidge et al, Pediatr Nephrol 2011

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Take home message

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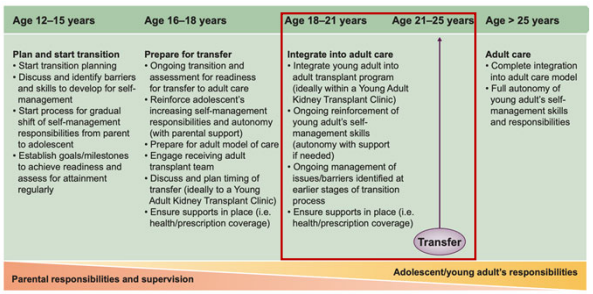
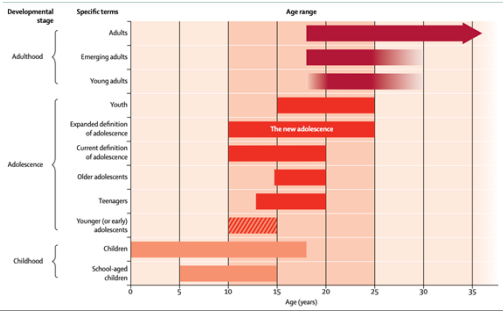
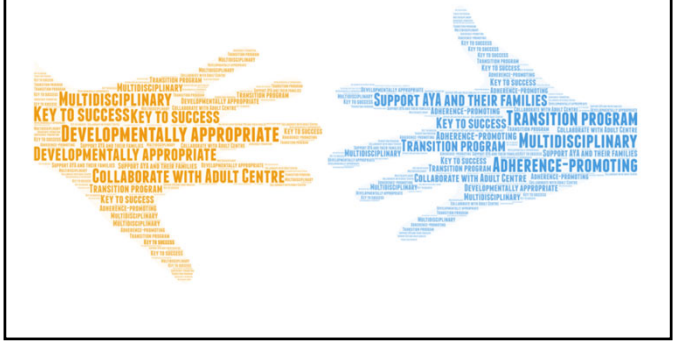


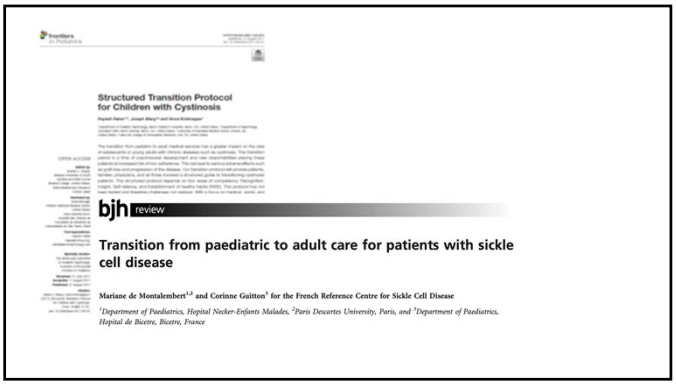
Teoh and Licht, Nephrol Dial Transplant 2022
Modified from Matsuda-Abedini et al, Pediatr Nephrol 2023

The (new) age of adolescence?



Sawyer et al, The Lancet 2018





Structured Transition Protocol for Children with Cystinosis

bjh review

Transition from paediatric to adult care for patients with sickle cell disease

Mariane de Montalembert[1,2] and Corinne Guitton[3] for the French Reference Centre for Sickle Cell Disease

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Licht Lab 2024

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Dr. Mina Matsuda-Abedini
and
Dr. Rupesh Raina
for having shared slides

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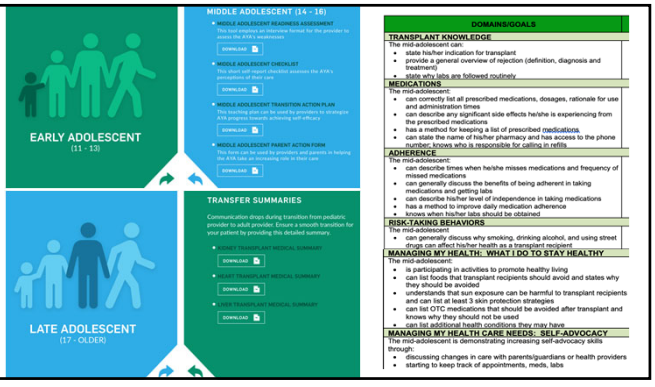
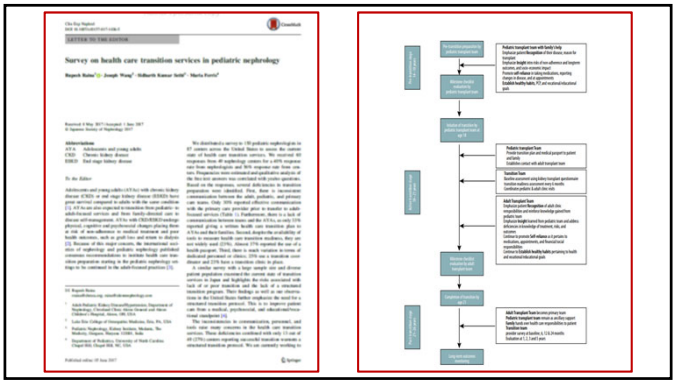
https://www.nyast.org/education/specialty-resources/peds-transition





Survey on health care transition services in pediatric nephrology

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Latest updates on the clinical trials and treatment in Alport syndrome

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Division of Nephrology and RI Cell Biology Program
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Toronto, ON
20.8.2024

Disclosures

- **Scientific advisor and/or speaker**
  - Alexion, AstraZeneca Rare Disease
  - Apellis Pharmaceuticals, Inc.
  - Catalyst Biosciences
  - Eleva GmbH
  - Novartis
  - Oak Bay Biosciences
  - Otsuka Pharmaceuticals, Inc.
  - Pfizer Inc.
  - Samsung Bioepis Co, Ltd.
- **DSMB member**
  - Argenx – Axio Research
  - Early Protect Alport / Double Protect Alport / EMPA Alport
  - OPKO Health, Inc.

Overview

- Pathogenesis of Alport syndrome
- Therapeutic targets in Alport syndrome
- Impact of early diagnosis on Alport syndrome outcome

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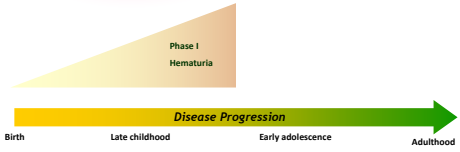
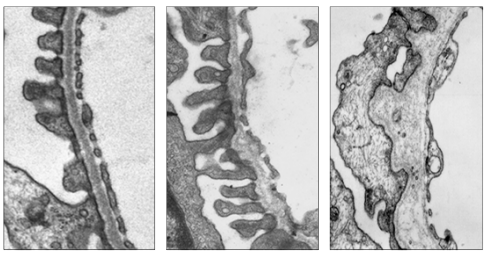
Pathogenesis of Alport syndrome

The clinical course of Alport syndrome

Alport syndrome:
A disease progressing
to ESRD

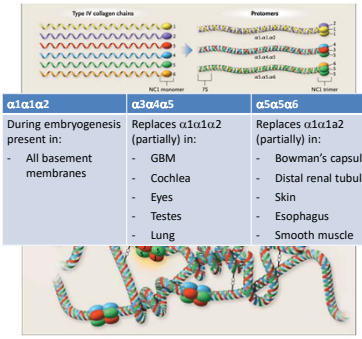


Progressive GBM damage in Alport syndrome



Normal | Early AS | Late AS

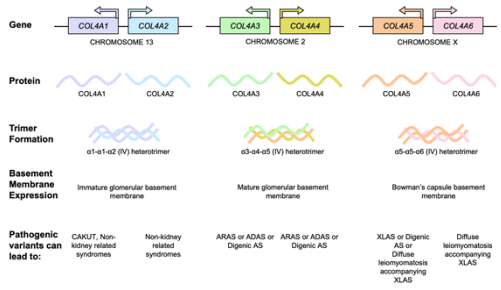
Organ-specific distribution of collagen IV α3/α4/α5



α1α1α2	α3α4α5	α5α5α6
During embryogenesis present in: - All basement membranes	Replaces α1α1α2 (partially) in: - GBM - Cochlea - Eyes - Testes - Lung	Replaces α1α1a2 (partially) in: - Bowman's capsule - Distal renal tubule - Skin - Esophagus - Smooth muscle

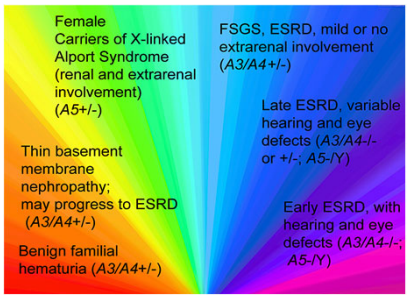
Hudson et al, N Engl J Med 2003

The genotype # phenotype spectrum in Alport syndrome



De Gregorio et al, Kidney Med 2023

The genotype # phenotype spectrum in Alport syndrome



Miner, Kidney Int 2014; Kashtan et al, Kidney Int 2018

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Therapeutic targets in Alport syndrome

International Alport Syndrome Workshop (Singapore, 20.8.2024)

Alport Syndrome Workshop Community

Table 1 | Current Phase 2 and 3 trials enrolling patients with AS

Drug/sponsor	Target and theorized mechanism	Trial phase and design	Main eligibility criteria
SAR339375/Sanofi[13]	Anti-microRNA-21 Theorized mechanism: antifibrotic	Phase 2: randomized, double-blind, placebo-controlled Enrollment target: 45 48 weeks randomized + 48-week open-label extension	Age 18–55 yr Male or female Confirmed AS diagnosis eGFR >35 ml/min per 1.73 m² EITHER: 1. eGFR decline of ≥4 ml/min per 1.73 m² per yr 2. Proteinuria >2000 mg/g 3. Male age 18–23 yr with eGFR <90 ml/min per 1.73 m²
Bardoxolone methyl/ Reata Pharmaceuticals[14]	Activates Nrf2 pathway and inhibits nuclear factor-κB pathway Theorized mechanism: antioxidant, mitochondria-protective, anti-inflammatory	Phase 2/3/: Phase 2: open-label Enrollment: 30 12 weeks + open-label extension Phase 3: randomized, double-blind, placebo-controlled Enrollment: 187 48 weeks randomized + 4-week washout + 48-week open-label extension	Age 12–60 yr Male or female Confirmed AS diagnosis; eGFR ≥30 and ≤90 ml/min per 1.73 m²; albumin-to-creatinine ratio ≤3500 mg/g

AS, Alport syndrome; eGFR, estimated glomerular filtration rate.

Table 3 | Recommended eligibility criteria for a conventional drug clinical trial in Alport Syndrome (AS)

Eligibility criteria	
Diagnosis of AS (see Table 2)	
AND	
Between the ages of 12[a] and 60 yr, inclusive	
AND	
eGFR <60 ml/min per 1.73 m²	eGFR >60 ml/min per 1.73 m²
	AND ≥1 of the following: • Recent history of progressively worsening eGFR • Proteinuria >300 mg/24 h on 24-h urine collection[30–33] • Proteincreatinine ratio >300 mg/g on random urine collection[30–33]

eGFR, estimated glomerular filtration rate.
[a]See SPECIAL CONSIDERATIONS FOR PEDIATRIC AND ADOLESCENT CLINICAL TRIALS. Note that the age of 12 yr is a general suggestion. Factors such as the mechanism of action of the investigational agent, its safety profile, and the endpoints of the clinical trial should be carefully considered when determining the eligible lower age limit.

Weinstock et al, Kidney Int 2020

TABLE 2 | Clinical trials for Alport Syndrome listed on clinicaltrials.gov.

	Drug name and sponsor	Mechanism of action	Status	Phase and study name	Number of patients	Intervention	ClinicalTrials.gov Identifier
√	Bardoxolone methyl/ Reata Pharma-ceuticals	Nrf2 activator NF-κB inhibitor	Completed Recruiting	Phase 3 CARDINAL Phase 3 EAGLE	157 480	Oral bardoxolone vs placebo for 100 weeks Oral bardoxolone for up to 5 years (single arm)	NCT03019185 NCT03749447
√	Lademirsen (RG-012, SAR339375) / Genzyme, a Sanofi Company	Anti-microRNA-21 drug, Reduces P42/P44 MAPK pathway activation	Active, not recruiting	Phase 2 HERA	43	Weekly subcutaneous injection of anti-microRNA-21 drug vs. placebo for 110 weeks	NCT02855268
√	Sparsentan Travere Therapeutics	Dual endothelin type A receptor and angiotensin II type 1 receptor antagonist	Recruiting	Phase 2 EPPIK	57	Oral sparsentan for 108 weeks (single arm) Includes pediatric patients with AS and other proteinuric kidney diseases	NCT05003986
√	Atrasentan Chinook Therapeutics	Endothelin type A receptor antagonist	Recruiting	Phase 2 AFFINITY	80	Oral atrasentan for 52 weeks (single arm) Includes adult patients with AS and other proteinuric kidney diseases	NCT04573920
√	Hydroxychloroquine (HCQ) Shanghai Children's Hospital	Immunomodulatory drug	Recruiting	Phase 2 CHXLAS	50	Oral HCQ + benazepril vs. benazepril monotherapy for 6 months	NCT04937907
√	Benazepril, valsartan and Fluvastatin Mario Negri Institute for pharmacologic research	Drug combination inhibits ACE, ARB and HMG CoA reductase	Completed	Phase 2: Effects of an Intensified treatment with ACE-I, ATA II and statins in AS	9	Drugs: benazepril, valsartan and Fluvastatin (single arm)	NCT00309257
√	Ramipril Institut fuer anwendungsorientierte Forschung und klinische Studien GmbH	Angiotensin converting enzyme inhibitor	Completed	Phase 3, Early prospective therapy trial to delay renal failure in Children with AS (EARLY PROTECT)	66	Ramipril (blinded) Placebo to ramipril Ramipril (open-label)	NCT01486979
√	RSR01 & River 3 Renal Corp	Lipid-modifying drug	Not yet recruiting	Phase 2, Study to evaluate RSR01 in patients with Alport syndrome and patients with Focal Segmental Glomerulosclerosis	50	Oral RSR01 for 12 weeks	NCT05267262

Chavez et al, Front Med 2022

Treatment trials (selection)

ACE-inhibition
*Phase 3 randomized, placebo-controlled **EARLY PRO-TECT** Alport trial (Ramipril)*

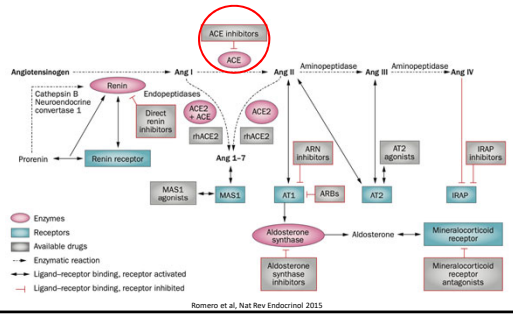
Non-steroidal mineralocorticoid receptor antagonist
*Phase 3 randomized, placebo-controlled **FIONA** trial (Finerenone)*

Gene therapy
*Phase 2 open-label study **ELX-02** in Alport Syndrome ("read-through")*

Metabolism / cell survival
*Phase 2 open label study **R3R01**-ASFSGS-201 (lipid pathway podocyte)*

SGLT2-inhibition
*Phase 3 randomized, placebo-controlled **DOUBLE PRO-TECT** Alport trial (Dapagliflozin)*

RAAS and RAAS inhibition



Romero et al, Nat Rev Endocrinol 2015

EARLY PRO-TECT Alport (NCT01485978)

A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome.

EARLY PRO-TECT Alport

at baseline
oligo-symptomatic
children
N=66

randomized-controlled-arm
22
Ramipril
Placebo
therapy up to 6 years

progression of albuminuria
6-monthly intervals

44
Ramipril
open treatment-arm

- age 2 years and older
- pre-emptive stage of disease with isolated hematuria or with micro-albuminuria
- eGFR at about 125 ml/min/1.73 m²
- normal blood pressure

100% risk of early renal failure

Placebo-like
untreated boys
from US-registry
N=28

AEs & SAEs: 3/11 (27%) | 5/9 (56%)
Safety First
disease progression
AEs & SAEs: 17/42 (40%) | 12/28 (43%)

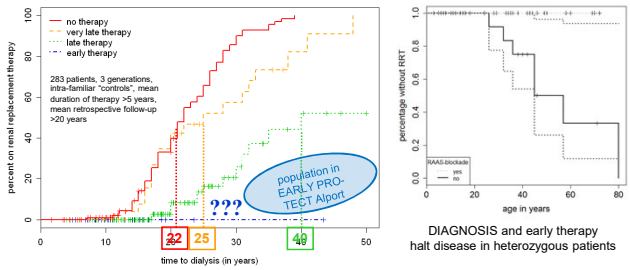
co-primary endpoints
Safety
Efficacy
1x ⇒ 2x to 3x progression of albuminuria

CONCLUSION:
Early initiation of ramipril showed no safety signals. Pre-emptive therapy appears to slow early disease progression and may justify screening of patients with isolated hematuria for Alport-related gene-variants.

ISN kidney INTERNATIONAL
Gross et al., 2019

Validation of therapeutic target via registry data

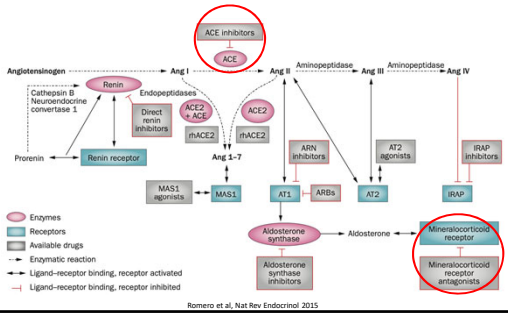
„Classical" Alports **100%** Risk of ESKD **1-30%** Heterozygous Alports



DIAGNOSIS and early therapy halt disease in heterozygous patients

Gross / Licht et al, Kidney Int 2012 *Early ACEi in Alport syndrome delays renal failure and improves life expectancy*
Stock et al, Pediatr Nephrol 2019 *Potential of RAAS-blockade to halt disease in Alport with heterozygous mutations*

RAAS and RAAS inhibition



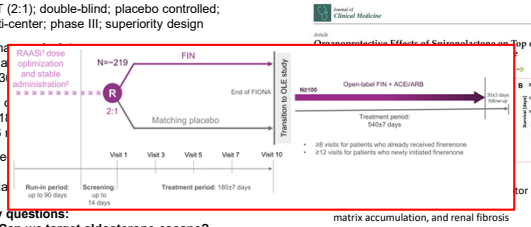
Romero et al, Nat Rev Endocrinol 2015

FIONA (Bayer; NCT05196035) [recruiting]

Finerenone (Bayer) in children with proteinuric kidney diseases (many AS cases)

RCT (2:1); double-blind; placebo controlled;
multi-center; phase III; superiority design

Prima
Urina
of ≥3
219
- 1-1
- <6
- Pre
- Tria



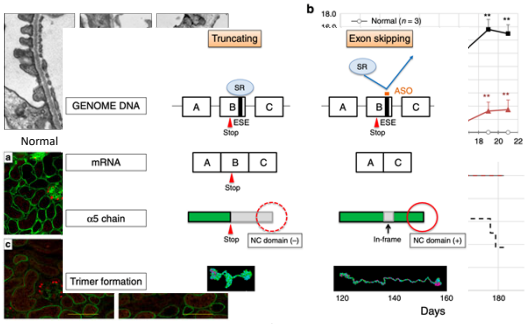
tor antagonist

Key questions:
- **Can we target aldosterone-escape?**
- **Less side effects than spironolactone?**

matrix accumulation, and renal fibrosis
- significantly improved lifespan
(however, effect not-superior to ACEi mono-therapy)

Bakris et al, N Engl J Med 2020 Benefit of MAR antagonist in DM Type II (FIGARO-DKD & FIDELIO-DKD)
Schaefer et al, Trials 2024 Study design for FIONA

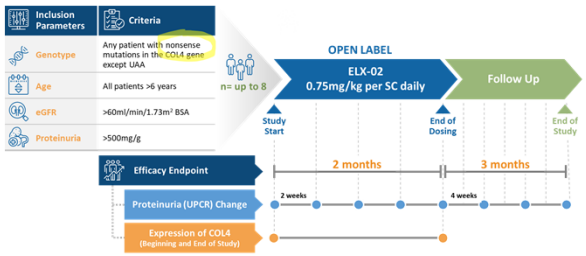
ELX-02 open label Phase 2 (Eloxx; NCT05448755) [recruiting]



Yamamura et al, Nature Communications 2020

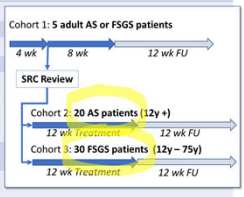
ELX-02 Open Label Phase 2 (Eloxx; NCT05448755) [recruiting]

Press release (8.2023):
N=3 patients treated with ELX-2 showed improvement in podocyte foot process effacement after 8 weeks



Phase 2 Clinical Study R3R01-ASFSGS-201 (River; NCT05267262) [recruiting]

Title	A Phase II, Multi-center, Open-Label Study to Assess Safety, Tolerability, Efficacy and Pharmacokinetics of R3R01 in Alport Syndrome Patients with Uncontrolled Proteinuria on ACE/ARB Inhibition and in Patients with Primary Steroid-Resistant Focal Segmental Glomerulosclerosis
Protocol number	**R3R01-ASFSGS-201**
Clinicaltrials.gov	NCT05267262
Sponsor	River 3 Renal Corp
Investigational drug	R3R01 for 12 weeks (with 12 weeks FU)
Nr of Centers	Up to 30 centers in the US and Europe
Study design	• Run-in with 5 adult patients • Scientific Review Committee (SRC) evaluation • Continuation with full AS and FSGS cohorts including adolescents (12y and older) after SRC and if approved by CA/EC
Primary objectives	• Safety and Tolerability • ≥30% reduction in proteinuria at 12 weeks
Secondary objectives	• SF-36 • UPCR response/remission



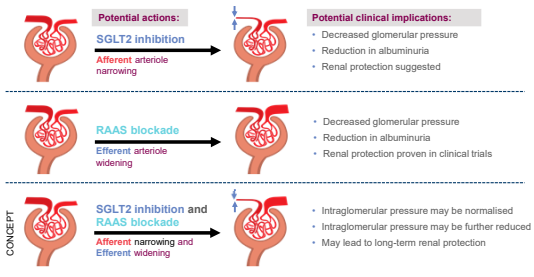
DOUBLE PRO-TECT Alport

ClinicalTrials.gov Identifier: NCT05944016
EU Trial No. 2023-508502-18-00

A confirmatory, multicenter, randomized, double-blind, placebo-controlled clinical trial to assess the effect of Dapagliflozin on the progression of chronic kidney disease in adolescent and young adult patients with Alport syndrome

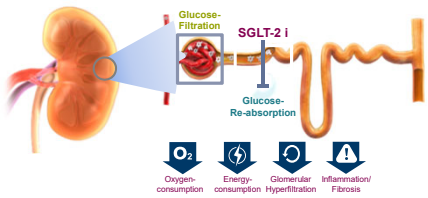
Prof. Dr. Oliver Gross
Nephrology and Rheumatology
University Medicine Goettingen, Germany
gross.oliver@med.uni-goettingen.de
www.alport.de

Dual SGLT2 and RAAS inhibition as new early & targeted approach for (glomerular) kidney diseases in children



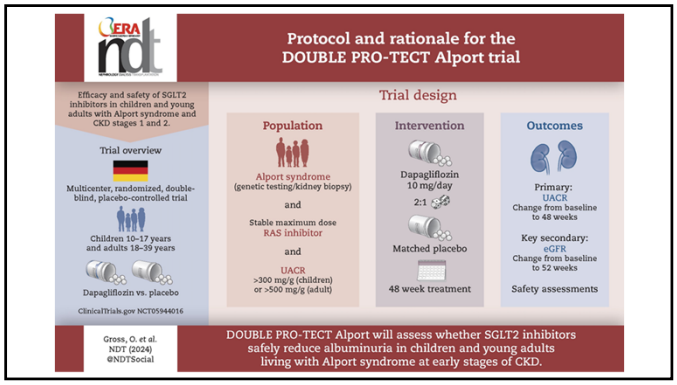
Adapted from: Cherney et al, Circulation 2014; Lewis et al, N Engl J Med 2001; Kon et al, Kidney Int 1993

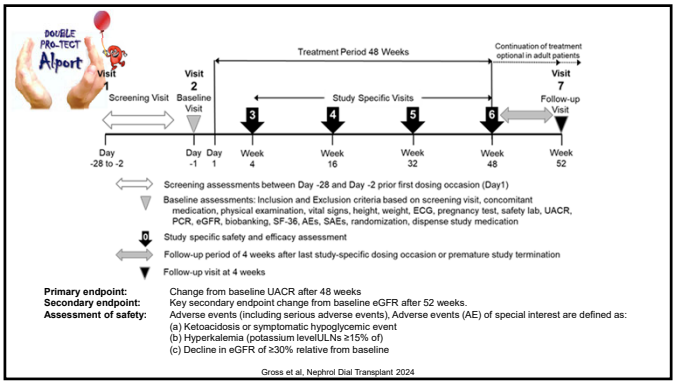
POWER SAVE MODE: Relevance of SGLT-2 for glucose reabsorption



Up to 600 g of glucose daily can be re-absorbed by SGLT-2 (using high amounts of energy and oxygen)
SGLT-2 inhibitors lead to reduction of work-load in the kidneys at various levels

Vallon and Thomson, Diabetologia 2017; Meng et al, J Med Chem 2008; Cherney et al, Nephrol Dial Transplant 2020; Vergara A, Clin Kidney J 2019; Gerich et al, Diabet Med 2010





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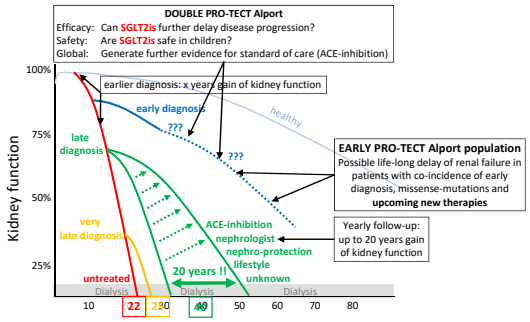
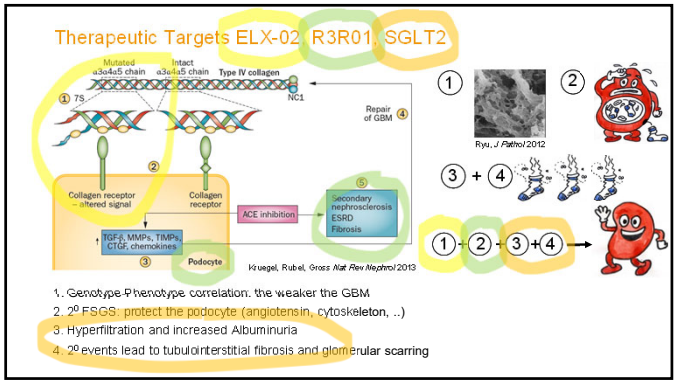
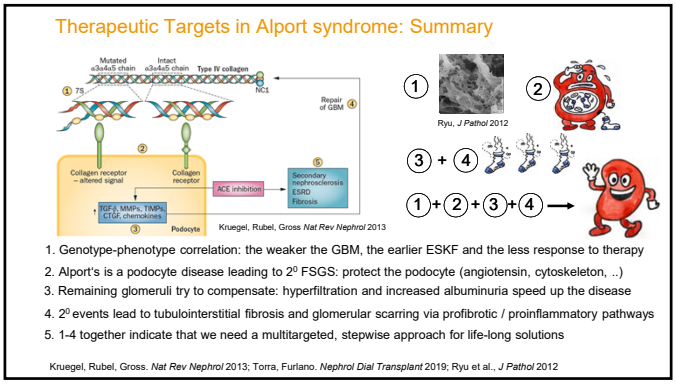
Impact of early diagnosis on Alport syndrome outcome

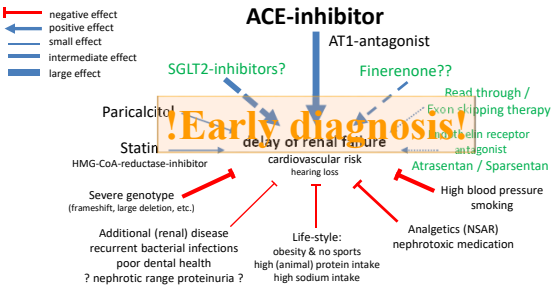
International Alport Syndrome Workshop (Singapore, 20.8.2024)







"Add on" treatment approach for Alport syndrome



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Research Article

Life Science Alliance

Genetic reprogramming with stem cells regenerates glomerular epithelial podocytes in Alport syndrome

Valerie S LeBleu[1,2,3,4], Keizo Kanasaki[2], Sara Lovisa[1], Joseph L Alge[1,4], Jiha Kim[1], Yang Chen[1], Yingqi Teng[2], Behzad Gerami-Naini[2], Hikaru Sugimoto[1,2], Noritoshi Kato[2], Ignacio Revuelta[2], Nicole Grau[5,6], Jonathan P Sleeman[5,7], Gangadhar Taduri[2], Akane Kizu[2], Shahin Rafii[8], Konrad Hochedlinger[9,10], Susan E Quaggin[11], Raghu Kalluri[1,2,10,12,13,14]

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Recurrence of native disease post-transplant
Transplant in patients with complement system dysregulation

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Toronto, ON
23.8.2024

Disclosures

- **Scientific advisor and/or speaker**
  - Alexion, AstraZeneca Rare Disease
  - Apellis Pharmaceuticals, Inc.
  - Catalyst Biosciences
  - Eleva GmbH
  - Novartis
  - Oak Bay Biosciences
  - Otsuka Pharmaceuticals, Inc.
  - Pfizer Inc.
  - Samsung Bioepis Co, Ltd.
- **DSMB member**
  - Argenx – Axio Research
  - Early Protect Alport / Double Protect Alport / EMPA Alport
  - OPKO Health, Inc.

Overview

- Introduction
- Transplant in aHUS
- Transplant in C3G
- Conclusion

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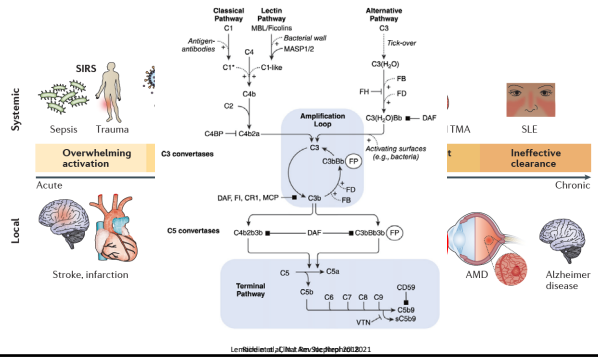
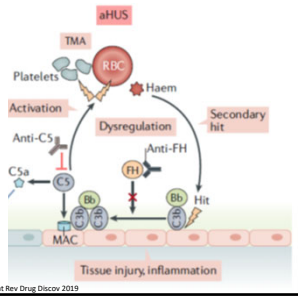
Introduction



Disease specific complement dysregulation



Question 1: Which answer is *incorrect*?

A. aHUS and C3G patients carry a significant risk of disease recurrence in native kidneys and kidney grafts.

B. The concepts of complement-modulating treatment are equal pre- and post-TX.

C. Plasma treatment (infusion / exchange) remains a viable option for aHUS and C3G patients.

D. Combined liver # kidney TX can be considered for all types of genetic mutations in aHUS.

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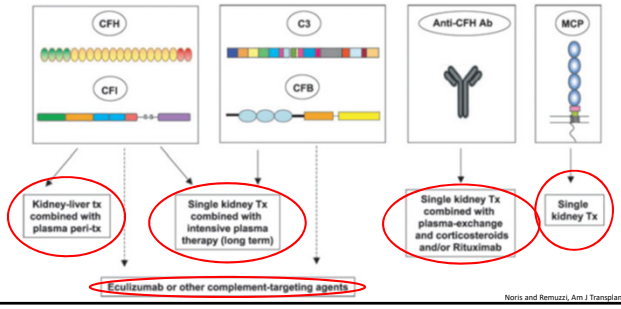
Transplant in aHUS

5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

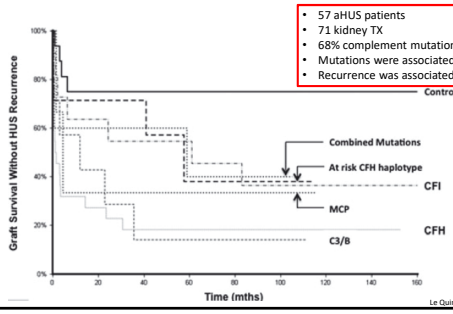
Kidney TX in aHUS – the pre-eculizumab era



Noris and Remuzzi, Am J Transplant 2010

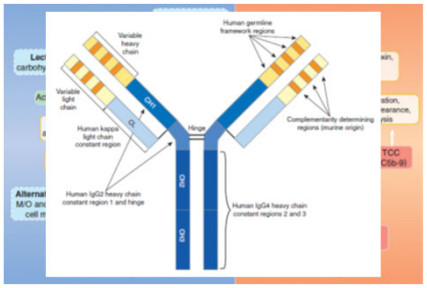
Historical graft survival in kidney TX in aHUS patients

- 57 aHUS patients
- 71 kidney TX
- 68% complement mutation
- Mutations were associated with recurrence risk
- Recurrence was associated with graft loss



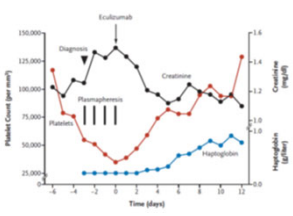
Le Quintrec et al, Am J Transplant 2013

Complement blockade via eculizumab

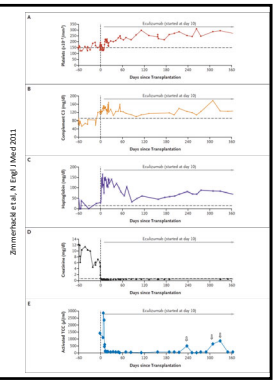


Rother et al, Nat Biotechnol 2007

Eculizumab in kidney TX
1st adult & 1st pediatric patient

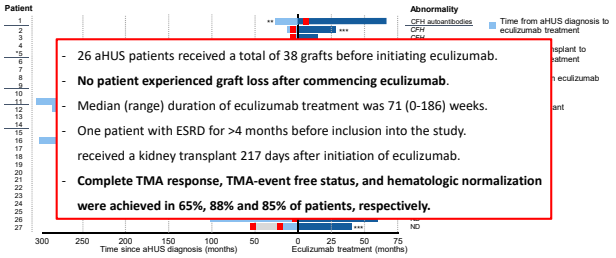


Nurnberger et al, N Engl J Med 2009



Zimmerhackl et al, N Engl J Med 2011

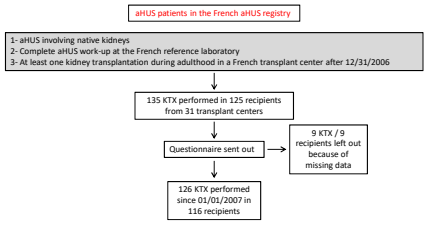
Eculizumab in kidney TX



- 26 aHUS patients received a total of 38 grafts before initiating eculizumab.
- **No patient experienced graft loss after commencing eculizumab**.
- Median (range) duration of eculizumab treatment was 71 (0-186) weeks.
- One patient with ESRD for >4 months before inclusion into the study. received a kidney transplant 217 days after initiation of eculizumab.
- **Complete TMA response, TMA-event free status, and hematologic normalization were achieved in 65%, 88% and 85% of patients, respectively.**

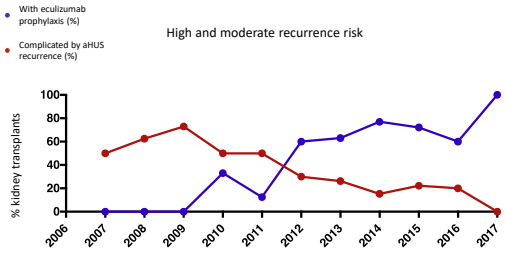
Legendre et al, Transplant Int 2017

Nationwide French study



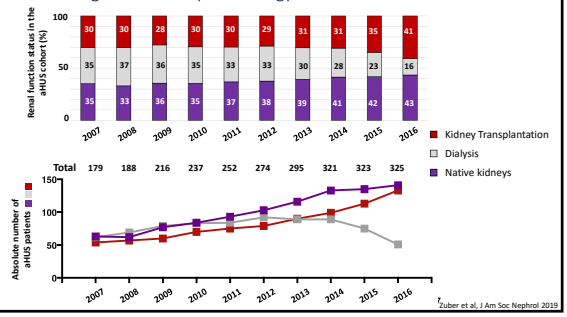
Zuber et al, J Am Soc Nephrol 2019

Compliance with risk stratification



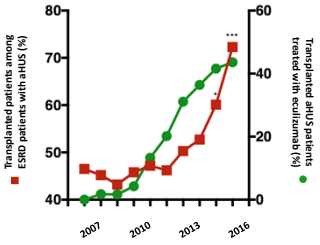
Zuber et al, J Am Soc Nephrol 2019

Fundamental changes in aHUS epidemiology



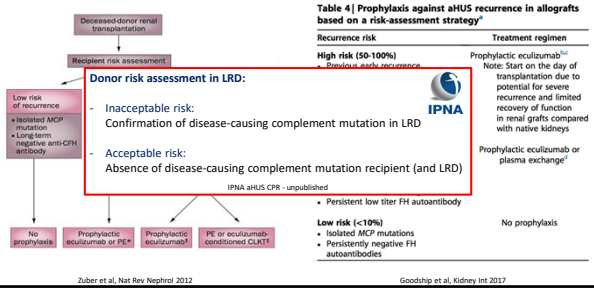
Zuber et al, J Am Soc Nephrol 2019

Fundamental changes in aHUS epidemiology



Zuber et al, J Am Soc Nephrol 2019

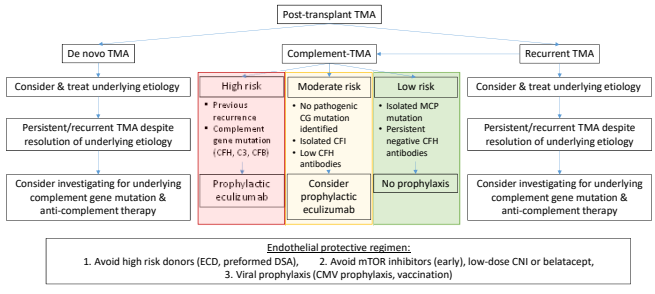
Risk stratification in kidney TX



Zuber et al, Nat Rev Nephrol 2012

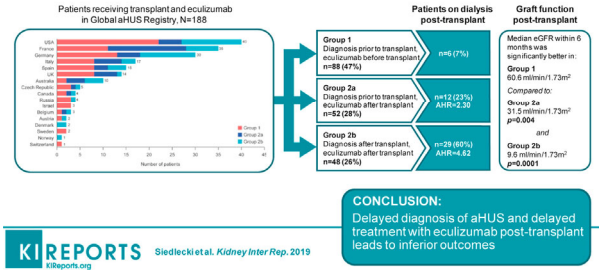
Goodship et al, Kidney Int 2017

Kidney TX in aHUS patients



Adapted from Zuber et al, Am J Transplant 2012; Goodship et al, Kidney Int 2017; Zuber et al, Transplant Rev 2013

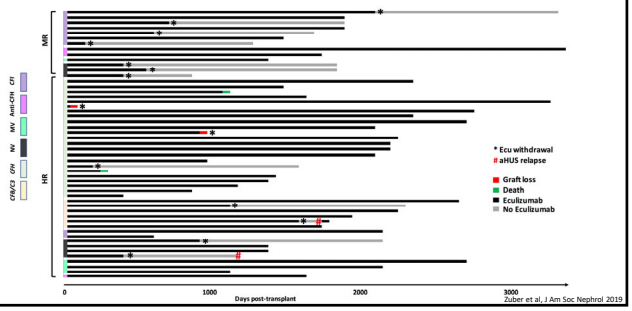
Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome



KIREPORTS KiReports.org Siedlecki et al. *Kidney Inter Rep.* 2019

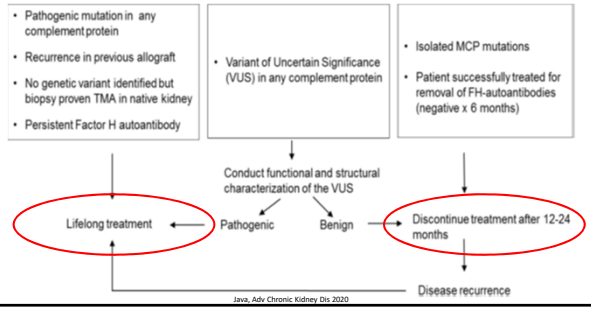
CONCLUSION:
Delayed diagnosis of aHUS and delayed treatment with eculizumab post-transplant leads to inferior outcomes

Eculizumab (prophylactic) discontinuation post kidney TX



Zuber et al, J Am Soc Nephrol 2019

Treatment duration post kidney TX



Java, Adv Chronic Kidney Dis 2020

An alternative approach… (CUREiHUS)

- Due to the high cost of eculizumab, alternative strategies were explored aiming to minimize the burden of endothelial injury and thus TMA triggers.
- Strategies included:
  - Living donation
  - Low-dose CNI
  - Aggressive BP management
- Eculizumab-free protocol, except for use for treatment in patients with post-TX recurrence
- Patients & outcome:
  - 17 (12 F) LRD transplants in aHUS patients
  - 15/17 met high-risk criteria
  - Only one patient experienced TMA recurrence

Duineveld et al, Am J Kidney Dis 2017

An alternative approach… (CUREiHUS)

- Since 2016, kidney TX in aHUS patients in The Netherlands without eculizumab prophylaxis.
- Eculizumab used for treatment of post-TX recurrence only.
- 1.2016-10.2020, 15 adult aHUS patients (12 F) with post-TX recurrence.
- Time interval to recurrence bimodal:
  - 7 patients presented *early* within median of 3 months (0.3-8.8)
  - 8 patients presented *late* within median of 46 months (18-69)
    (3 with TMA, 5 without TMA but with chronic deterioration of eGFR)
- Eculizumab treatment resulted in improvement or stabilization of eGFR in 14/15.
- After F/U of 29 median of months (3-54):
  - 6 patients had eGFR <30 ml/min x 1.73 m^2
  - Graft loss in 3 patients
  - Overall recurrence rate 23%

Duineveld et al, Kidney Int Rep 2023

Outcome of aHUS patients on eculizumab post TX – a meta-analysis

- 18 studies (13 cohort studies and 5 case series).
- N=380 adult aHUS patients.
- Eculizumab for prevention vs. treatment of post kidney TX aHUS recurrence.
- **Eculizumab for prophylaxis:**
  Incidence rates of TMA and graft loss due to TMA were 6.3% and 5.5%, respectively.
- **Eculizumab for treatment of recurrence:**
  Estimated rates of graft loss due to TMA was 22.5% (22.6% in patients with genetic mutations).
- Most frequently found mutations in patients with TMA recurrence were CFH > CFI > C3.

Gonzalez Suarez et al, J Clin Med 2019; Tang et al, Ren Fail 2023

Question 2: Which answer is *incorrect*?

A. Kidney transplant in aHUS patients should consider recipient and donor risk.

B. CFH, C3 and CFB mutations along with high titer CFH autoantibodies are considered high recipient risk conditions.

C. The absence of a genetic mutation defines an exclusion criteria for an LRD.

D. Post-TX eculizumab treatment is informed by genetics, CFH autoantibody titers, and the history of relapses.

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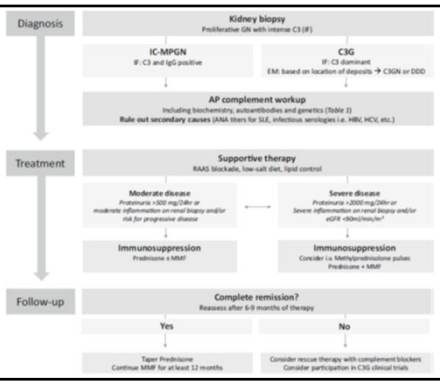
Transplant in C3G

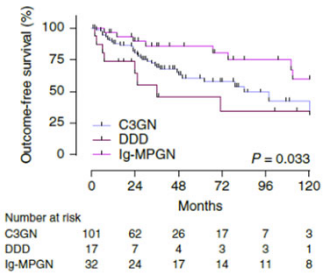
5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

Current treatment recommendation for C3G



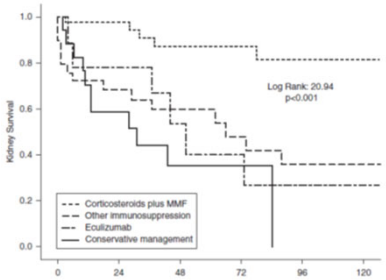
Vivarelli et al, Pediatr Nephrol 2022

Outcome of C3G and IC-MPGN patients - *Histology*



Lomax-Browne et al, Clin J Am Soc Nephrol 2022

Outcome of C3G and IC-MPGN patients - *Treatment*



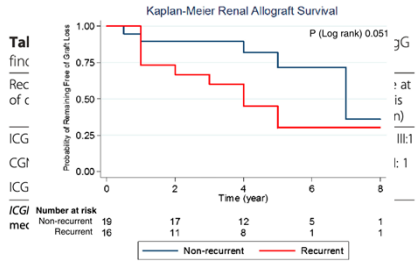
Caravaca-Fontan et al, Clin J Am Soc Nephrol 2020

Graft survival in kidney TX in C3G patients - *cohorts*

- 32.4% risk of graft loss from recurrence at 5 years post TX in children with MPGN.
  (Van Stralen et al, Nephrol Dial Transplant 2013 – ESPN/ERA-EDTA registry)
- Greater risk of graft loss from recurrence in children with DDD.
  (Braun et al, J Am Soc Nephrol 2005 – NAPRTCS registry)
- 66.7% risk of graft loss from recurrence in C3G patients with median time to graft failure of 6.4 years.
  (Zand et al, J Am Soc Nephrol 2014)
- Cohort of n=35 C3G patients:
  Recurrence risk of 43% in MPGN, 55% in DDD, and 60% in C3GN patients.
  (Servais et al, Kidney Int 2012 – French cohort)
- Cohort of n=13 C3G patients (6 DDD; 7 C3GN):
  - 69% overall graft survival at 5 years.
  - All 6 DDD recurred, and 3 (50%) failed due to recurrence.
  - 4/7 (57%) C3GN recurred, and 3/4 (75%) failed due to recurrence.
  (Medjeral-Thomas et al, J Am Soc Nephrol 2014 – English cohort)

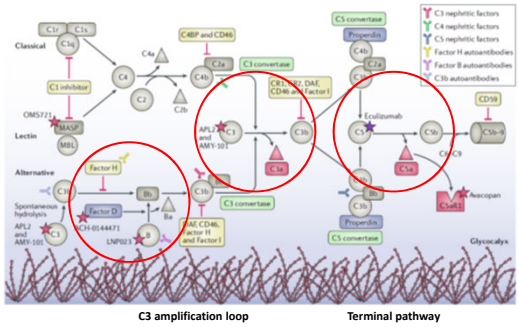
High risk of disease recurrence and graft failure due to recurrence in patients with MPGN < DDD < C3GN.

Graft survival in kidney TX in C3G patients after relapse



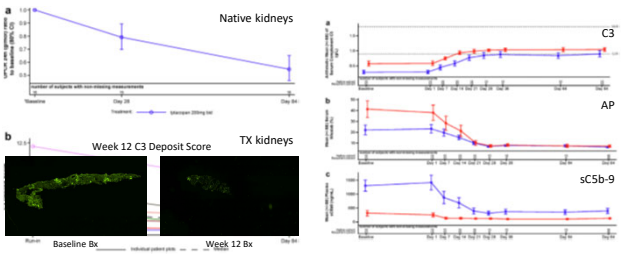
Alasfar et al, BMC Nephrology 2016

Future treatment options for C3G



Smith et al, Nat Rev Nephrol 2019

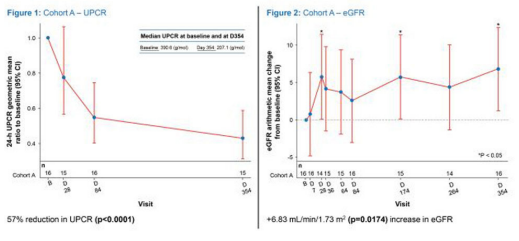
Iptacopan (Novartis) in C3G patients (Phase 2)
Factor B inhibitor



Wong et al, PO2536 (ePoster), ASN Kidney Week 2021; Wong et al, Kidney Int Reports 2023

Iptacopan (Novartis) in C3G patients (Phase 2) – Cohort A

12 months outcome



Nester et al, WCN23-0403 (Abstract)

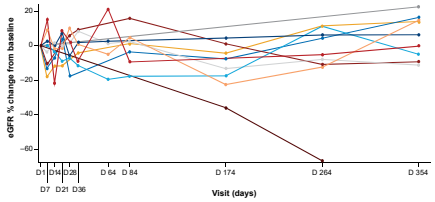
Iptacopan (Novartis) in C3G patients (Phase 2) – Cohort B

	Baseline	Month 3	Month 12
Median 24h UPCR	18.4 g/mol (9-445)	34% reduction	21% reduction
Mean 24h UPCR	121.0 g/mol (188.29)	CI: (0.40,1.08), p=0.0879	CI: (0.48,1.31), p=0.3151

- Most patients with recurrent C3G post kidney TX had proteinuria within normal range, which remained low after iptacopan treatment.
- UPCR values were available for 8/10 patients at baseline.
- Of these 8 patients, 6 had proteinuria within the normal range at baseline, which remained low after 1 year of iptacopan treatment.
- The remaining 2 patients had elevated UPCR at baseline (404.2 g/mol and 53.5 g/mol), which decreased by 25% and 66%, respectively, at 1 year.

Nester et al, J Am Soc Nephrol 2022 (Supplement; Abstract TH-PO505);
Nester et al, TH-PO505 (Poster), ASN Kidney Week 2022

Iptacopan (Novartis) in C3G patients (Phase 2) – Cohort B



eGFR was stable in C3G patients with post kidney TX recurrence at 12 months.

Nester et al, TH-PO505 (Poster), ASN Kidney Week 2022

Pegcetacoplan (Apellis-Sobi) in post-TX recurrence in IC-MPGN and C3G (Phase 2; NOBLE study)

C3 inhibitor

At Week 12, of the 10 patients (IC-MPGN: n=2; C3G: n=8) treated with pegcetacoplan:

- Eight (80%) patients showed a reduction in C3c staining (reflective of damage-causing deposits) by one or more orders of magnitude of intensity from baseline.
- Five (50%) patients showed a reduction in C3c staining by two or more orders of magnitude of intensity from baseline.
- Four (40%) patients showed zero staining intensity, indicating that C3 deposits were cleared.
- Additionally, in a subgroup of patients with high baseline levels (≥1g per day) pegcetacoplan showed a mean reduction of proteinuria (39.2% change from baseline).
- Other biomarkers also improved, including an increase in mean serum C3, reduction in mean serum C5b-9 and stabilization of kidney function (eGFR).

Sobi Press Release (17.10.2023)
Dixon et al, ASN Kidney Week (Abstract; Poster #SA-PO923)

Question 3: Which answer is *incorrect*?

A. Historically, C3G / IC-MPGN comes with a high risk of post-TX recurrence.

B. Post-TX recurrence comes with a high risk of graft loss.

C. Terminal complement pathway blockade (e.g. via eculizumab) significantly improves the outcome of TX in C3G / IC-MPGN patients.

D. Treatment targeting C3 activation (anti C3; anti CFB) holds promise to improve the outcome of TX in C3G / IC-MPGN patients.

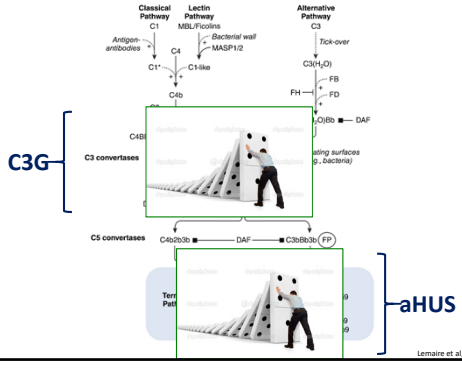
SickKids

Conclusion

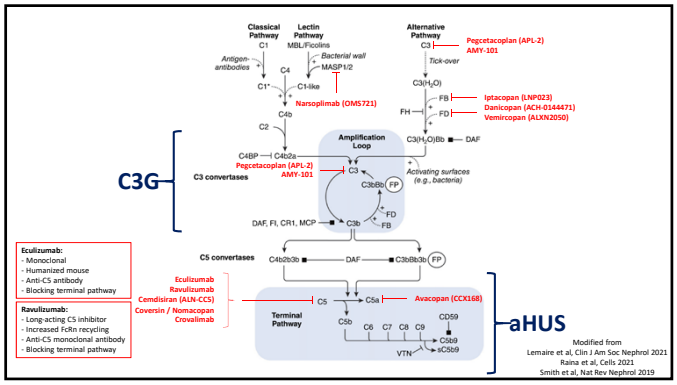
5th Primer in Pediatric Nephrology for Asia (Singapore, 21.-23.8.2024)

Take home messages

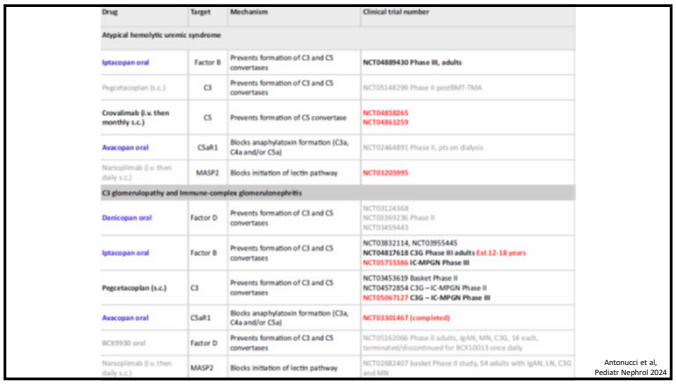
- Historically, aHUS and C3G / IC-MPGN come with a high risk of post-TX recurrence.
- Today, kidney TX in aHUS with terminal complement pathway blockade is safe.
- Optimal treatment duration is still debated and depends on genetics, autoantibodies, and recurrence history.
- In C3G / IC-MPGN TX, today best outcomes are achieved with prednisone & MMF.
- Blockade of (alternative pathway) C3 convertase holds promise to significantly improve outcomes in C3G / IC-MPGN both in native kidneys and in kidney grafts.



Lemaire et al, Clin J Am Soc Nephrol 2021

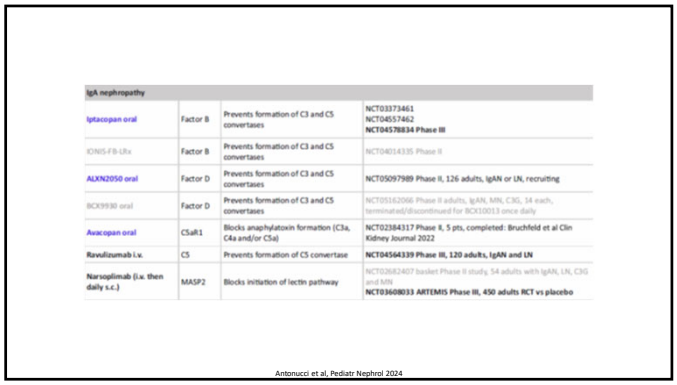


Modified from
Lemaire et al, Clin J Am Soc Nephrol 2021
Raina et al, Cells 2021
Smith et al, Nat Rev Nephrol 2019



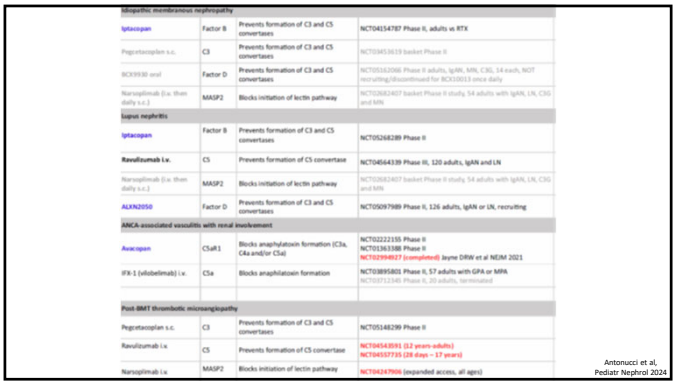
Drug	Target	Mechanism	Clinical trial number
Atypical hemolytic uremic syndrome			
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	NCT04889430 Phase III, adults
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT05148299 Phase II postBMT-TMA
Crovalimab (s.v. then monthly s.c.)	C5	Prevents formation of C5 convertase	NCT04858265 NCT04861259
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02464891 Phase II, pts on dialysis
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT03205995
C3 glomerulopathy and Immune-complex glomerulonephritis			
Danicopan oral	Factor D	Prevents formation of C3 and C5 convertases	NCT03124368 NCT03369236 Phase II NCT03459443
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	NCT03832114, NCT03955445 NCT04817618 C3G Phase III adults Ext 12-18 years NCT05755386 IC-MPGN Phase III
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT03453619 Basket Phase II NCT04572854 C3G – IC-MPGN Phase II NCT05067127 C3G – IC-MPGN Phase III
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT03301467 (completed)
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, terminated/discontinued for BCX10013 once daily
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN

Antonucci et al,
Pediatr Nephrol 2024



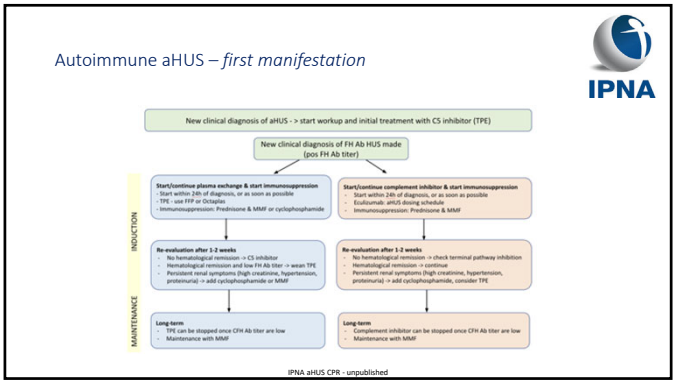
IgA nephropathy			
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	NCT03373461 NCT04557462 NCT04578834 Phase III
IONIS-FB-LRx	Factor B	Prevents formation of C3 and C5 convertases	NCT04014335 Phase II
ALXN2050 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05097989 Phase II, 126 adults, IgAN or LN, recruiting
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, terminated/discontinued for BCX10013 once daily
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02384317 Phase II, 5 pts, completed: Bruchfeld et al Clin Kidney Journal 2022
Ravulizumab i.v.	C5	Prevents formation of C5 convertase	NCT04564339 Phase III, 120 adults, IgAN and LN
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN NCT03608033 ARTEMIS Phase III, 450 adults RCT vs placebo

Antonucci et al, Pediatr Nephrol 2024



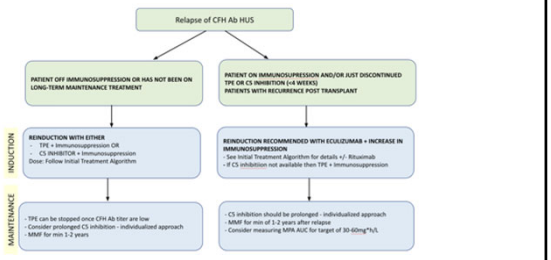
Idiopathic membranous nephropathy			
Iptacopan	Factor B	Prevents formation of C3 and C5 convertases	NCT04154787 Phase II, adults vs RTX
Pegcetacoplan s.c.	C3	Prevents formation of C3 and C5 convertases	NCT03453619 basket Phase II
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, NOT recruiting/discontinued for BCX10013 once daily
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN
Lupus nephritis			
Iptacopan	Factor B	Prevents formation of C3 and C5 convertases	NCT05268289 Phase II
Ravulizumab i.v.	C5	Prevents formation of C5 convertase	NCT04564339 Phase III, 120 adults, IgAN and LN
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN
ALXN2050	Factor D	Prevents formation of C3 and C5 convertases	NCT05097989 Phase II, 126 adults, IgAN or LN, recruiting
ANCA-associated vasculitis with renal involvement			
Avacopan	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02222155 Phase II NCT01363388 Phase II NCT02994927 (completed) Jayne DRW et al NEJM 2021
IFX-1 (vilobelimab) i.v.	C5a	Blocks anaphilatoxin formation	NCT03895801 Phase II, 57 adults with GPA or MPA NCT05721346 Phase II, 20 adults, terminated
Post-BMT thrombotic microangiopathy			
Pegcetacoplan s.c.	C3	Prevents formation of C3 and C5 convertases	NCT05148299 Phase II
Ravulizumab i.v.	C5	Prevents formation of C5 convertase	NCT04543591 (12 years-adults) NCT04557735 (28 days – 17 years)
Narsoplimab i.v.	MASP2	Blocks initiation of lectin pathway	NCT04247906 (expanded access, all ages)

Antonucci et al,
Pediatr Nephrol 2024



IPNA aHUS CPR - unpublished

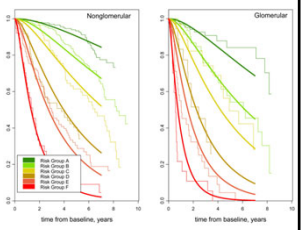
Autoimmune aHUS – *relapse*



IPNA aHUS CPR - unpublished

Introduction

- Marked heterogeneity in progression of CKD to kidney failure.



Endpoint: 50% reduction in eGFR, eGFR<15 or starting renal replacement therapy

Furth et al. (2018)

Introduction

- Marked heterogeneity in progression of CKD to kidney failure.
- Risk of progression is predicted by underlying diagnosis (glomerular/ non-glomerular), proteinuria, baseline eGFR
  - Easily applied to individual patients
- Renoprotective strategies delay the progression of CKD
  - Less complications of CKD
  - Later onset of renal replacement therapies

PROGNOSIS:

GROUP D - GLOMERULAR CAUSE

Percentile for Prognosis	Time to ESRD (years)
50th*	2.3 (95% CI: 1.7, 2.8)
25th	1.1 (95% CI: 0.8, 1.5)
10th	0.6 (95% CI: 0.4, 0.7)

https://jotform.com/form/81565256783164

Furth et al. (2018)

Contents

- Blood pressure control
  - Which patients
  - What targets
- Proteinuria control
  - RAAS blockade
  - SGLT2 inhibition
  - Novel agents
- Other modifiable risk factors

Question

John is an 8 year old boy with CKD secondary to hypoplastic dysplastic kidneys who is newly referred. His eGFR is 55ml/min/1.73m^2 and has no proteinuria. His office blood pressure is 108/71. His blood pressure centiles are as shown.

Centile	BP
50th	96/57
90th	108/70
95th	112/73

What is the most appropriate next course of action?

a) Review in 1 year
b) Review in 3 months, checking blood pressure at each visit
c) Perform 24h ambulatory blood pressure measurement
d) Start Amlodipine

Question

John is an 8 year old boy with CKD secondary to hypoplastic dysplastic kidneys who is newly referred. His eGFR is 55ml/min/1.73m^2 and has no proteinuria. His office blood pressure is 108/71. His blood pressure centiles are as shown.

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What is the most appropriate next course of action?

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d) Start Amlodipine

Blood pressure – Diagnosis

- Regular ambulatory blood pressure measurement (ABPM) is vital in the care of the CKD patient **regardless** of office blood pressure.

Routine performance of ABPM should be strongly considered in children and adolescents with high-risk conditions (see Table 12) to assess HTN severity and determine if abnormal circadian BP patterns are present, which may indicate increased risk for target organ damage.

American Academy of Paediatrics, 2017

In children with CKD or diabetes, regular ABPMs at 6–12-month intervals are recommended to rule out selective nocturnal HTN.

European Society for Hypertension, 2016

Practice Point 5.1: We suggest monitoring BP once a year with ABPM, and monitoring every 3–6 months with standardized auscultatory office BP in children with CKD.

KDIGO, 2021

Blood pressure – Diagnosis

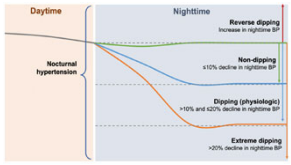
- High prevalence of masked hypertension in Paediatric CKD
  - **38%** masked hypertension in CKiD study
  - ~3x more than those with manifest HTN on office BP
- Non-dipping is a prominent feature of early hypertension
  - Nocturnal hypertension cannot be diagnosed on office BP.

Variable	SBP	DBP
BP status*		
normotension	106 (54)	108 (55)
white-coat hypertension	3 (1.5)	2 (1)
masked hypertension	66 (33)	67 (34)
confirmed hypertension	23 (12)	21 (11)
Wake BP		
mmHg (median [IQR])	116 (108 to 122)	70 (66 to 76)
≥95th percentile (n [%])	39 (17)	35 (15)
load (%; median [IQR])	13 (2 to 35)	8 (2 to 30)
load ≥25% (n [%])	81 (36)	69 (31)
Sleep BP		
mmHg (median [IQR])	102 (94 to 109)	59 (53 to 64)
≥95th percentile (n [%])	49 (22)	50 (22)
load (%; median [IQR])	14 (0 to 42)	16 (4 to 41)
load ≥25% (n [%])	86 (38)	95 (42)
Dipping		
% (mean [IQR])	11 (7 to 14)	17 (12 to 21)
abnormal (<10%)	88 (39)	36 (16)

Mitsfenes et al. (2010)

Blood pressure – Diagnosis

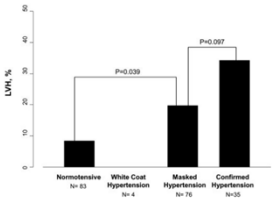
- High prevalence of masked hypertension in Paediatric CKD
  - **38%** masked hypertension in CKiD study
  - ~3x more than those with manifest HTN on office BP
- Non-dipping is a prominent feature of early hypertension
  - Nocturnal hypertension cannot be diagnosed on office BP.



Tang et al. (2023)

Blood pressure – Diagnosis

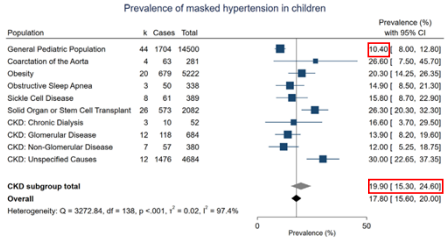
- High prevalence of masked hypertension in Paediatric CKD
  - **38%** masked hypertension in CKiD study
  - ~3x more than those with manifest HTN on office BP
- Non-dipping is a prominent feature of early hypertension
  - Nocturnal hypertension cannot be diagnosed on office BP.
- Masked hypertension produces at least as severe target organ damage as office-diagnosed hypertension.



Mitsfenes et al. (2010)

Blood pressure – Diagnosis

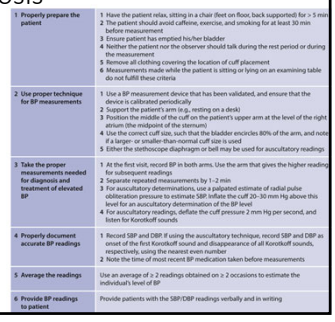
- Similar results in subsequent meta-analysis.
  - Prevalence ~20%
  - Risk ratio 2.44 (95% CI: 2.29-2.59) compared to general population.
- At higher risk…
  and
  … with more consequences



Chung et al. (2023)

Blood pressure – Diagnosis

- What if ABPM is not available?
- Standardised office BP may be an alternative
  - Protocolised
  - **Quiet room** without talking
  - **Preceding rest for at least 5 minutes**
  - No caffeine or exercise for 30min prior



KDIGO (2021)

Blood pressure – Diagnosis

- What if ABPM is not available?
- Standardised office BP may be an alternative
  - Protocolised
  - **Quiet room** without talking
  - **Preceding rest for at least 5 minutes**
  - No caffeine or exercise for 30min prior

Prediction of LVH (n=513)	Unadjusted OR[b] (95% CI)	Unadjusted *c* Statistic (95% CI)
Clinic systolic BP index measurements at a single visit	1.8 (1.4 to 2.4)	0.65 (0.56 to 0.73)
Mean of all clinic systolic BP indices at up to two visits	2.0 (1.5 to 2.8)	0.65 (0.58 to 0.73), Reference
Mean ABP wake systolic BP index	1.8 (1.3 to 2.4)	0.64 (0.57 to 0.71)
Mean ABP sleep systolic BP index	1.5 (1.2 to 2.0)	0.63 (0.56 to 0.71)
Prediction of ESKD (n=513)	**Unadjusted HR[b] (95% CI)**	**Unadjusted *c* Statistic (95% CI)**
Clinic systolic BP index at a single visit	1.5 (1.3 to 1.8)	0.61 (0.55 to 0.66)
Mean of all clinic systolic BP indices at up to two visits	1.5 (1.3 to 1.8)	0.61 (0.55 to 0.66), Reference[a]
Mean ABP wake systolic BP index	1.6 (1.3 to 2.0)	0.61 (0.56 to 0.67)
Mean ABP sleep systolic BP index	1.4 (1.2 to 1.7)	0.58 (0.52 to 0.64)

Ku et al. (2018)

Blood pressure – Diagnosis

- What if ABPM is not available?
- Standardised office BP may be an alternative
  - Protocolised
  - **Quiet room** without talking
  - **Preceding rest for at least 5 minutes**
  - No caffeine or exercise for 30min prior

Practice Point 5.1: We suggest monitoring BP once a year with ABPM, and monitoring every 3–6 months with standardized auscultatory office BP in children with CKD.

KDIGO, 2021

All centres may need to develop this local workflow regardless of ABPM availability.
→ Potential nurse-led quality improvement programme.

Question

John is a 8 year old boy with CKD secondary to hypoplastic dysplastic kidneys who is newly referred. His eGFR is 55ml/min/1.73m^2 and has no proteinuria. His office blood pressure is 108/71. His 24h ambulatory blood pressure is 117/75 with centiles as shown.

Centile	24h Ambulatory BP
50th	107/66
75th	112/70
90th	117/73
95th	120/75

Should we consider anti-hypertensive therapy?

a) Yes
b) No

Question

John is a 8 year old boy with CKD secondary to hypoplastic dysplastic kidneys who is newly referred. His eGFR is 55ml/min/1.73m^2 and has no proteinuria. His office blood pressure is 108/71. His 24h ambulatory blood pressure is 117/75 with centiles as shown.

Centile	24h Ambulatory BP
50th	107/66
75th	112/70
90th	117/73
95th	120/75

Should we consider anti-hypertensive therapy?

a) Yes
b) No

Blood pressure – Treatment aims

Recommendation 5.1: We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ABPM should be lowered to ≤50th percentile for age, sex, and height *(2C)*.

Key differences between the current and prior KDIGO recommendations in children with CKD include that the prior KDIGO guideline made a recommendation for the initiation of antihypertensive medication when the office SBP or DBP is consistently above the 90th percentile for age, sex, and height, whereas in the current guideline, all children with CKD and MAP consistently above the 50th percentile should be treated.

KDIGO, 2021

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

AAP, 2017

Blood pressure goal in hypertensive children (for office, home and 24-h ambulatory blood pressure measurements)

Children with CKD[c]	
Blood pressure goal	<75th percentile is recommended in children with nonproteinuric CKD <50th percentile is recommended in children with proteinuric CKD

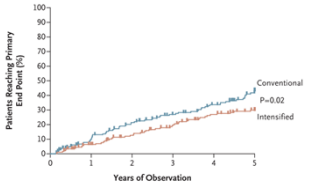
ESH, 2016

Blood pressure – Treatment aims

- In children with CKD and hypertension, controlling mean ambulatory blood pressure to <50th centile improves kidney survival (ESCAPE, 2009).
- Inclusion criteria
  - Children 3-18 years old with eGFR 15-80 ml/min/1.73m^2, AND
  - 24h mean ambulatory BP was elevated (>95th centile) or on anti-hypertensive medication
- Intervention
  - ALL were started on Ramipril to maximum dose (6mg/m^2), THEN
  - Randomly assigned to BP aim based on 24h mean ambulatory BP
    - Conventional: 50-90th centile
    - Intensified: <50th centile

Blood pressure – Treatment aims

- Hazard ratio= 0.65 (95% CI: 0.44-0.94)
- Difference of 12%

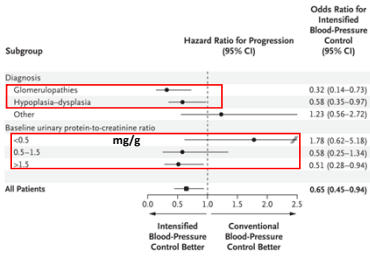


Endpoint: 50% reduction in eGFR, progression to eGFR<10, or start of renal replacement therapy

ESCAPE (2009)

Blood pressure – Treatment aims

- Hazard ratio= 0.65 (95% CI: 0.44-0.94)
- Difference of 12%
- Bigger effect in those with glomerulopathy vs hypoplasia-dysplasia (p=0.009)
- Trend towards bigger effect in those with proteinuria (p=0.06)



ESCAPE (2009)

Blood pressure – Treatment aims

- Intervention
  - ALL were started on Ramipril to maximum dose (6mg/m^2), THEN
  - Randomly assigned to BP aim based on 24h mean ambulatory BP
    - Conventional: 50-90th centile
    - Intensified: <50th centile

On Ramipril alone, >50% of patients already had 24h mean ambulatory BP <50th centile

The randomised intervention was on a cohort that was at that point mainly non-hypertensive.
E.g. In our case, a child with CKD and with 24h MAP 50th – 95th centile.

Blood pressure – Treatment aims

- Intervention
  - ALL were started on Ramipril to maximum dose (6mg/m^2), THEN
  - Randomly assigned to BP aim based on 24h mean ambulatory BP
    - Conventional: 50-90th centile
    - Intensified: <50th centile

On Ramipril alone, >50% of patients already had 24h mean ambulatory BP <50th centile

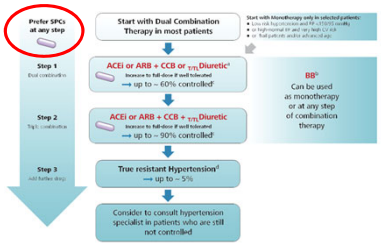
Conventional: 0.5 ± 0.9 additional pills
Intensified: 0.9 ± 1.1 additional pills

Strict Blood-Pressure Control and Progression of Renal Failure in Children

STRICT blood pressure control does not require Superhuman efforts.

Blood pressure – Treatment aims

- Fixed dose combinations (Single pill combinations)
  - Recommended as first line therapy in adults due to *greater efficacy*
  - Very limited Paediatric data
  - BUT may at least **improve compliance** when on combination therapy (especially when on stable doses)

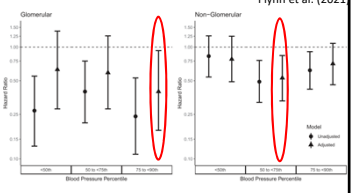


ESH (2023)

Blood pressure – Treatment aims

Flynn et al. (2021)

- 24h ABPM aims are not easily translatable to office BP (even protocolized).
  - CKID study: Risk of progression lowest for 50-75th for non-glomerular but wide confidence intervals means difficult to compare between group.
- KDIGO recommendations are reasonable for in-office titration → ABPM to confirm control.



Practice Point 3.4.3: In children with CKD, when ABPM is not available, it is reasonable to target manual auscultatory office SBP, obtained in a protocol-driven standardized setting, of 50th–75th percentile for age, sex, and height unless achieving this target is limited by signs or symptoms of hypotension.

KIDGO (2024)

Question

Karen is a 16 year old girl with CKD secondary to genetic FSGS. She has nephrotic range proteinuria of 300mg/mmol (3000 mg/g) and her BP is at the 50th centile. Her eGFR is 60ml/min/1.73m^2.

What is the most appropriate next step?

a) Start Amlodipine
b) Start Carvedilol
c) Start Dapagliflozin
d) Start Ramipril
e) Start Spironolactone

Question

Karen is a 16 year old girl with CKD secondary to genetic FSGS. She has nephrotic range proteinuria of 300mg/mmol (3000 mg/g) and her BP is at the 50th centile. Her eGFR is 60ml/min/1.73m^2.

What is the most appropriate next step?

a) Start Amlodipine
b) Start Carvedilol
c) Start Dapagliflozin
d) Start Ramipril
e) Start Spironolactone

Proteinuria – RAASi

- ACEi/ARBs are the recommended therapy for proteinuric (microalbuminuric) CKD even in children.

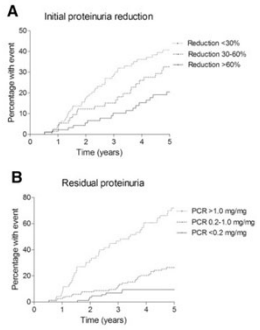
Recommendation 3.6.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with CKD and severely increased albuminuria (G1–G4, A3) without diabetes *(1B)*.

Recommendation 3.6.2: We suggest starting RASi (ACEi or ARB) for people with CKD and moderately increased albuminuria (G1–G4, A2) without diabetes *(2C)*.

KIDGO (2024)

Proteinuria – RAASi

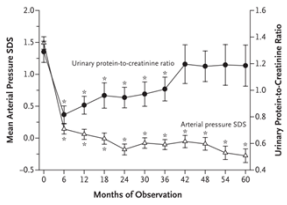
- ACEi/ARBs are the recommended therapy for proteinuric (microalbuminuric) CKD even in children.
- ESCAPE study: Reduction in proteinuria following Ramipril predicted prognosis.



Van den Belt (2018)

Proteinuria – RAASi

- ACEi/ARBs are the recommended therapy for proteinuric (microalbuminuric) CKD even in children.
- ESCAPE study: Reduction in proteinuria following Ramipril predicted prognosis.
- But what if there is residual proteinuria or if, as in ESCAPE, proteinuria returns?



ESCAPE (2009)

Proteinuria – RAASi

- "Aldosterone escape"
  - Compensatory upregulation of aldosterone or other vasoactive mediators
  - **Should lead to salt and water retention**
- Best evidence is in adults with T2DM, where **finerenone** reduced admission for heart failure and reduced the risk of eGFR decline.
- Is this a direct effect or due to improved cardio-renal axis?

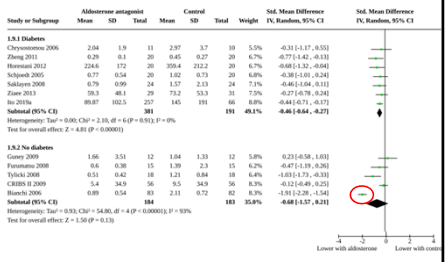
Recommendation 3.8.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.

Practice Point 3.8.5: A steroidal MRA may be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among people with a low GFR.

KIDGO (2024)

Proteinuria – RAASi

- But in the non-DM CKD population
  - Significant **heterogeneity** in terms of proteinuria reduction
  - In exchange for risk of hyperkalaemia and AKI (no heterogeneity)
  - No evidence showing improvement in long-term outcomes
- Paediatric trials awaited



Chung et al., Cochrane (2020)

Proteinuria – RAASi

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  - Significant **heterogeneity** in terms of proteinuria reduction
  - In exchange for risk of hyperkalaemia and AKI (no heterogeneity)
  - No evidence showing improvement in long-term outcomes
- Paediatric trials awaited

Investigating the use of finerenone in children with chronic kidney disease and proteinuria: design of the FIONA and open-label extension studies

Franz Schaefer[1*], Giovanni Montini[2,3], Hee Gyung Kang[4], Johan Vande Walle[5], Joshua Zaritsky[6], Michiel F. Schreuder[7], Mieczyslaw Litwin[8], Andrea Scalise[9], Helen Scott[10], James Potts[10], Pablo Ivelli[11], Stefanie Breitenstein[11] and Bradley A. Warady[12,13]

Schaefer et al. (2024)

Question

- Karen is a 16 year old girl with CKD secondary to genetic FSGS. She has nephrotic range proteinuria of 300mg/mmol (3000 mg/g) and her BP is at the 50th centile. Her eGFR is 60ml/min/1.73m^2. You have started her on Ramipril 10mg, but her proteinuria remains at 200mg/mmol (2000mg/g).
  Her elder brother with the same condition has been put on SGLT2 inhibitors by his adult nephrologist, and her mother asks if you can do the same.

Question

- Which of the following is false?
  a) The renoprotective effect of SGLT2 inhibitors in adults with diabetic CKD depends on the level of proteinuria.
  b) The renoprotective effect of SGLT2 inhibitors in adults with non-diabetic CKD depends on the level of proteinuria.
  c) SGLT2 inhibitors are licensed in children for diabetes.
  d) SGLT2 inhibitors are licensed in children for CKD.

Question

- Which of the following is false?
  a) The renoprotective effect of SGLT2 inhibitors in adults with diabetic CKD depends on the level of proteinuria.
  b) The renoprotective effect of SGLT2 inhibitors in adults with non-diabetic CKD depends on the level of proteinuria.
  c) SGLT2 inhibitors are licensed in children for diabetes.
  d) SGLT2 inhibitors are licensed in children for CKD.

Proteinuria – SGLT2 inhibition

We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:
- **eGFR ≥20 ml/min per 1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.

KDIGO (2024)

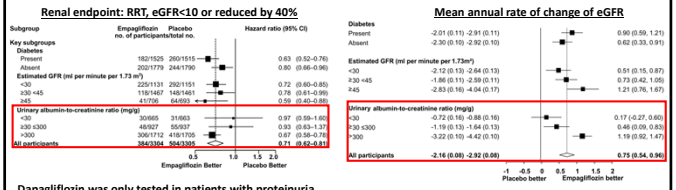
SGLT2 inhibitors: approved for adults and cats but not for children with CKD

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

- A magic bullet in adult CKD, but no evidence in children (non-diabetic CKD).
- Patient selection to minimize the risk-benefit ratio is a prudent approach.

Proteinuria – SGLT2 inhibition

- In adult CKD, biggest renoprotective benefits were seen in proteinuric CKD.



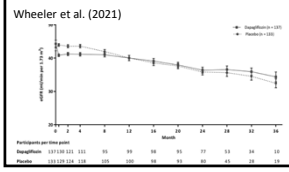
Dapagliflozin was only tested in patients with proteinuria, i.e. UACR 200-5000 mg/g.

EMPA-Kidney Collaborative Group (2023)

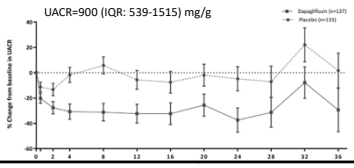
Proteinuria – SGLT2 inhibition

- In adult CKD, biggest renoprotective benefits were seen in proteinuric CKD.
- This partly because like ACEi/ARB, SGLT2 inhibition reduces intraglomerular pressure and thus reduces proteinuria, e.g. IgA subgroup in DAPA-CKD (270/1398 non-DM participants).

Wheeler et al. (2021)

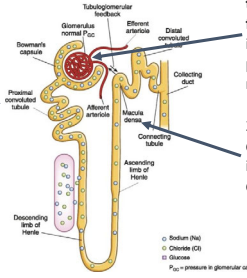


UACR=900 (IQR: 539-1515) mg/g



Proteinuria – SGLT2 inhibition

1) **Decreased** Na re-absorption in PCT



3) **Increased tubuloglomerular feedback** reducing intraglomerular pressure and single nephron GFR

2) **Increased** Na delivery distally including macula densa

Renalfellow.org

Proteinuria – SGLT2 inhibition

- Early data suggest that these anti-proteinuric benefits are also present in the pediatric population for heavy proteinuria.
- Pilot study
  - Children with genetic glomerulopathy on ACEi with residual proteinuria
  - Dapagliflozin 5mg (≤30kg) or 10mg (>30kg)

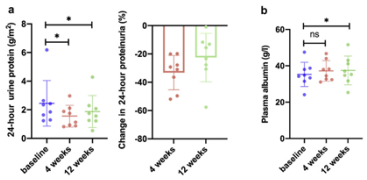
No.	Sex	Clinical characteristics: Age (yr)	BW (kg)	Diagnosis	Genetic diagnosis	24-h proteinuria (g/m^2)
1	F	11.2	47.5	Proteinuria	*PAX2*	2.35
2	F	13.8	43.7	Proteinuria	*NUP160*	2.63
3	M	9.8	33.6	Dent disease	*CLCN5*	1.64
4[c]	M	11.9	42.2	Alport syndrome	*COL4A5*	6.21
5	M	8.1	24	Alport syndrome	*COL4A5*	2.42
6	F	14.2	43.4	Alport syndrome	*COL4A3*	1.84
7	M	6.4	24.2	Alport syndrome	*COL4A5*	1.23
8	M	8.4	28.2	Alport syndrome	*COL4A5*	6.18
9[c]	F	9.4	27	FSGS	Negative	1.28

Average proteinuria: 2.86g/m2/day= **4.94**g/1.73m2/d

Liu et al. (2022)

Proteinuria – SGLT2 inhibition

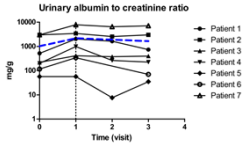
- Early data suggest that these anti-proteinuric benefits are also present in the pediatric population for heavy proteinuria.
- Pilot study
  - Children with genetic glomerulopathy on ACEi with residual proteinuria
  - Dapagliflozin 5mg (≤30kg) or 10mg (>30kg)



Reduction in proteinuria 33.3% (95% CI: 23%-43%) at 4 weeks and 22.6% (95% CI: 8%-37%) at 12 weeks.

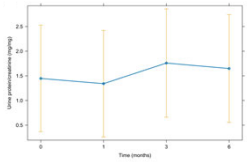
Liu et al. (2022)

Proteinuria – SGLT2 inhibition



UACR: 1213 → 972 mg/g (p=0.068)
Dapagliflozin 5-10mg

Van Reeth et al. (2024)



UPCR: **600**mg/g → 700 mg/g (p=0.4)
Dapagliflozin 5-10mg

Choi et al. (2024)

Proteinuria – SGLT2 inhibition

- Safety: Recent large trials in pediatric T2D.

Clinical Trial · Lancet Diabetes Endocrinol. 2022 May;10(5):341-350.
doi: 10.1016/S2213-8587(22)00052-3. Epub 2022 Apr 1.

Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study

William V Tamborlane [1], Lori M Laffel [2], Naim Shehadeh [3], Elvira Isganaitis [2], Michelle Van Name [4], Jayantha Ratnayake [5], Cecilia Karlsson [6], Ensio Norjavaara [6]

Age: 10-24 years

News | Article | June 13, 2024

FDA Approves Dapagliflozin for Children With Type 2 Diabetes

Author(s): Hayden E. Klein

Clinical Trial · Lancet Diabetes Endocrinol. 2023 Mar;11(3):169-181.
doi: 10.1016/S2213-8587(22)00387-4. Epub 2023 Feb 1.

Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial

Lori M Laffel [1], Thomas Danne [2], Georgeanna J Klingensmith [3], William V Tamborlane [4], Steven Willi [5], Philip Zeitler [6], Dietmar Neubacher [7], Jan Marquard [8], DINAMO Study Group

Age: 10-17 years

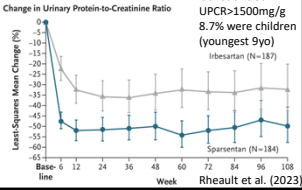
US FDA approves Jardiance® (empagliflozin) for the treatment of type 2 diabetes in children 10 years and older

RIDGEFIELD, Conn. and INDIANAPOLIS, Wed, 06/21/2023 - 13:15

Proteinuria – SGLT2 inhibition

- Can consider off-label use with appropriate counselling in
  - Children ≥ 10 years old
  - Severe nephrotic range proteinuria
  - Consider enrolling in a clinical trial
- Watch this space
  - Sparsentan
  - Novel ARB + Endothelin-1 antagonist
  - Already licensed for adult IgA nephropathy

FILSPARI® (sparsentan) tablets 200 mg/400 mg



Genetic FSGS
UPCR>1500mg/g
8.7% were children (youngest 9yo)

Rheault et al. (2023)

Question

John (CKD secondary to hypoplastic dysplastic kidneys) is now 13 years old and his eGFR has fallen to 25ml/min/1.73m^2. He does not want any more medication for renoprotection.

Treating which of the following CKD complications may also slow the rate of CKD progression?

a) Acidosis
b) Anaemia
c) Hyperphosphataemia
d) Vitamin D deficiency
e) None

Question

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Treating which of the following CKD complications may also slow the rate of CKD progression?

a) Acidosis
b) Anaemia
c) Hyperphosphataemia
d) Vitamin D deficiency
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Pleiotropic effects

- Many many associations
  Which is causative?
- But this is not why we treat CKD complications …

Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort Anaemia, dyslipidaemia

Low Serum Bicarbonate and CKD Progression in Children

Denver D. Brown [1], Jennifer Roem [2], Derek K. Ng [3], Kimberly J. Reidy [4], Juhi Kumar [4], Matthew K. Abramowitz [5], Robert H. Mak [6], Susan L. Furth [7], George J. Schwartz [8], Bradley A. Warady [9], Frederick J. Kaskel [3], and Michal L. Melamed [3]

Fibroblast Growth Factor 23 and Risk of CKD Progression in Children

Anthony A. Portale [1], Myles S. Wolf [2], Shari Messinger [3], Farzana Perwad [4], Harald Jüppner [5], Bradley A. Warady [3], Susan L. Furth [3], and Isidro B. Salusky [4]

Normal 25-Hydroxyvitamin D Levels Are Associated with Less Proteinuria and Attenuate Renal Failure Progression in Children with CKD

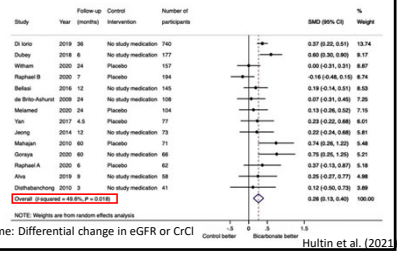
Rukshana Shroff [1], Helen Aitkenhead [2], Nikola Costa [3], Antonella Trivelli [3], Mieczyslaw Litwin [4], Stefano Picca [5], Ali Anarat [3], Peter Sallay [6], Fatih Ozaltin [7], Aleksandra Zurowska [7], Augustina Jankauskiene [8], Giovanni Montini [9], Marina Charbit [9], Franz Schaefer [9], and Elke Wühl [9] for the ESCAPE Trial Group

Pleiotropic effects

- Overall benefit
  - But statistically significant heterogeneity
  - Due to trial quality or presence of placebo
- Restriction to placebo-controlled trials: NS

Practice Point 3.10.1: In people with CKD, consider use of pharmacological treatment with or without dietary intervention to prevent development of acidosis with potential clinical implications (e.g., serum bicarbonate <18 mmol/l in adults).

KDIGO (2024)



Outcome: Differential change in eGFR or CrCl

Hultin et al. (2021)

Conclusions

1. All CKD patients should undergo ABPM at least annually.
   - Use standardized office blood pressure measurement every 3-6 months.
2. Hypertensive patients should be treated till ambulatory mean arterial pressure is ≤ 50th centile.
   - Titrate control to 50-75th centile using standardized office BP measurements.
   - Fixed combination pills may promote compliance in adolescents needing a 2nd agent.
3. Strongly consider treating even non-hypertensive patients if their ambulatory mean arterial pressure is >50th centile.

Conclusions

4. RAAS inhibition using ACEi/ARBs must be initiated in proteinuric patients.
   - The overall benefits of adding on mineralocorticoid receptor antagonists, especially readily available spironolactone, is uncertain.
5. Consider SGLT2 inhibition only in children ≥10 years old, with high nephrotic proteinuria at high risk of progression
   - Such use is off-label and requires shared decision making with the family.
6. Correcting metabolic acidosis may confer additional renoprotective benefits.
7. Do not forget preventative advice: AVOID AKI
   - Early IV hydration during intercurrent illness
   - Counsel on nephrotoxin exposure (over the counter medication, **while in-hospital,** traditional medications)

Thank you.

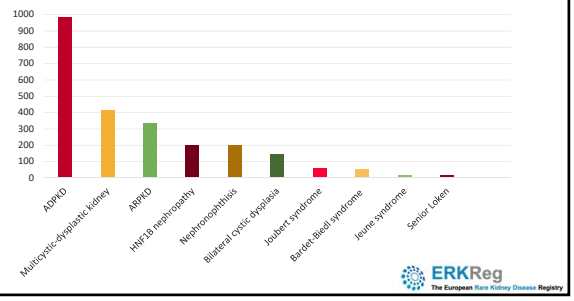
Questions?

Cystic Kidney Diseases: Diagnosis, Management and Outcomes

Franz Schaefer

Division of Pediatric Nephrology
Center for Pediatrics and Adolescent Medicine
University of Heidelberg, Germany

Cystic Kidney Diseases in Children



Case 1

You are called by a gynecologist in your hospital who has identified kidney cysts in a 20-week fetus at routine prenatal screening.

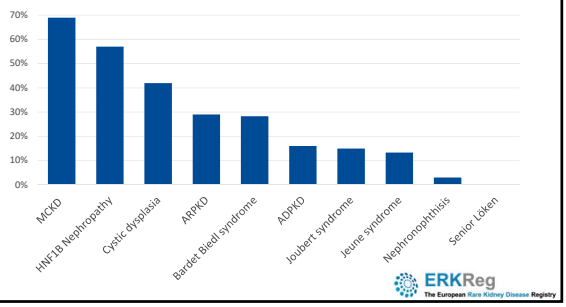
The mother-to-be is a healthy 25-year-old woman in her first pregnancy. There is no history of kidney disease in her or her husband's family.

Ultrasound shows multiple small cysts in both kidneys without any other fetal anomalies.

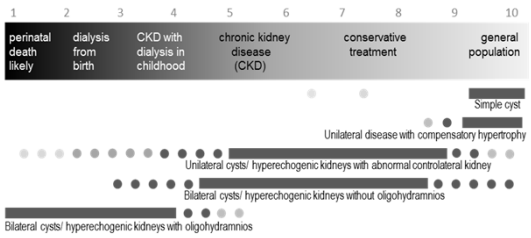
-> What are the most likely differential diagnoses?

-> What is the prognosis for this child?

Prenatally Diagnosed Cases per Disease



Counseling Regarding Prognostic Spectrum



Morphological Classification of Cystic Kidney Disorders


Single cyst with normal parenchyma


Unilateral multiple cysts or hyperechogenicity


Bilateral multiple cysts or hyperechogenicity

Single Cyst

Likely diagnosis: **Single cortical cyst**

Differential diagnoses:
- Duplex urinary tract with dilated pelvis, segmental multicystic dysplasia
- Extrarenal cyst (e.g. adrenal)
- Cystic tumor
- Initial lesion of polycystic kidney disease

Prenatal prognosis: very good (90% resolve, 4% other diagnosis)

Imaging: Prenatally: US follow-up after 4-6 weeks
Postnatally: US within first 4 weeks

Genetics: not required (neither pre- nor postnatally)

Unilateral Cysts / Hyperechogenicity

Likely diagnosis: **Multicystic dysplastic kidney**

Differential diagnosis:
Cystic dysplasia (± obstruction)
Unilateral origin of bilateral cystic nephropathy

Prognosis: mixed - 13 % mortality (from extrarenal anomalies)

Imaging: Screen contralateral kidney & other organs
Prenatally: US after 4 weeks, then guided by findings
MRI if MCDK is ectopic (exclude teratoma)
Postnatally: US on day 3-7

Genetic testing: only in case of extrarenal manifestaions

Bilateral Cysts/Hyperechogenicity

Likely diagnosis: **Bilateral cystic dysplasia (30% HNF1B nephropathy)**

Likely diagnosis: **ARPKD**

Differential diagnoses:
ADPKD
Bardet-Biedl, Meckel-Gruber, other syndromic diseases
Infantile nephronophthisis
Chromosomal aberrations
LUTO
Tubular dysgenesis
Inborn errors of metabolism
Prenatal drug exposure (ACEi/ARB)

Bilateral Cysts/Hyperechogenicity

Prognosis


TOP frequent
CKD in 70%

Prenatal mortality: 9%
CKD in 34 %
Spontaneous improvement in 31%

TOP very frequent
CKD in 100%

TOP very frequent
CKD in 86%

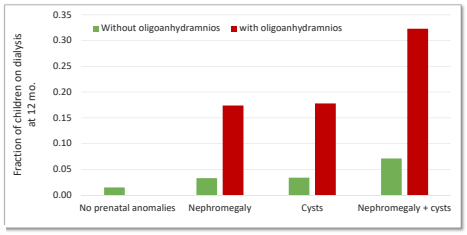
Prenatal Risk Classification

Oligohydramnios: important prognostic marker

Prenatal kidney function tests -> postnatal kidney function
- Fetal urine markers: low evidence, only in LUTO
- Serum: β2-microglobulin - glomerular marker with insufficient predictive power
  Risk of cordocentesis

Prenatal lung evaluation -> postnatal lung function
- 2D/3D lung volume not superior to oligohydramnios state

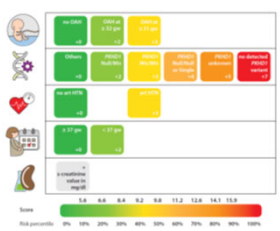
Prenatal Findings Predict Dialysis Risk at Age 1 Year in Children with ARPKD

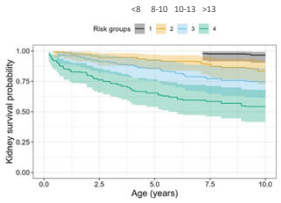


ARegPKD

Burgmaier et al., *J Peds 2019*

Risk Prediction Score for Infants with ARPKD





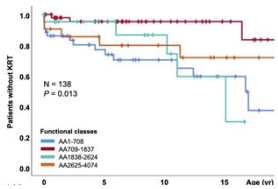
ARegPKD

Burgmaier et al. KI in revision

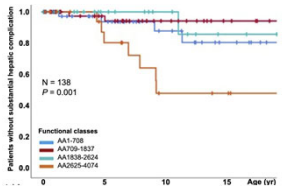
Genotype Associates with Organ-Specific Outcomes in Children with ARPKD

ARegPKD

Time without KRT



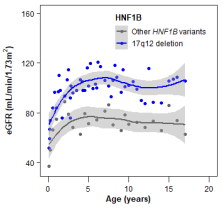
Time without substantial hepatic complication



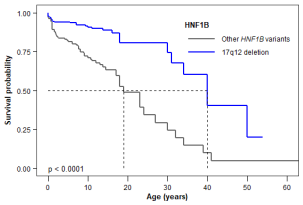
Burgmaier et al. Kidney Int 2021

eGFR Course in HNF1B Nephropathy

GFR evolution in childhood



Progression to CKD stage 3



ERKNet The European Rare Kidney Disease Reference Network

Buffin-Meyer et al. KI Reports 2024

Prenatal Therapies

Glucocorticoids for lung maturation clearly indicated until 34th gestational week
Thereafter: 1 treatment cycle „reasonable“

Repeated amnio-infusions for renal anhydramnios:

- Small case series suggest positive effect on pulmonary development
- Risk of iatrogenic amnionic infection / membrane rupture / hemorrhage

Postnatal Management of Cystic Kidney Diseases

Perform imaging, consider genetic testing

- If compensatory hypertrophy present: kidney function exams not necessarily indicated
- Occasional clinical checkup recommended

+ Oligohydramnion

- Check urine output
- Check kidney function
- Involve pediatric nephrologist if kidney function compromised

Dialysis in Neonates

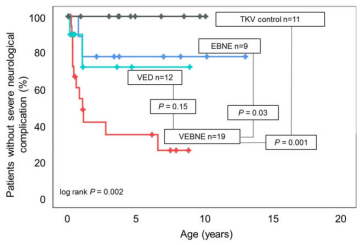
Recommendation 4.5 (strength: level 2, evidence: level B):

Renal replacement therapy should be offered to neonates with life-threatening kidney failure due to cystic renal disease.

Depending on individual circumstances, it can be appropriate to opt against renal replacement therapy and to pursue a palliative care plan.

- Neonatal dialysis well established therapy with comparable mortality as in older infants and children
- Neonatal age per se does not justify withholding therapy
- Comorbidities (and underlying disease) should be considered
- Joint decision-making with parents

Increased Risk of Neurological Complications After Bilateral Nephrectomy in First 3 Months of Life



Severe neurological complications:
- CNS ischemia, infarction, hypoxic encephalopathy
- Optical nerve atrophy with loss of vision

Burgmaier et al. Sci Rep 2020

Case 2

A young mother of two infants who herself is affected by ADPKD (but asymptomatic) asks her pediatrician to explore whether she has transmitted the disease to the children.
Her father just became dialysis dependent at age 58.

➔ Should the pediatrician serve this request?

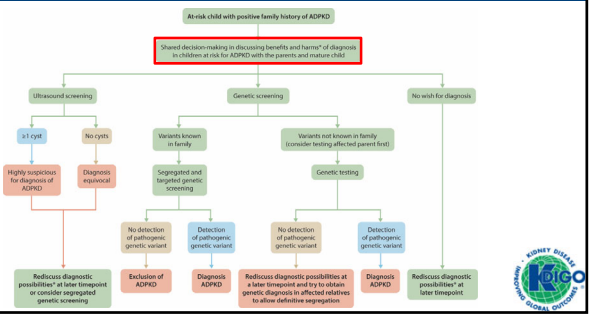
➔ How can this be done?

Radiological Diagnosis of ADPKD

- In a fetus or neonate with a positive family history, **hyperechogenic and/or enlarged kidneys** (>2 SD) on ultrasound are suggestive of ADPKD.
- In a child under 15 years with a **positive family history**, sonographic detection of **one or more kidney cysts** is highly suggestive of ADPKD.
- Normal ultrasound in an at-risk child does not exclude ADPKD. However, it is not necessary to **rescreen** at intervals shorter than **3 years**.

Neocyst Consensus Statement, Nat Rev Nephrol 2019

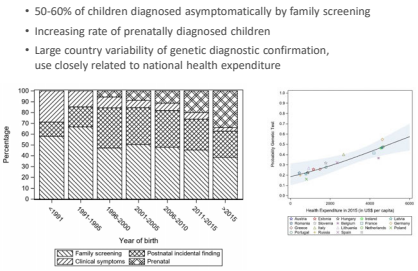
Diagnosis of Children at Risk of ADPKD

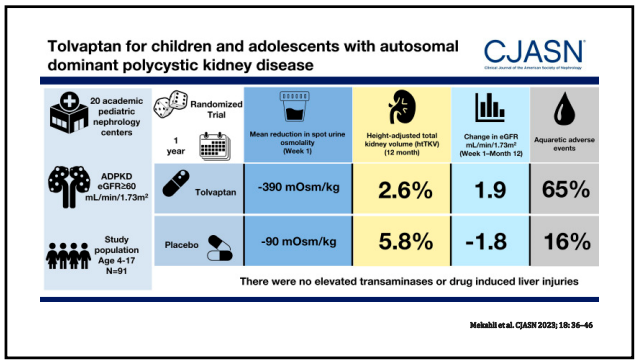


ADPKD in Children: Diagnostic Practice Patterns

2,154 children from ADPedKD, ERKReg, RaDaR registries

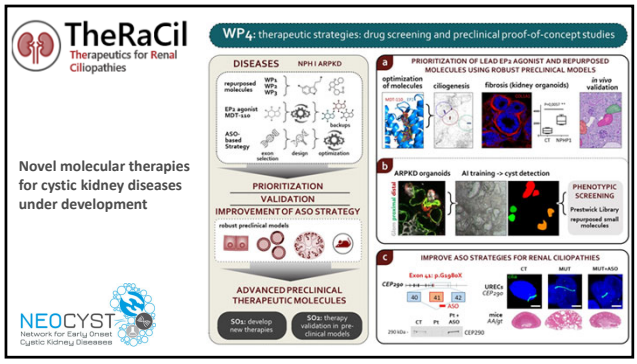
- 50-60% of children diagnosed asymptomatically by family screening
- Increasing rate of prenatally diagnosed children
- Large country variability of genetic diagnostic confirmation, use closely related to national health expenditure





Adverse Effects of Aquaretic Treatment

	Tolvaptan	Placebo
24h urine volume (n=12/8)	7.2 ± 2.8 L	2.5 ± 2.1 L
Nocturia	7/48 (15%)	3/43 (6%)
Pollakiuria	9/48 (19%)	0/43 (0%)
Polydipsia	5/48 (10%)	1/43 (2%)
Polyuria	13/48 (27%)	2/43 (4%)
Orthostatic hypotension	5/48 (10%)	0/43 (0%)
Serum sodium increase	2/48 (4%)	0/43 (0%)
Serum creatinine increase	9/48 (19%)	2/43 (4%)
Any aquaretic treatment emergent AEs	**31/48 (65%)**	**7/43 (16%)**
Any deydration-related AEs	**17/48 (35%)**	**6/43 (14%)**



Question 1

Which is the most common cystic kidney disease in children?

A. ARPKD
B. ADPKD
C. HNF1B nephropathy
D. Multicystic kidney dysplasia
E. Nephronophthisis

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Question 2

Which is the most common etiology of bilateral fetal kidney cysts?

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Question 3

Which of the following statements is correct?

A. Postnatal kidney function can be reliably predicted from serum B2M in chord blood
B. Oligoanhydramnios and fetal nephromegaly reliably predict ESKD within the 1st year of life
C. Most patients with HNF1B nephropathy will remain in CKD stage 3 throughout childhood
D. Whole HNF1B gene deletions are associated with earlier kidney disease progression than point mutations
E. Bilateral nephrectomy for ‚malignant' ARPKD in the first three months of life increases the risk of neurological complications

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Question 4

Which of the following findings is sufficient to make the diagnosis of ADPKD?

A. Hyperechogenic kidneys in a fetus with a family history of ADPKD.
B. A single kidney cyst in a child under 15 years of age with a family history of ADPKD
C. A 30% decrease of urine osmolality in response to Tolvaptan
D. A and B are correct.
E. B and C are correct.

Question 4

Which of the following findings is sufficient to make the diagnosis of ADPKD?

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D. A and B are correct.
E. B and C are correct.

Question 5

Which statement is correct?

A. Isolated cortical cysts are always indicative of ADPKD
B. Normal ultrasound findings rule out ADPKD in adolescents
C. At least 50% of children with ADPKD are diagnosed electively in the asymptomatic stage
D. A prenatal diagnosis of ADPKD justifies termination of pregnancy
E. Tolvaptan does not decrease urine osmolality in children younger than 12 years

Question 5

Which statement is correct?

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D. A prenatal diagnosis of ADPKD justifies termination of pregnancy

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Pediatric Peritonitis Guideline Update

Franz Schaefer

University of Heidelberg, Germany

ISPD GUIDELINES/RECOMMENDATIONS

CONSENSUS GUIDELINES FOR THE PREVENTION AND TREATMENT OF CATHETER-RELATED INFECTIONS AND PERITONITIS IN PEDIATRIC PATIENTS RECEIVING PERITONEAL DIALYSIS: 2012 UPDATE

Bradley A. Warady,[1] Sevcan Bakkaloglu,[2] Jason Newland,[1] Michelle Cantwell,[3] Enrico Verrina,[4] Alicia Neu,[5] Vimal Chadha,[1] Hui-Kim Yap,[6] and Franz Schaefer[7]

Department of Pediatric Nephrology,[1] Children's Mercy Hospitals and Clinics, Kansas City, Missouri, USA; Gazi University,[2] Ankara, Turkey; Great Ormond Street Hospital,[3] London, England; G. Gaslini Children's Hospital,[4] Genoa, Italy; Johns Hopkins University School of Medicine,[5] Baltimore, Maryland, USA; Department of Pediatrics,[6] National University of Singapore, Singapore; and University Children's Hospital,[7] Heidelberg, Germany

ISPD Pediatric Peritonitis Guideline Initiative

Clinical experts:

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Alicia Neu	USA
Vimal Chadha	USA
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Peter Nourse	South Africa
Hui Kim Yap	Singapore
Sevcan Bakkaloglu	Turkey
Enrico Verrina	Italy
Dagmara Borzych	Poland
Franz Schaefer	Germany

Nurse expert:
Brandy Begin

Infectious disease experts:
Rebecca Same
Jason Newland

Pharmacology experts:
Annie Wirtz
Valerie Smith

Evidence review team:
Reem Mustafa
Ibrahim El Mikati

ISPD Clinical Practice Recommendation: Prevention and Management of Peritonitis and Catheter Related Infections in Children

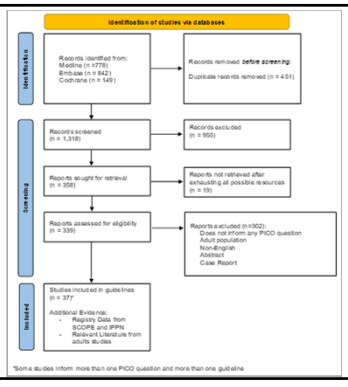
1. Training
2. Catheter Type and Placement
3. Early Exit Site Care
4. Chronic Exit Site Care
5. Connectology
6. Ostomy patients
7. Adjunctive Prophylactic Antibiotic Therapy
8. Diagnosis of PD-Related Peritonitis
9. Empiric Antibiotic Therapy
10. Subsequent Antibiotic Therapy
11. Modification for Gram-Positive Peritonitis
12. Modification of Therapy for Gram-Negative Peritonitis
13. Modification of Therapy for Culture-Negative Peritonitis
14. Modification of Therapy for Fungal Peritonitis
15. Mycobacterial Peritonitis
16. Relapsing, Recurrent and Repeat Peritonitis
17. Adjunctive Therapy
18. Catheter Removal and Replacement
19. Diagnosis of Catheter-Related Infection
20. Treatment of Catheter-Related Infection
21. Evaluation of Primary Response
22. Monitoring of Infection Rates and Risk Factor Assessment

PICO Questions

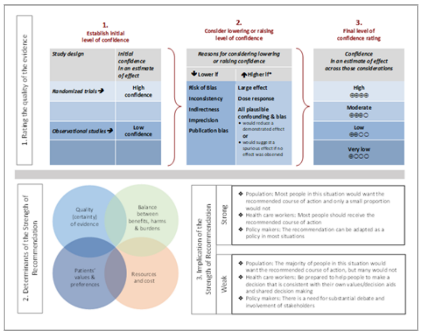
54 PICO (population-intervention-comparator-outcomes) questions, covering all aspects of PD associated infections in children

1	Duration of training longer vs shorter
2	Home visits vs no home visits
3	Retraining frequency vs another
4	Formal vs informal training assessment
5	Repeat competency testing vs. none
6	Use of adult learning principles vs none
7	Tenchknoff characteristic vs another characteristic
8	Laparoscopic vs open catheter placement
9	Prophylaxis Antibiotic therapy vs none
10	Topical antimicrobial agent at exit site vs none
11	Once weekly dressing change vs more
12	Daily exit site care vs 3 times a week
13	Topical antibiotic prophylaxis vs not
14	Flush before fill design vs. Traditional spike system
15	Gastrostomy Before/After PD
16	Open vs laparoscopic gastrostomy
17	Using prophylactic antibiotics and antifungals for gastrostomy placement
18	Adjunctive antifungal with antibiotics
19	Prophylactic antibiotic for invasive procedures (dental or GI/GU)
20	MRSA suspected, vanco+cefepime vs cefepime alone
21	Aminoglycoside vs cefepime or ceftazidime
22	Two vs three weeks duration of treatment
23	For gram positive infection, adding rifampin vs not
24	For gram positive infection, antibiotic X vs Y
25	For MRSA, antibiotic X vs Y
26	If infection susceptible to cefazolin, using cefazolin vs other beta lactam ab
27	For pseudomonas, single agent vs two
28	For gram negative infection, cefazolin vs cefepime or ceftazidime
29	Negative culture, two weeks treatment vs less
30	Negative culture, discontinue glycopeptide vs not
31	Fungal peritonitis, catheter removal vs treatment and removal
32	Fungal peritonitis, amphotericin B vs fluconazole or echinocandins
33	Fungal peritonitis, catheter removal time X vs Y
34	Fungal peritonitis, catheter replacement time X vs Y
35	With relapsing peritonitis, catheter removal time X vs Y
36	With relapsing peritonitis, standard treatment vs based on previous peritonitis
37	With relapsing peritonitis, catheter removal vs conservative treatment alone
38	With relapsing peritonitis, immediate vs delayed catheter replacement after removal
39	With relapsing peritonitis, fibrinolytic agent vs none
40	With relapsing peritonitis, urokinase vs rTPA/Taurolodine
41	With relapsing peritonitis, same or longer duration of treatment as initial episode
42	PD + hypogammaglobulinemia, using IVIG vs not
43	Exit site with granulation, silver nitrate vs not
44	Exit site with granulation, topical antibiotic vs not
45	With refractory exit-site or tunnel infection, catheter removal and replacement vs antibiotics
46	With refractory exit-site or tunnel infection with staph or pseudomonas, catheter removal vs ab
47	With refractory peritonitis, catheter removal vs not
48	With surgical peritonitis, catheter removal vs not
49	With mycobacterial peritonitis, catheter removal vs not
50	Diagnosis of infection with presence of purulent discharge alone vs objective scoring
51	Diagnosis of infection with clinical assessment and ultrasound vs clinical assessment alone
52	With intractable CRTI, cuff shaving vs catheter removal
53	With uncomplicated exit site infection, empiric therapy vs not
54	With APD +PD, short vs prolonged dwell time

Literature Search



Evidence Rating: Grade Methodology



Bias Assessment

Author, Year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Alhameedi, 2006	Serious	Serious	Low	Low	Low	Low	Serious
Auron, 2006	Critical	Low	Low	Low	Low	Low	Low
Chan, 2019	Serious	Low	Critical	Low	Critical	Low	Low
Furth, 2000	Low	Low	Low	Low	Low	Low	Low
Garcia-Lopez, 1994	Critical	Low	Serious	Serious	Low	Low	Low
Hoshii, 2006	Low	Low	Low	Low	Low	Low	Low
Jones, 1995	Critical	Critical	Critical	Critical	Serious	Low	Low
Lane, 2010	Serious	Low	Low	Low	Low	Low	Low
Lalan, 2017	Critical	Critical	Low	Serious	Critical	Low	Serious
Ledermann, 2002	Serious	Serious	Low	Low	Low	Low	Low
Lindley 2012	Low	Low	Low	Serious	Low	Low	Low
Macchini, 2006	Critical	Critical	Low	Serious	Serious	Low	Serious
Nguyen, 1987	Serious	Serious	Low	Serious	Low	Low	Low
Ponce, 2018	Low	Low	Low	Low	Low	Low	Low
Prestidge, 2015	Serious	Low	Serious	Critical	Critical	Low	Low
Ramage, 1999	Critical	Serious	Low	Low	Low	Low	Low
Robitaille, 1995	Critical	Low	Low	Serious	Low	Serious	Low
Sardegna, 1998	Critical	Critical	Low	Low	Low	Low	Low
Teo, 2020	Serious	Low	Critical	Serious	Serious	Low	Low
von Schnakenburg, 2006	Serious	Serious	Low	Low	Serious	Low	Low
Warady, 2003	Low	Low	Low	Low	Low	Low	Low
Yoshino, 2004	Low	Critical	Low	Low	Low	Low	Low

Evidence Summary Tables

Question: Prophylaxis antibiotic therapy compared to None for Pediatric patients requiring catheter placement to commence chronic peritoneal dialysis [PICO 9]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis antibiotic therapy	None	Relative (95% CI)	Absolute (95% CI)	
Peritonitis											
2	observational studies[a]	not serious	serious[b]	serious[c]	serious[d]	none	Ranged between 1 in 28 patient-months (56 episodes of peritonitis in 23 individuals) and 1 infection per 63 patient-months (8 episodes of peritonitis in 5 individuals) 1 in 21 patient-months (28 episodes in 15 individuals) in no prophylaxis arm				⊕◯◯◯ Very low
Peritonitis within first 2 weeks of catheter insertion											
1	observational studies[e]	not serious	not serious	not serious	serious[d]	none	6/61 (9.8%)	7/16 (43.8%)	not estimable		⊕◯◯◯ Very low
Catheter removal due to infection											
2	observational studies[f]	not serious	not serious	not serious	serious[d]	none	Reported to be removed in 2/57 with a follow-up of 642 patient-months and 1/18 with a follow-up of 500 patient-months Not reported in no prophylaxis arm.				⊕◯◯◯ Very low

PICO Questions

Insufficient pediatric evidence (0 or 1 published study) for **36 of 54 PICOs**

PICO #	Short Description	Published studies
1	Duration of training longer vs shorter	3
2	Home visits vs no home visits	2
3	Retraining frequency vs another	3
4	Formal vs Informal training assessment	1
5	Repeat competency testing vs. none	0
6	Use of adult learning principles vs none	0
7	Tenchknoff characteristic vs another characteristic	12
8	Laparoscopic vs open catheter placement	2
9	Prophylaxis Antibiotic therapy vs none	4
10	Topical antimicrobial agent at exit site vs none	3
11	Once weekly dressing change vs more	3
12	Daily exit site care vs 3 times a week	3
13	Topical antibiotic prophylaxis vs not	3
14	Flush before fill design vs. Traditional spike system	2
15	Gastrostomy Before/After PD	6
16	Open vs laparoscopic gastrostomy	3
17	Using prophylactic antibiotics and antifungals for gastrostomy placement	3
18	Adjunctive antifungal with antibiotics	1
19	Prophylactic antibiotic for invasive procedures (dental or GI/GU)	0
20	MRSA suspected, vanco+cefepime vs cefepime alone	0
21	Aminoglycoside vs cefepime or ceftazidime	0
22	Two vs three weeks duration of treatment	0
23	For gram positive infection, adding rifampin vs not	1
24	For gram positive infection, antibiotic X vs Y	1
25	For MRSA, antibiotic X vs Y	1
26	If infection susceptible to cefazolin, using cefazolin vs another beta lactam antibiotic	1
27	For pseudomonas, single agent vs two	1
28	For gram negative infection, cefazolin vs cefepime or ceftazidime	0
29	Negative culture, two weeks treatment vs less	0
30	Negative culture, discontinue glycopeptide vs not	0
31	Fungal peritonitis, catheter removal vs treatment and removal	1
32	Fungal peritonitis, amphotericin B vs fluconazole or echinocandins	1
33	Fungal peritonitis, catheter removal time X vs Y	1
34	Fungal peritonitis, catheter replacement time X vs Y	0
35	With relapsing peritonitis, catheter removal time X vs Y	0
36	With relapsing peritonitis, standard treatment vs based on previous peritonitis	1
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38	With relapsing peritonitis, immediate vs delayed catheter replacement after removal	0
39	With relapsing peritonitis, fibrinolytic agent vs none	2
40	With relapsing peritonitis, urokinase vs rTPA/Taurolodine	0
41	With relapsing peritonitis, same or longer duration of treatment as initial episode	0
42	PD + hypogammaglobulinemia, using IVIG vs not	2
43	Exit site with granulation, silver nitrate vs not	0
44	Exit site with granulation, topical antibiotic vs not	1
45	With refractory exit-site or tunnel infection, catheter removal and replacement vs antibiotics	0
46	With refractory exit-site or tunnel infection with staph or pseudomonas, catheter removal vs antibiotics	0
47	With refractory peritonitis, catheter removal vs not	2
48	With surgical peritonitis, catheter removal vs not	0
49	With mycobacterial peritonitis, catheter removal vs not	1
50	Diagnosis of infection with presence of purulent discharge alone vs objective scoring	1
51	Diagnosis of infection with clinical assessment and ultrasound vs clinical assessment alone	0

PICO Questions

Unpublished data from SCOPE initiative and IPPN registry informing **25 PICOs, leaving only 9 PICOs without any evidence**

PICO #	Short Description	Published studies	SCOPE	IPPN
1	Duration of training longer vs shorter	3	Yes	Yes
2	Home visits vs no home visits	2	Yes	Yes
3	Retraining frequency vs another	3		Yes
4	Formal vs Informal training assessment	1		Yes
5	Repeat competency testing vs. none	0		
6	Use of adult learning principles vs none	0		
7	Tenckhhoff characteristic vs another characteristic	12		
8	Laparoscopic vs open catheter placement	2	Yes	
9	Prophylaxis Antibiotic therapy vs none	4		
10	Topical antimicrobial agent at exit site vs none	3		
11	Once weekly dressing change vs more	3		
12	Daily exit site care vs 3 times a week	3		
13	Topical antibiotic prophylaxis vs not	3		
14	Flush before fill design vs. Traditional spike system	2		
15	Gastrostomy Before/After PD	6	Yes	
16	Open vs laparoscopic gastrostomy	3		
17	Using prophylactic antibiotics and antifungals for gastrostomy placement	3		
18	Adjunctive antifungal with antibiotics	1	Yes	Yes
19	Prophylactic antibiotic for invasive procedures (dental or GI/GU)	0	Yes	
20	MRSA suspected, vanco+cefepime vs cefepime alone	0		No cefepime
21	Aminoglycoside vs cefepime or ceftazidime	0		Yes
22	Two vs three weeks duration of treatment	0		Yes
23	For gram positive infection, adding rifampin vs not	1		Yes
24	For gram positive infection, antibiotic X vs Y	1		Yes
25	For MRSA, antibiotic X vs Y	1		Yes
26	If infection susceptible to cefazolin, using cefazolin vs another beta lactam antibiotic	1		Yes
27	For pseudomonas, single agent vs two	1		Yes
28	For gram negative infection, cefazolin vs cefepime or ceftazidime	0		Yes
29	Negative culture, two weeks treatment vs less	0		Yes
30	Negative culture, discontinue glycopeptide vs not	0		Yes
31	Fungal peritonitis, catheter removal vs treatment and removal	1		
32	Fungal peritonitis, amphotericin B vs fluconazole or echinocandins	1		
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35	With relapsing peritonitis, catheter removal time X vs Y	0		Yes
36	With relapsing peritonitis, standard treatment vs based on previous peritonitis	1		
37	With relapsing peritonitis, catheter removal vs conservative treatment alone	0		Yes
38	With relapsing peritonitis, immediate vs delayed catheter replacement after removal	0		Yes
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46	With refractory exit-site or tunnel infection with staph or pseudomonas, catheter removal vs antibiotics	0		
47	With refractory peritonitis, catheter removal vs not	2		
48	With surgical peritonitis, catheter removal vs not	0		Yes
49	With mycobacterial peritonitis, catheter removal vs not	1		
50	Diagnosis of infection with presence of purulent discharge alone vs objective scoring	1		
51	Diagnosis of infection with clinical assessment and ultrasound vs clinical assessment alone	0		

Training Recommendations

- Formalized teaching program
- Training session length and total duration tailored to needs
  (>20 hours per caregiver associated with lower peritonitis rates in children)
- Formal assessment, including post-training
  written and demonstration competency testing
- Home visit
- Regular retraining/reassessment of all children on PD and/or their caregivers

Catheter Type and Placement, Early Exit Site Care

- Use of double-cuff Tenckhoff catheter with downward or lateral exit-site orientation
- PD catheter placement technique based on patient suitability and surgeon expertise
- Perioperative intravenous antibiotics be provided prior to insertion of PD catheter
- Delay first PD catheter dressing change for at least 7 days post-PD catheter insertion

Chronic Exit Site Care

- Routine PD catheter exit site care to be conducted with **sterile cleansing solution 2-3 times per week**
- **Topical antibiotic** to be applied to PD catheter exit-site as part of routine exit site care

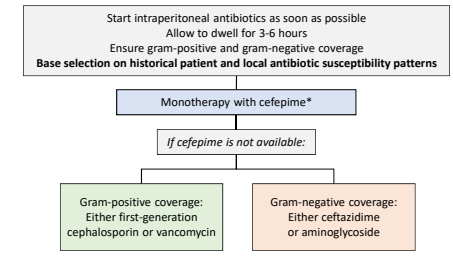
Ostomy Patients

- Place gastrostomy tube either **prior to or concurrently with** PD catheter
- *In children not yet receiving PD:*
  Place gastrostomy either by **open or laparoscopic** surgical technique or by **percutaneous endoscopic technique** (PEG).
- *In children receiving PD:*
  place gastrostomy tube by **open surgical** procedure or **laparoscopically**
- Provide **prophylactic antibiotic and antifungal** therapy to children on PD in association with gastrostomy placement

Adjunctive Prophylactic Antimicrobial Therapy

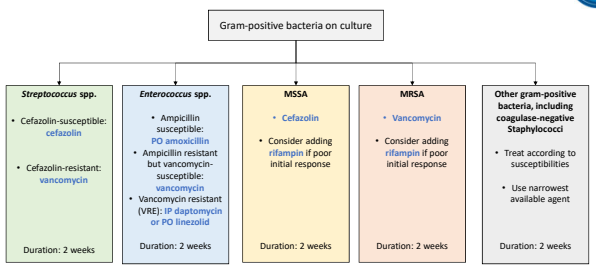
- Prophylactic nystatin or fluconazole therapy for children on PD receiving **intraperitoneal or systemic antibiotic therapy**
- Using prophylactic antibiotics for certain **GI** (eg. colonoscopies) or **GU** procedures (eg. invasive gynecological), in accordance with local guidelines.
- Do **NOT** use prophylactic antibiotics for **dental** procedures.

Empiric Antibiotic Therapy

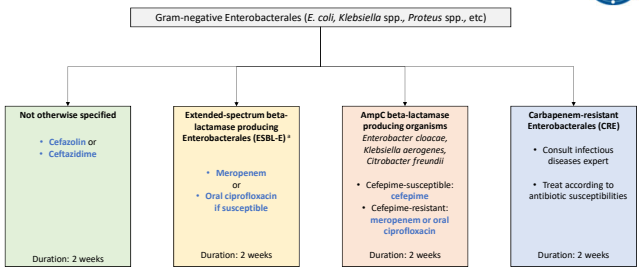


- If center's MRSA rate exceeds 10% or patient has history of MRSA colonization: add vancomycin to cefepime or replace first gen. cephalosporin by vancomycin for gram-positive coverage.

Modification for Gram-Positive Bacteria

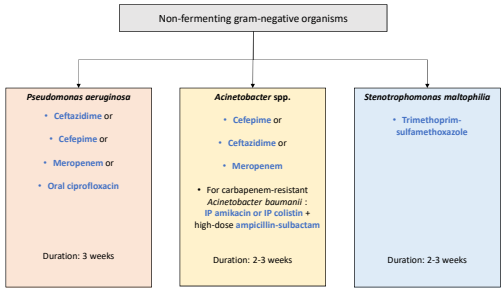


Modification for Gram-Negative Enterobacterales

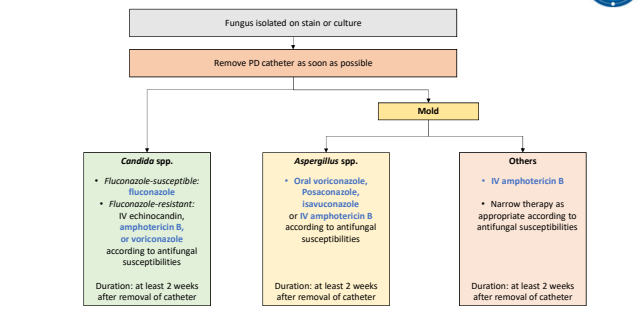


Note: all antibiotics listed in order of preference, if organism is susceptible
*Enterobacterales that are not susceptible to a 3rd generation cephalosporin (ceftriaxone, cefotaxime, ceftazidime) should be presumed to be ESBL-E

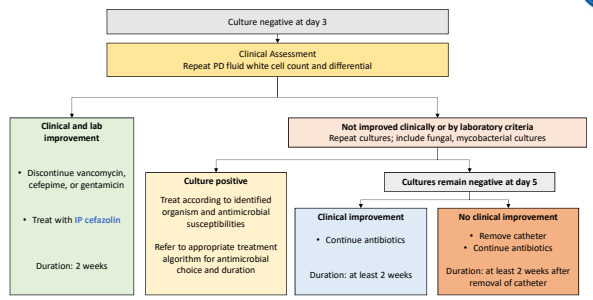
Modification for Non-Fermenting Gram-Negative Organisms

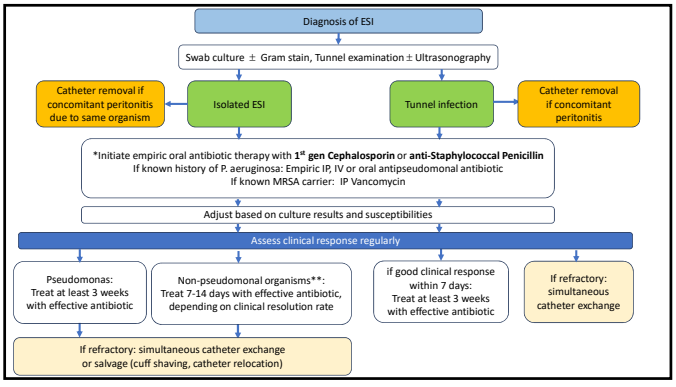


Modification for Fungal Peritonitis



Modification for Culture-Negative Peritonitis





Catheter Removal and Replacement

Catheter should be removed in the following circumstances:

- Refractory bacterial peritonitis
- Fungal peritonitis

Two-stage catheter exchange for **fungal and refractory** bacterial peritonitis

Simultaneous catheter exchange for **relapsing peritonitis** and **refractory exit-site or tunnel infection**

Question 1

Which statement regarding prophylaxis of PD-associated infections is correct?

A. The first PD catheter dressing change should be delayed for at least 1 week post PD catheter insertion
B. Routine PD catheter exit site care to be conducted daily with sterile cleansing solution
C. Prophylactic antibiotics should be administered within 6 hours of dental procedures
D. In children on PD, percutaneous gastrostomy placement is the method of choice
E. All of the above

Question 1

Which statement regarding prophylaxis of PD-associated infections is correct?

A. The first PD catheter dressing change should be delayed for at least 1 week post PD catheter insertion
B. Routine PD catheter exit site care to be conducted daily with sterile cleansing solution
C. Prophylactic antibiotics should be administered within 6 hours of dental procedures
D. In children on PD, percutaneous gastrostomy placement is the method of choice
E. All of the above

Question 2

The duration of appropriate antibiotic therapy for PD-associated peritonitis should be

A. 2 weeks for Pseudomonas
B. 3 weeks for S.aureus
C. 1 week for S.epidermidis
D. 1 week for Enterococcus faecium
E. 2 weeks for Enterobacter cloacae

Question 2

The duration of appropriate antibiotic therapy for PD-associated peritonitis should be

A. 2 weeks for Pseudomonas
B. 3 weeks for S.aureus
C. 1 week for S.epidermidis
D. 1 week for Enterococcus faecium
E. 2 weeks for Enterobacter cloacae

Question 3

If dialysate culture remains sterile ...

A. ... after 3 days, all antibiotic therapy can be discontinued
B. ... after 3 day and if there is clinical improvement, antibiotic treatment should be changed to cefazoline monotherapy
C. ... after 5 days, all antibiotic therapy can be discontinued
D. ... after 5 days, the catheter should always be removed

Question 3

If dialysate culture remains sterile ...

A. ... after 3 days, all antibiotic therapy can be discontinued
B. ... after 3 day and if there is clinical improvement, antibiotic treatment should be changed to cefazoline monotherapy
C. ... after 5 days, all antibiotic therapy can be discontinued
D. ... after 5 days, the catheter should always be removed

Question 4

In children with PD associated peritonitis, the PD catheter should be removed if ...

A. no clinical improvement is observed within 2 days
B. dialysate culture remains sterile for 5 days
C. fungi are detected by stain or culture
D. pseudomonas is grown in culture
E. All of the above

Question 4

In children with PD associated peritonitis, the PD catheter should be removed if ...

A. no clinical improvement is observed within 2 days
B. dialysate culture remains sterile for 5 days
C. fungi are detected by stain or culture
D. pseudomonas is grown in culture
E. All of the above

Question 5

Simultaneous removal and re-insertion of the PD catheter is NOT recommmended for ...

A. refractory peritonitis
B. refractory tunnel infection
C. relapsing peritonitis
D. Any of the above

Question 5

Simultaneous removal and re-insertion of the PD catheter is NOT recommmended for ...

A. refractory peritonitis
B. refractory tunnel infection
C. relapsing peritonitis
D. Any of the above

Stanford MEDICINE

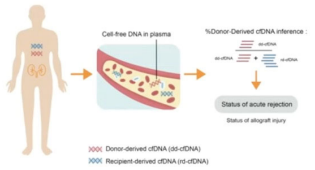
Stanford Children's Health | Lucile Packard Children's Hospital Stanford

ABMR Established and New Therapies

Paul C. Grimm MD,
Prof. Of Pediatrics
Stanford University

Donor-derived cell-free DNA (dd-cfDNA): Introduction

- Allograft cell injury leads to increases of dd-cfDNA in the bloodstream of the recipient
- Reliable marker of endothelial cell injury
- dd-cfDNA can be elevated in rejection, infection, and drug-induced kidney injury
- cfDNA is highly dynamic with a half life < 1 hour
- Reported as % dd-cfDNA over total cfDNA in blood, or as absolute fraction
- 3 clinically available assays:
  - Allosure (CareDx)
  - Prospera (Natera)
  - TRAC (Viracor Eurofins)



Am J Transplant 2015;15(10):2641-51.
Proc Natl Acad Sci USA. 2011 106(15):6229-34.
Clin. Med. 2020, 9(5), 1480.

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Combine cfDNA and Gene Expression

Combining Blood Gene Expression and Cellfree DNA to Diagnose Subclinical Rejection in Kidney Transplant Recipients

Sookhyeon Park,[1,2] Kexin Guo,[1,3] Raymond L. Heilman,[4] Emilio D. Poggio,[5] David J. Taber,[6] Christopher L. Marsh,[7] Sunil M. Kurian,[8] Steve Kleiboeker,[9] Juston Weems,[9] John Holman,[10] Ubai Zhao,[1,3] Rohita Sinha,[9] Susan Brietigam,[1] Christabel Rebello,[1] Michael M. Abecassis,[11,12] and John J. Friedewald[1,2]

Design, setting, participants, & measurements We performed a *post hoc* analysis of simultaneous blood gene expression profile and donor-derived cfDNA assays in 428 samples paired with surveillance biopsies from 208 subjects enrolled in an observational clinical trial (Clinical Trials in Organ Transplantation-08). Assay results were

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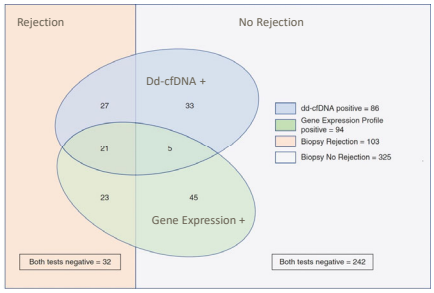
CTOT-8 COMBINED –428 Bx from 208 Patients



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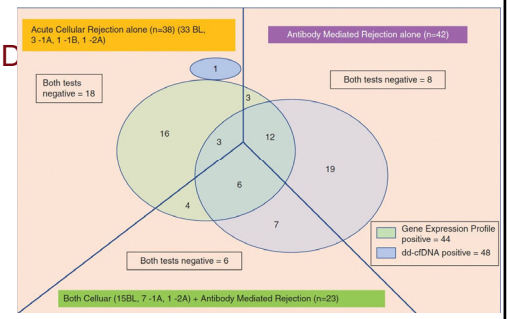
CTOT-8 COMBINED



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CTOT-8 COMBINED

Acute Cellular Rejection alone (n=38) (33 BL, 3 -1A, 1 -1B, 1 -2A)

Antibody Mediated Rejection alone (n=42)

Results For diagnosing subclinical rejection, the gene expression profile demonstrated a negative predictive value of 82%, a positive predictive value of 47%, a balanced accuracy of 64%, and an area under the receiver operating curve of 0.75. The donor-derived cfDNA assay showed similar negative predictive value (84%), positive predictive value (56%), balanced accuracy (68%), and area under the receiver operating curve (0.72). When both assays were negative, negative predictive value increased to 88%. When both assays were positive, positive predictive value increased to 81%. Combining assays using multivariable logistic regression, area under the receiver operating curve was 0.81, significantly higher than the gene expression profile ($P<0.001$) or donor-derived cfDNA alone ($P=0.006$). Notably, when cases were separated on the basis of rejection type, the gene expression profile was significantly better at detecting cellular rejection (area under the receiver operating curve, 0.80 versus 0.62; $P=0.001$), whereas the donor-derived cfDNA was significantly better at detecting antibody-mediated rejection (area under the receiver operating curve, 0.84 versus 0.71; $P=0.003$).

Conclusions A combination of blood-based biomarkers can improve detection and provide less invasive monitoring for subclinical rejection. In this study, the gene expression profile detected more cellular rejection, whereas donor-derived cfDNA detected more antibody-mediated rejection.

CJASN 16: 1539–1551, 2021. doi: https://doi.org/10.2215/CJN.05530421

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Omnigraf- Combined TruGraf and Cell Free DNA

JMIR RESEARCH PROTOCOLS — Fleming et al

Protocol

Clinical Utility of the OmniGraf Biomarker Panel in the Care of Kidney Transplant Recipients (CLARITY): Protocol for a Prospective, Multisite Observational Study

James N Fleming, PharmD; Timothy Cober, PharmD; Janelle Hickey, PharmD; Leslie Stach, PharmD; Allison Kawano, MSc; Amanda Szczepanik, PharmD; Alicia Watson, PhD; Yuka Imamura, PhD; Juston Weems, PhD; Patricia West-Thielke, PharmD
Transplant Genomics, Inc, Framingham, MA, United States

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Transplant Genomics, Inc

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Omnigraf- Combined TruGraf and Cell Free DNA

Effective April 1, 2023, revised billing guidance from the Palmetto GBA MolDX® program concerning the reimbursement of non-invasive molecular diagnostic tests limits Medicare reimbursement to only one molecular test for a given patient encounter. As such, our OmniGraf dual-biomarker rejection panel is no longer commercially available. We remain committed to providing the most advanced and reliable tests to the transplant community, and we continue to offer TruGraf Kidney and Viracor TRAC as individual tests to ensure that transplant clinicians have access to the most advanced diagnostic tools available.

TRUGRAF Kidney

Microfluidic gene expression classification of the 120 specific genes that express during subclinical acute rejection.

TRAC

Next-generation sequencing of donor-derived cell-free DNA, analyzing the whole genome (70,000+ SNPs) for evaluating clinical acute rejection.

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Question

- Patient 5 years old waiting 3 years for kidney on HD.
  Flow cross match T cell + 40 channel shift (positive is>70) NEGATIVE
  Flow cross match B cell + 70 channel shift (positive is>110) NEGATIVE
  Current bead testing shows Class I DSA low level 900 MFI.
  Serum from 3 years ago shows same DSA with MFI of 15,000
  Plan-5 day Thymoglobulin induction, tacrolimus, mycophenolate, & steroid based. In addition:
  - a) "Chill baby" what's past is past, treat the patient like any other
  - b) Rituximab 1 dose ~10 days later
  - c) Increase thymoglobulin to 7-10 days of 1.5mg/kg/dose
  - d) Plasmapheresis of 1 plasma volume immediately prior to transplant

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Question

- Patient 5 years old waiting 3 years for kidney on HD.
  Flow cross match T cell + 40 channel shift (positive is>70)
  Flow cross match B cell + 70 channel shift (positive is>110)
  Current bead testing shows Class I DSA low level 900 MFI.
  Serum from 3 years ago shows same DSA with MFI of 15,000
  Plan-5 day Thymoglobulin induction, tacrolimus, mycophenolate, & steroid based. In addition:
  - a) "Chill baby" what's past is past, treat the patient like any other
  - b) Rituximab 1 dose ~10 days later
  - c) Increase thymoglobulin to 7-10 days of 1.5mg/kg/dose
  - d) Plasmapheresis of 1 plasma volume immediately prior to transplant

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Rituximab for cryptic (past positive, current negative) sensitization

Rituximab Prevents an Anamnestic Response in Patients With Cryptic Sensitization to HLA

Andrea A. Zachary,[1,3] Donna P. Lucas,[1] Robert A. Montgomery,[2] and Mary S. Leffell[1]

Background. Some patients sensitized to HLA antigens do not have antibody present in serum specimens that are available before transplantation. However, such patients are at risk for an anamnestic response resulting from a proinflammatory response to the trauma of transplant surgery. Quantifying HLA-specific B cells provides a way to identify these patients and provide treatment to prevent an anamnestic response.
Methods. B cells were isolated before transplantation from 39 patients, 20 of whom were treated with rituximab at the time of transplantation. Ninety-nine tests were performed to quantify HLA-specific B cells by staining with HLA tetramers. Patients were considered sensitized or nonsensitized based on the frequencies of HLA-specific B cells. Pretransplantation and posttransplantation sera were tested for the detection of antibody specific for the tetramer antigen.
Results. Of the 24 cases where patients were considered sensitized to HLA antigens but did not have antibody before transplantation, no posttransplantation antibody to the tetramer antigen was detected in 10 cases when patients were treated with rituximab, but antibody was detected in 13 of 16 cases when there was no rituximab treatment ($P=0.00006$). The mean frequencies of B cells specific for HLA-B7 were the same in rituximab-treated patients who did not make antibody and in nontreated patients who did make antibody (6.0% vs. 5.7%; $P=0.8$).
Conclusions. Elimination of peripheral HLA-specific B cells in patients who are sensitized to HLA antigens but lacking detectable antibody abrogates an anamnestic response.

Keywords: Rituximab, HLA antibody, Anamnestic response, Sensitization.
(*Transplantation* 2013;95: 701–704)

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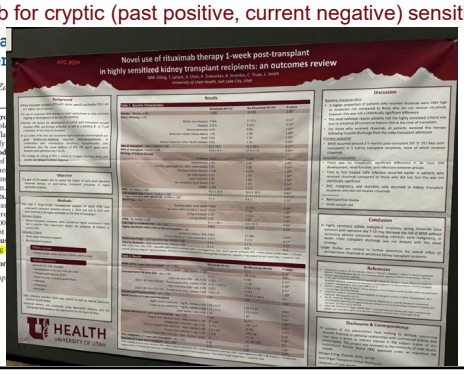
Rituximab for cryptic (past positive, current negative) sensitization



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Cornerstones of DSA Management

- Prevention
- Surveillance

Prevention-MMF discontinuation

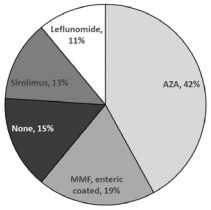
- 288 Pediatric patients, 7 centers

Received: 19 April 2023 | Revised: 19 July 2023 | Accepted: 9 September 2023
DOI: 10.1111/petr.14628

ORIGINAL ARTICLE WILEY

Prevalence of mycophenolate mofetil discontinuation and subsequent outcomes in pediatric kidney transplant recipients: A PNRC study

Asha Moudgil[1] | Kristen Sgambat[1] | Elizabeth Benoit[2] | Michael E. Seifert[3] | Madhumithaa Bharadwaj[4] | Amrish Jain[4] | Asif Mansuri[5] | Lyndsay Harshman[6] | Chryso Katsoufis[7] | Michael Somers[2]



Prevention-MMF discontinuation

- 288 Pediatric patients, 7 centers

Received: 19 April 2023 | Revised: 19 July 2023 | Accepted: 9 September 2023

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ipants. Common reasons for discontinuation included infections (35%), diarrhea (32%), leukopenia (15%), and others (18%). Increased cumulative alloimmunity (55% vs. 42%, $p = .02$), increased number of hospitalizations (82% vs. 67%, $p = .01$), and viral replications (79% vs. 47%, $p < .0001$) were observed in the MMF discontinuation group compared to the continuation group. Greater eGFR decline also occurred in the MMF discontinuation group over 2 years of follow-up (−7 vs. −1 mL/min/1.73 m^2, $p = .05$).

Higher minimum MMF levels protect from dnDSA

- Retrospective study of 32 pediatric renal allografts
- 9.4 years of followup
- 84% developed DSA
- Mean tacrolimus or MMF levels did not predict DSA

Pediatr Transplantation 2015

Pediatric Transplantation
DOI: 10.1111/petr.12637

Minimum mycophenolic acid levels are associated with donor-specific antibody formation

Filler G, Todorova EK, Bax K, Alvarez-Elias AC, Huang S-HS, Kobrzynski MC. (2015) Minimum mycophenolic acid levels are associated with donor-specific antibody formation. *Pediatr Transplant*, 00: 1–5. DOI: 10.1111/petr.12637.

Guido Filler[1,2,3], Ekaterina Kirilova Todorova[1], Kevin Bax[1], Ana Catalina Alvarez-Elias[1], Shih-Han Susan Huang[1,3] and Marta Caroline Kobrzynski[1]

Higher minimum MMF levels protect from dnDSA

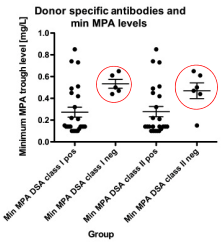


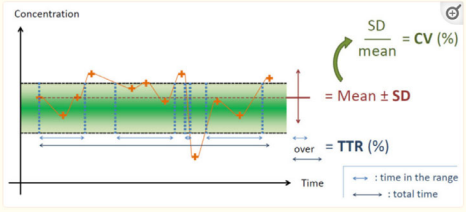
Fig. 2. Minimum MPA trough levels in patients who did or did not form class I or class II DSA. There was a significantly higher MPA trough level in the non-formers when compared to those who formed DSA.


Minimum mycophenolic acid levels are associated with donor-specific antibody formation

Lessons Learned

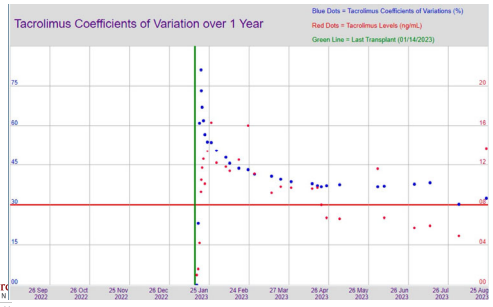
- After recovering from a bad infection (BK or adenovirus) or being cured from PTLD, the clinician will tend to keep the immunosuppression lighter than they normally would for fear of recurrence.
- DON'T succumb to this fear
- In most patients, that graft will develop DSA± ABMR if you don't return to normal immunosuppression

DSA Prevention-Tacrolimus Intra-patient Variability

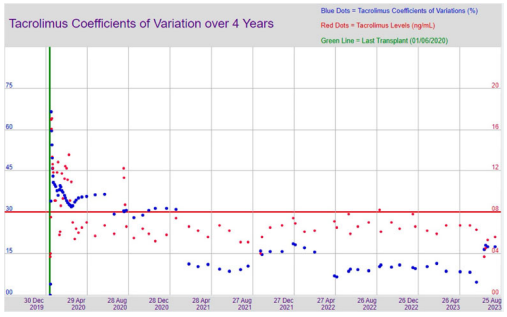


- Intrapatient variability of tacrolimus calculated using the coefficient of variation (CV) according to the equation CV = SD / Mean x 100%

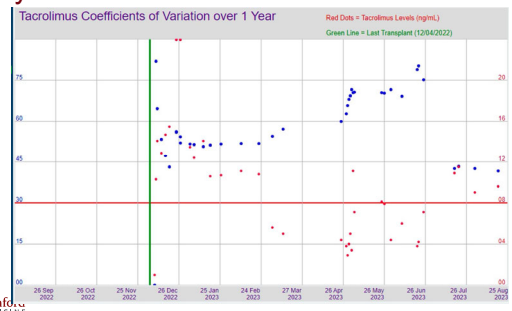
Newly transplanted



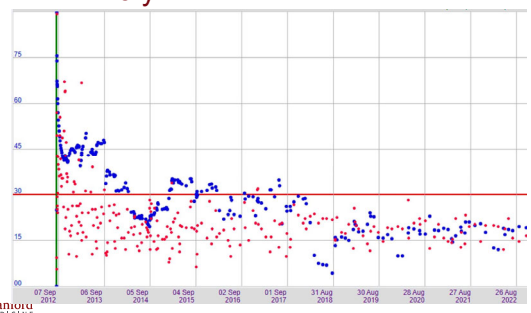
Stable post transplant



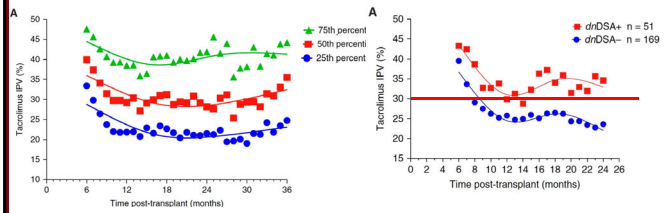
Early nonadherence



Stable for 10 years



Tacrolimus CV



Tacrolimus CV

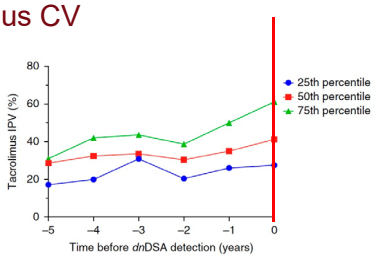


Figure 3. | Tacrolimus IPV trended upward in the time leading up to *de novo* DSA detection. Percentile curves for tacrolimus IPV over time before C1q-binding *de novo* DSA detection (n=51) in the outcome cohort (time of *de novo* DSA detection =0 years). *dn*DSA, *de novo* DSA.

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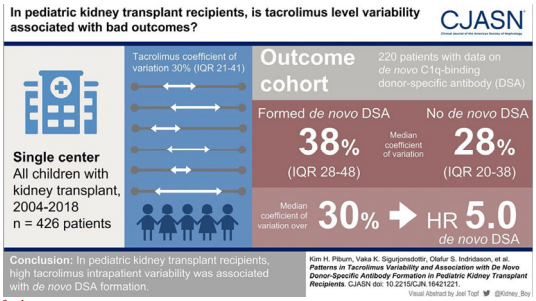
Tacrolimus CV



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Patterns in Tacrolimus Variability and Association with *De Novo* Donor-Specific Antibody Formation in Pediatric Kidney Transplant Recipients

Kim H. Piburn,[1] Vaka K. Sigurjonsdottir,[1,2,3] Olafur S. Indridason,[2] Lynn Maestretti,[4] Mary Victoria Patton,[4] Anne McGrath,[4] Runolfur Palsson,[2,3] Amy Gallo,[5] Abanti Chaudhuri,[1] and Paul C. Grimm[1]

CJASN 17: 1194–1203, 2022. doi: https://doi.org/10.2215/CJN.16421221

Our cohort received testing at multiple laboratories, with many patients often getting blood drawn at more than one laboratory per patient preference and insurance coverage demands. The assays used for tacrolimus monitoring included those run by Stanford Lab (immunoassay) (21), Quest Diagnostics (liquid chromatography-mass spectrometry) (22), and LabCorp (liquid chromatography-mass spectrometry) (23), whereas a variety of assays were in use at other community and hospital laboratories. Intrapatient

variability of tacrolimus was quantified by calculating the coefficient of variation ($\sigma/\mu \times 100\%$) over the immediate 6-month period (*i.e.*, retrospective moving window) prior to each tacrolimus level.

In the outcome cohort, all patients were tested for *de novo*

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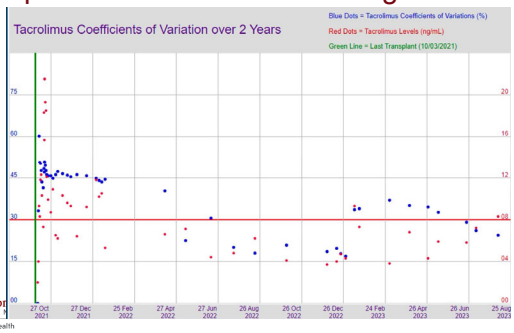
Unexpected deterioration-> changed caretaker



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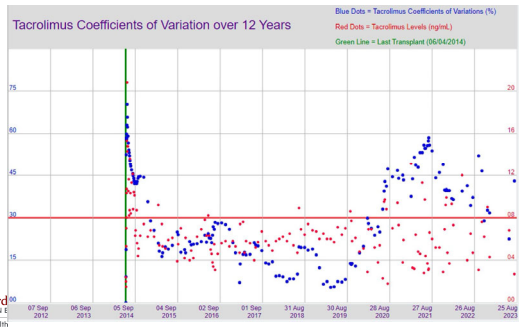
Major life event



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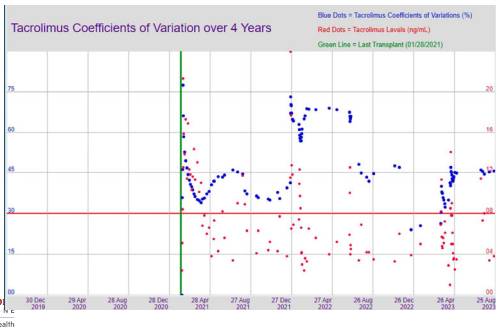
Recurrent diarrhea



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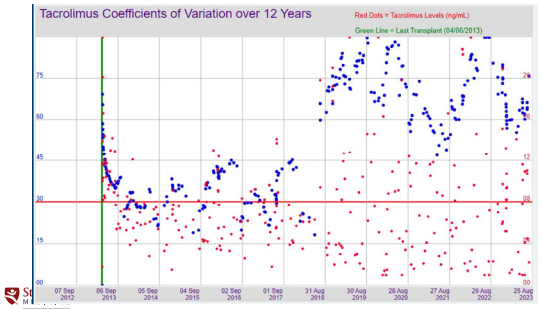
Change in life circumstances



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Evaluating the Risk and Benefit of Once Daily Mycophenolate Acid in Pediatric Kidney Transplant Recipients

L. Maestretti[1], A. McGrath[1], A. Fong[1], A. Brubaker[2], A. Gallo[2], P. Grimm[2], A. Chaudhuri[2]
Lucile Packard Children's Hospital Stanford[1], Stanford University[2]

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Objectives/Aims

- *The main objective is to demonstrate that once daily dosing of Mycophenolate Acid (Myfortic) ® is well tolerated, mounts a good MMF level, improves adherence and does not increase the risk to the allograft.*
- *Risk defined as the development of acute cellular rejection (ACR), antibody mediated rejection (AMR), donor specific antibodies (DSAs), and graft loss.*

CONTACT

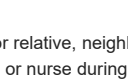
Anne McGrath, MS, CPNP-PC
Stanford Children's Health
Lucile Packard Children's Hospital Stanford
Email: amcgrath@stanfordchildrens.org
Phone: 650-498-5480
Website:

INTRODUCTION

METHODS AND MATERIALS

Retrospective chart review of all patients placed on once daily regimen as described above.

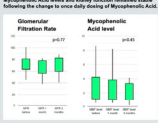
Evaluated the cohort for ACR, AMR, DSAs, graft function, Mycophenolate toxicity, infection, and graft loss.



RESULTS

- 16 patients were included who had history suggestive of immunosuppression non-adherence and were converted from a twice daily to a once daily regimen:
  - 37.5% were steroid-based
  - 50% presented with biopsy proven ACR
  - 25% patients had AMR and de novo DSAs
- Age range was 14-22 years, 62.5% patients were female.
- Regimen initiated in January 2019.
- Follow up period for all patients was at least 3 months.
- **No new ACR with new regimen.**
  - 2 patients had incomplete resolution of previous ACR requiring further anti-rejection therapy.
- One patient developed de-novo DSA within a month.
- GFR (estimated by the CKID Under 25 GFR equation) remained unchanged.
- **No graft loss.**
- Trough tacrolimus level and MMF level did not change (Figure).
- **Median MMF trough level at 3 months remained >3 µg/ml.**
- There were no infections nor evidence of neutropenia.
- The regimen was well tolerated with no report of gastrointestinal or other side effects.

Mycophenolic Acid levels and kidney function remained stable following the change to once daily dosing of Mycophenolic Acid.



DISCUSSION

Smaller patient population.

Once daily Mycophenolate Acid is well tolerated, mounts a good MMF level and offers patients the ability for once-a-day immunosuppression regimen improving adherence and not increasing the risk of graft loss.

The safety and efficacy of this regimen should be studied in a large scale randomized controlled study.

Envarsus vs Immediate release tacrolimus

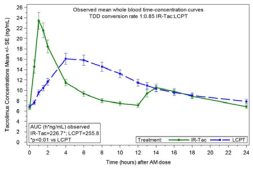


Figure 3. Observed mean tacrolimus whole blood time-concentration curves for immediate-release tacrolimus (IR-Tac) and LCPT (extended-release tacrolimus; originally LifeCycle Pharma Tacrolimus). Abbreviations: AUC, area under the curve; SE, standard error; TDD, total daily dose.

Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients

Jennifer Trofe-Clark, Daniel C. Brennan, Patricia West-Thielke, Michael C. Milone, Mary Ann Lim, Robin Reubaeu, Vincenza Nigro, and Roy D. Bloom

Stanford MEDICINE Children's Health

Received: 13 December 2020 | Revised: 21 April 2021 | Accepted: 22 April 2021
DOI: 10.1111/petr.14036

ORIGINAL ARTICLE

WILEY

Impact of once-daily ER-Tac on trough concentration variability in a stable AYA renal transplant recipient cohort

Mary Moss Chandran[1] | Eliza Blanchette[2] | Jens Goebel[3] | Margret Bock[3]

Once a day observed therapy

- Steroid, Envarsus® and Myfortic®

- Any time that works!
- A single reliable person
- Parent, Grandparent, older sib or relative, neighbor
- School or school teacher, coach or nurse during school days

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Surveillance

- DSA monitoring
  - Monthly for the first year
  - Quarterly for the second year
  - Yearly thereafter
  - Increase frequency if clinical suspicion or life changes
    - Suggestion of nonadherence
    - Moving away from home, school
    - Confessional

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Question

- A teenaged patient receives an uneventful kidney transplant with a negative crossmatch. 2 years later, his creatinine increases, he admits he has been missing a lot of medications, and his biopsy shows acute antibody mediated rejection (small amount of tubulitis but lots of microvascular disease PTC2 and glomerulitis). His DSA testing reports a DSA against DQ7 with an MFI of 20,000. However, your records show his (recipient) HLA typing also includes DQ7. What is the most likely explanation?
  - a) the lab must have mixed up the typing
  - b) he has developed an autoantibody against DQ7
  - c) he has developed a DSA against an unshared DQ alpha chain epitope
  - d) this is an example of the PROZONE effect

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Question

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  - c) he has developed a DSA against an unshared DQ alpha chain epitope
  - d) this is an example of the PROZONE effect

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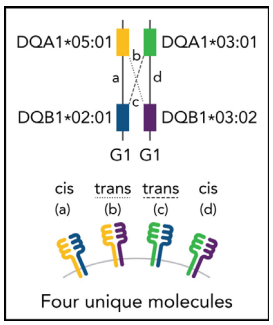
DSA against an unshared DQ alpha chain epitope

- DQ antigens have 2 polymorphic chains α and β
- DQ serotyping only reports the β chain
- An unshared α chain can be the source of a DQ7 antibody.



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DSA against an unshared DQ alpha chain epitope

- DQ antigens have 2 polymorphic chains α and β
- DQ serotyping only reports the β chain
- An unshared α chain can be the source of a DQ7 antibody.

SAB Results

Bead ID	Antigen ID	MFI	DQA1	DQB1	Serology
40	rDQ0301	0	DQA1*0301	DQB1*0301	DQ7
41	G0328DQ0301	18242	DQA1*0303/0505	DQB1*0301	DQ7

- You can detect with higher resolution (molecular) tissue typing, or testing the DSA with Single Antigen Beads

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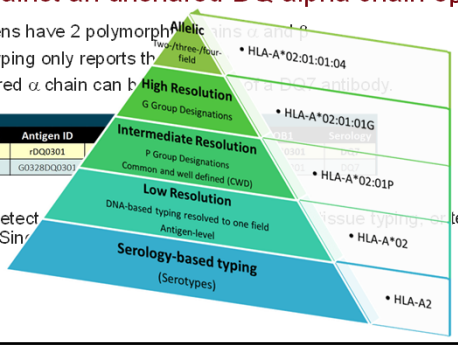
DSA against an unshared DQ alpha chain epitope

- DQ antigens have 2 polymorph
- DQ serotyping only reports th
- An unshared α chain can b

Bead ID	Antigen ID
40	rDQ0301
41	G0328DQ0301



- You can detect testing the DSA with Sin

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Complement Binding DSA

- Anti-HLA antibodies can bind complement
  - IgM isotype
  - Some IgG isotypes

Complement activation	IgG1	IgG2	IgG3	IgG4
	++	+	+++	-

Loupy et al

- 1016 patients, Paris 2005-2011
- If IgG DSA detected, serum sent to Pittsburgh for C1q using One Lambda reagents (Zeevi)
- Follow-up mean 4.8 years
- Antibody Status
  - None- 69%
  - IgG but no C1q- 24%
  - C1q binding- 8%
- NEJM 2013:369;1215-1226


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Complement-Binding Anti-HLA Antibodies and Kidney-Allograft Survival
ABSTRACT

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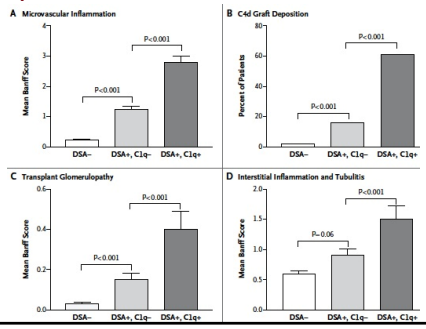
Biopsies in First Year



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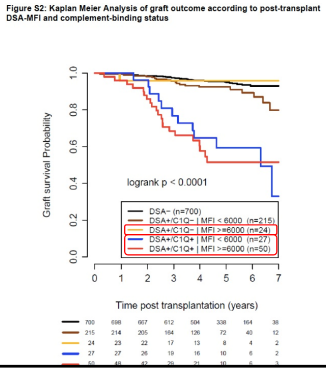
Graft Survival by antibody status



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C1q DSA Stanford Pediatrics

- 193 consecutive patients with no anti HLA sensitization transplanted 2000 - 2008
- 19.2% developed de novo DSA
  - 43% OF THOSE were C1q positive
- Most steroid free, protocol biopsies
- Followup 53±29 months
- Median time to onset of de novo DSA was 28.7±27 months

Complement-fixing donor-specific antibodies identified by a novel C1q assay are associated with allograft loss

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C1q DS

- 5 Year Graf
  - Cohort >90
  - DSA+ 71.4
- Of those DS
  - C1q positive
  - C1q negativ

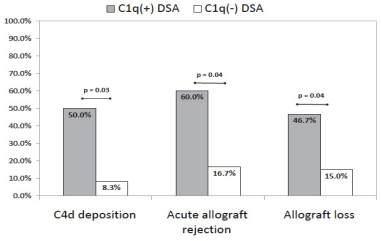

Fig. 1. Rates of biopsy C4d deposition, acute allograft rejection, and allograft loss in patients with C1q(+) and C1q(−) DSA. Patients with C1q(+) DSA, when compared to patients with C1q(−) DSA, were significantly more likely to have peritubular capillary C4d deposition on biopsy, acute rejection on biopsy, and allograft loss. All patients with C1q(+) and C1q(−) DSA had DSA detectable by standard IgG SAB assay.

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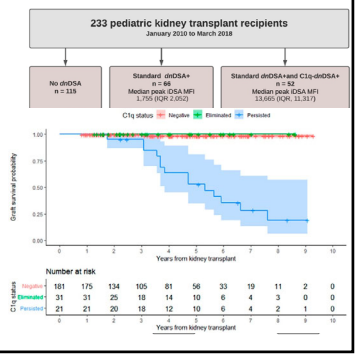
Treating DSA is useful

- Retrospective

Complement-Binding Donor-Specific Anti-HLA Antibodies: Biomarker for Immunologic Risk Stratification in Pediatric Kidney Transplantation Recipients



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Standardized Protocol for de novo DSA or AMR

- Biopsy
  - If any cellular rejection, treat with steroid pulse and/or thymoglobulin if severe
- IVIG
  - 2g/kg/dose monthly X 4 doses
  - IF MFI is falling, continue monthly until C1q- (or MFI<5000)
- Rituximab
  - 500mg/M2 X1
  - Follow B cell flow cytometry
  - Repeat Rituximab if B cells repopulate while treating DSA
- If steroid free -> make steroid based
- Optimize MMF dosing
  - Target trough level is normally 2-4 but we increase ->4-6

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Escalation of MMF to treat DSA's

- Clinical Transplants 2014
- 30 patients selected to undergo stepwise increase in Mycophenolate dose to a maximum of 3g/day. Limited by patient tolerance
- Concurrent cohort

CHAPTER 17

Improved Long-Term Survival in Kidney Transplant Recipients with Donor-Specific HLA Antibodies After Mycophenolic Acid Escalation

Lorita M. Rebellato[1], Karen Parker[2], Matthew J. Everly[3], Kimberly P. Briley[1], William Kendrick[4], Scott Kendrick[4], Carl E. Haisch[3], Paul I. Terasaki[3], and Paul Bolin[4]

Departments of [1]Pathology, [2]Surgery, and [4]Medicine, Brody School of Medicine at East Carolina University, Greenville, NC; [3]Vidant Medical Center, Greenville, NC; [3]Terasaki Foundation Laboratory, Los Angeles, CA; [4]Eastern Nephrology Associates, Greenville, NC
Corresponding author: rebellato@ecu.edu

Escalation of MMF to treat DSA

- Lower rates of graft loss
- No difference in viral infection

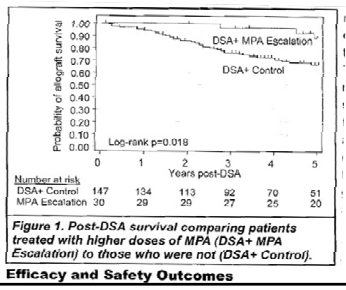

Figure 1. Post-DSA survival comparing patients treated with higher doses of MPA (DSA+ MPA Escalation) to those who were not (DSA+ Control).

Efficacy and Safety Outcomes

Question

- Dear Dr Grimm, …17year old male, 8 years post-transplant who developed mild proteinuria in the past few months and creatinine increased to 150 from 180 after enalapril. His **class II DSA came back positive for HLA-DQ2 > 6000** which is considered strong. DSA negative 1 year ago.
  Biopsy showed **Patchy peritubular capillaritis (ptc1-2), no glomerulitis (g0), negative C4d. The pathologist called probable AMR.**
  …would you do pheresis? What dose IVIG would you use?
  Next steps
  - a) Plasmapheresis followed by IVIG
  - b) Rituximab and 4 monthly doses of 2g/kg IVIG, then reassess
  - c) Plasmapheresis with a proteosome inhibitor like bortezomib
  - d) Since the C4d is negative, continue the patient on current therapy

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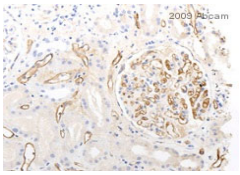
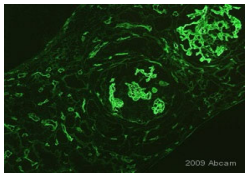
Banff 2017-ABMR

Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury, including 1 or more of the following:
   Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
   Intimal or transmural arteritis (v > 0)[1]
   Acute thrombotic microangiopathy, in the absence of any other cause
   Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, *including 1 or more of the following:*
   Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   At least moderate microvascular inflammation [(g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
   Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, *if thoroughly validated*
3. Serologic evidence of donor-specific antibodies (DSA to HLA or other antigens). **C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met**

C4d 2 detection techniques





Discussion

- Dear Dr Grimm, …17year old male, 8 years post-transplant who developed mild proteinuria in the past few months and create went up to 150 from 180 after enalapril. His **class II DSA came back positive for HLA-DQ2 > 6000** which is considered strong. DSA negative 1 year ago Biopsy showed **Patchy peritubular capillaritis (ptcl-2), no glomerulitis (g0), negative C4d. The pathologist called probable AMR.** …would you do pheresis? What dose IVIG would you use?

- Questions to direct management
  - Graft dysfunction?
  - Concomitant Cellular Rejection?
  - Cause of immunosuppression failure?

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Does isolated ABMR really exist?

- Doesn't the B cell and plasma cell need T cell cytokines and help to trigger their program of antibody production?
- If the biopsy only shows pure AMR have you just missed the patches of TCMR?
- Should you take more cores? Another biopsy? Or just treat with IV methylprednisolone or similar?

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Plasmapheresis

- Have transplanted and managed ~ 600 pediatric patients @ Stanford
- Have used post transplant plasmapheresis for DSA/AMR 5-6 times.

Stanford MEDICINE Children's Health

When Standard Protocol Fails

- Plasma Cell Memory
  - Long lived Plasma Cells may survive for decades
  - Immunologic "Tick-Over"
    - Continuous repopulation of Plasma Cells by Memory B cells

Stanford MEDICINE Children's Health

Whe

- Pla
  - Lc
  - Im

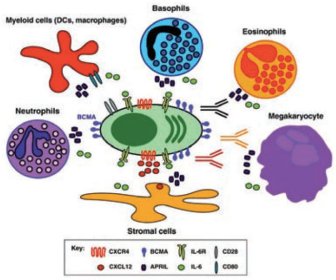

Figure 1: PC survival niche. In the bone marrow, PC is adjacent to a reticular stromal cell secreting CXCL12. A second hematopoietic niche component provides PC survival factors APRIL and IL-6 that signal through BCMA/TACI and IL-6 receptor, respectively.

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When the standard protocol fails

- Alternative B cell agents
  - Obinituzumab ?
- We have used tocilizumab (IL6 directed therapy) ~ a dozen times
  - 1 or 2 have had dramatic response, the rest, stabilized their antibody status
- Plasma cell directed therapy
  - Plasmapheresis with bortezomib-transient effect, neurotoxicity
  - Plasmapheresis with carfilzomib-irreversible plasma cell agent, cardiomyopathy
- Imlifidase
- Daratumumab
- Belatacept

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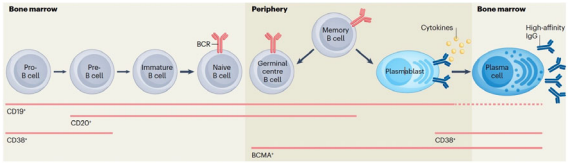
CD20 agents (Rituximab) target B cells, but leave plasma cells behind



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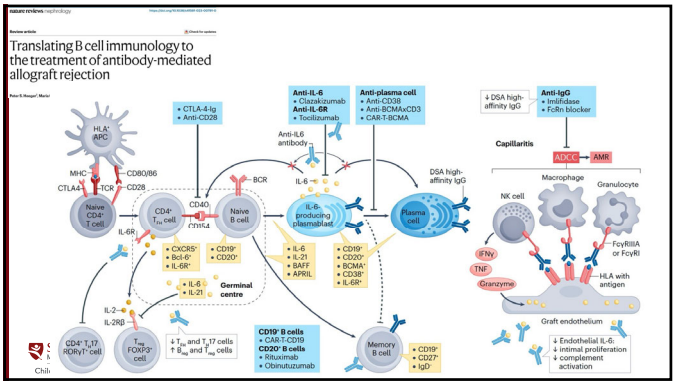

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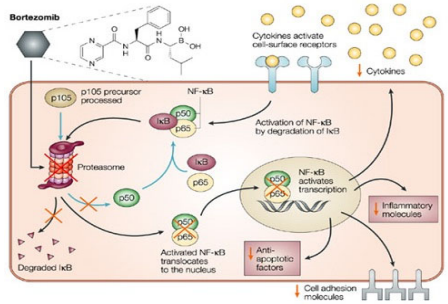
Proteasome Inhibition



Nature Reviews | Drug Discovery

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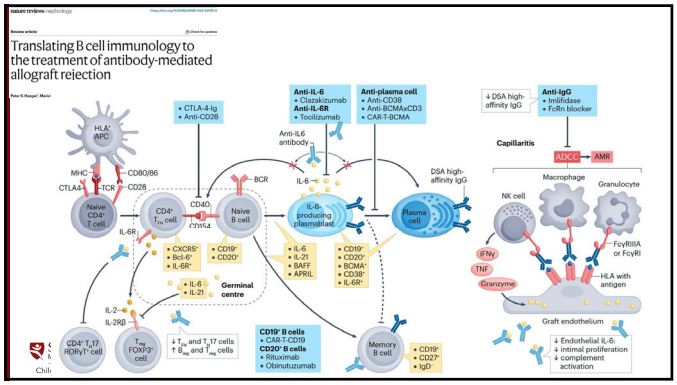

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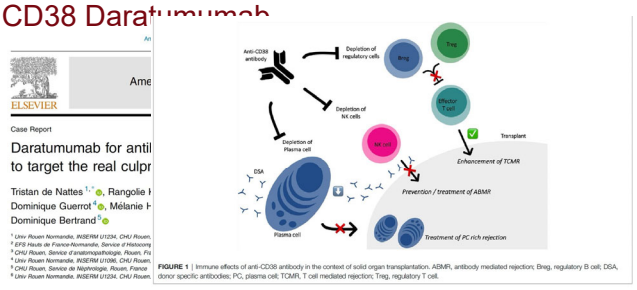
CD38 Daratumumab



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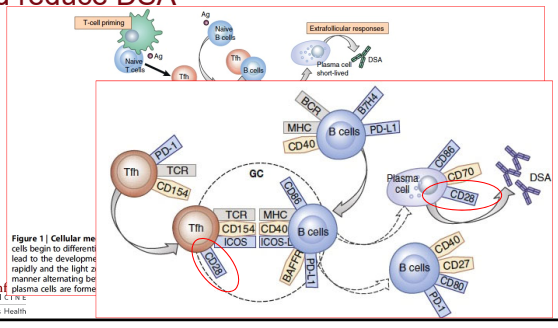
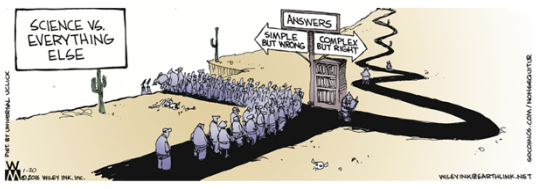
Belatacept might be very important to prevent and reduce DSA





Immunosuppression Strategies

Paul C. Grimm MD,
Prof. Of Pediatrics
Stanford University

Question

- Patient is a teenager with BMI of 35, receives living donor kidney transplant from parent. Immunosuppression is **thymoglobulin** induction with **tacrolimus** and **mycophenolate**, **steroid free**.
  In the second postoperative week, his blood sugars are consistently 200-300. What is the best immunosuppressive option?
  - a) maintain on tacrolimus
  - b) switch from tacrolimus to cyclosporine
  - c) start belatacept protocol and stop tacrolimus
  - d) switch to sirolimus, cellcept, prednisone

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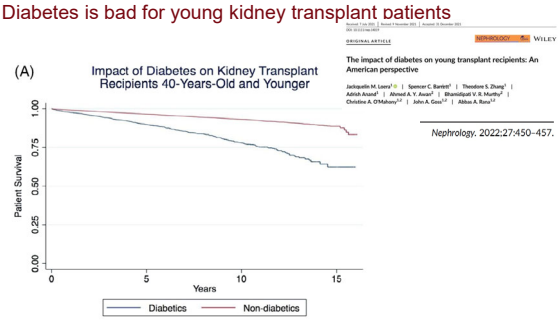
Diabetes is bad for young kidney transplant patients



ORIGINAL ARTICLE
NEPHROLOGY WILEY
The impact of diabetes on young transplant recipients: An American perspective
Nephrology. 2022;27:450–457.

FIGURE 1 (A) Kaplan–Meier curve comparing diabetic and non-diabetic transplant recipient survival over time.

New onset Diabetes Mellitus after transplant (NODAT)

- African or Central/South American genetic endowment
- Family History
- Genetic Predisposition, i.e. MODY5, 17q12 microdeletion, HNF1B
- Obesity
- Hepatitis C Virus infection
- Pre-existing glucose intolerance
- High steroid dose

Incidence of Pediatric NODAT

- 20-35% for TAC
- 2-9% for Cyclosporine
- Reviewed by Garro et al. Ped. Neph 2015;30:405-416

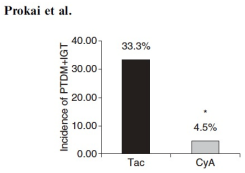
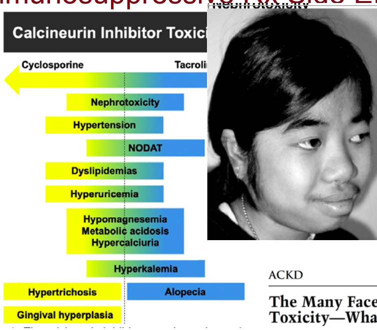


Fig. 1. Incidence of PTDM plus IGT in Tac (■) and CyA-treated (▤) children (*$p < 0.05$).

Immunosuppressive Rx Side Effects



ACKD

The Many Faces of Calcineurin Inhibitor Toxicity—What the FK?

Samira S. Farouk and Joshua L. Rein

Adult NODAT

- Retrospective review of 54 adult renal allograft recipients with NODAT on TAC/MMF/Pred
- 34 patients switched to cyclosporine
  - 42% (14) recovered from NODAT
- 20 patients stayed on tacrolimus
  - No recovery

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre experience in renal transplanted patients and review of the literature

Lidia Ghisdal,[1] Nora Ben Bouchta,[1] Nilufer Broeders,[1] Laurent Crenier,[2] Anh-Dung Hoang,[1] Daniel Abramowicz[1] and Karl Martin Wissing[1]

1 Department of Nephrology and Renal Transplantation, CUB Hopital Erasme, Bruxelles, Belgium
2 Department of Endocrinology, CUB Hopital Erasme, Bruxelles, Belgium

Pediatric NODAT

- Retrospective study of 45 pediatric and young adult cases of NODAT
- In 6 cases, TAC was switched to cyclosporine
  - 3 of those (50%) recovered from NODAT

Pediatr Transplantation 2008: 12: 643–649

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Pediatric Transplantation

Post-transplant diabetes mellitus in children following renal transplantation

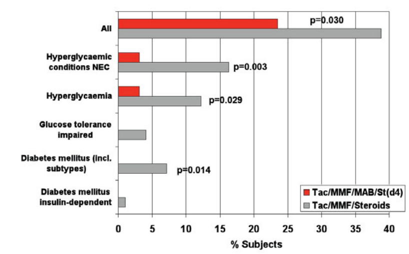
Prokai A, Fekete A, Kis E, Reusz GS, Sallay P, Korner A, Wagner L, Tulassay T, Szabo AJ. Post-transplant diabetes mellitus in children following renal transplantation. Pediatr Transplantation 2008: 12: 643–649. © 2008 Wiley Periodicals, Inc.

A. Prokai[1], A. Fekete[1], E. Kis[1], G. S. Reusz[1], P. Sallay[1], A. Korner[1], L. Wagner[2], T. Tulassay[1] and A. J. Szabo[1]

[1]First Department of Pediatrics, Semmelweis

Twist Study

A Randomized Trial to Assess the Impact of Early Steroid Withdrawal on Growth in Pediatric Renal Transplantation: The TWIST Study



NODAT

- Rather than converting from TAC to cyclosporine, consider converting to Belatacept

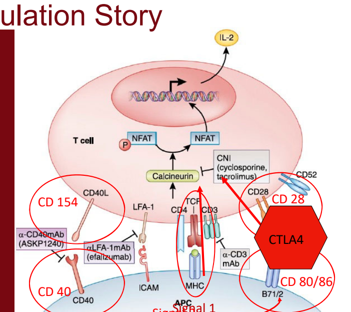
3.3.1.2.3. *Belatacept.* We found eight RCTs that reported PTDM outcomes in KT recipients receiving belatacept compared to CNI, with a total population of 2219 patients (Supplementary Table S4, Fig. 3). In the de novo belatacept group [103–106], we found a 50% lower PTDM risk (4 studies, 1481 participants, RR 0.50, 95% CI [0.32, 0.79]; $I^2 =$ 0%). Most RCTs included induction treatment with basiliximab or thymoglobulin. The CNI was tacrolimus in two studies [104,106] and CsA in the other two [103,105].

Transplantation Reviews

Review article

Immunosuppressive drug combinations after kidney transplantation and post-transplant diabetes: A systematic review and meta-analysis

Costimulation Story



Belatacept (Nulojix)

- Costimulation blocker does not deplete immune cells
- CTLA-4 IgG chimeric molecule
- IV dose every 4 weeks
- Some easily treatable rejections in comparison to CNI
- Much higher risk of PTLD if primary EBV disease

Stanford MEDICINE Children's Health

How does Belatacept fit in?

- Nonadherent teenagers and families?
- Sensitized? DSA?
- Post Transplant Diabetes?

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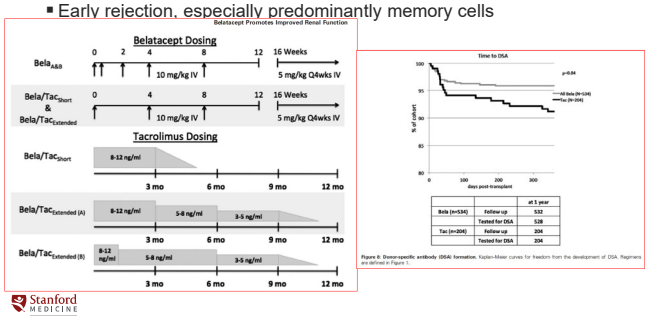
Belatacept Learning Curve

- Early rejection, especially predominantly memory cells



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Approach to NODAT- Early Basal **Insulin Rx**

- 50 Post kidney transplant adult RCT
  - Experimental-Basal insulin treatment was initiated with a morning dose of 6, 8, or 10 IU of isophane insulin if blood glucose on the previous evening was >7.8, 10, or 13.3 mmol/L, respectively.
  - Standard of care-Treatment @ blood glucose >10 mmol/L with sulfonylurea gliclazide, blood glucose levels >14 mmol/L corrected with short-acting insulin
  - 12 Month Outcome- all patients in the treatment group were insulin-independent, whereas 7 (28%) of 25 controls required antidiabetic agents.

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Approac

nature medicine LETTERS https://doi.org/10.1038/s41591-018-0089-4

Verapamil and beta cell function in adults with recent-onset type 1 diabetes

Fernando Ovalle[1], Tiffany Grimes[1], Guanlan Xu[1], Anish J. Patel[1], Truman B. Grayson[1], Lance A. Thielen[1], Peng Li[2] and Anath Shalev[1]*

Pancreatic beta cell loss is a key factor in the pathogenesis of type 1 diabetes (T1D), but therapies to halt this process are lacking. We previously reported that the approved antihypertensive calcium-channel blocker verapamil, by decreasing the expression of thioredoxin-interacting protein, promotes the survival of insulin-producing beta cells and reverses diabetes in mouse models[1]. To translate these findings into humans, we conducted a randomized double-blind placebo-controlled phase 2 clinical trial (NCT02372253) to assess the efficacy and safety of oral verapamil added for 12 months to a standard insulin regimen in adult subjects with recent-onset T1D.

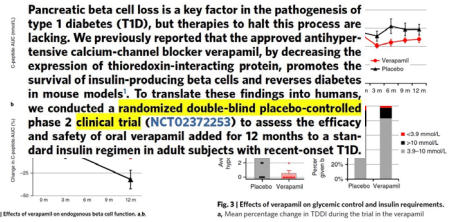

Fig. 2 | Effects of verapamil on endogenous beta cell function. a,b.

Fig. 3 | Effects of verapamil on glycemic control and insulin requirements. a, Mean percentage change in TDDI during the trial in the verapamil

Stanford MEDICINE Children's Health

Approac

nature medicine LETTERS https://doi.org/10.1038/s41591-018-0089-4

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Verapamil treatment, compared with placebo was well tolerated and associated with an improved mixed-meal-stimulated C-peptide area under the curve, a measure of endogenous beta cell function, at 3 and 12 months (prespecified primary endpoint), as well as with a lower increase in insulin requirements, fewer hypoglycemic events and on-target glycemic control (secondary endpoints). Thus, addition of once-daily oral verapamil may be a safe and effective novel approach to promote endogenous beta cell function and reduce insulin requirements and hypoglycemic episodes in adult individuals with recent-onset T1D.

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Approach to NODAT-

- Converted 14 insulin dependent patients to SGLT2 alone ”cold turkey”
- Positive
  - All patients lost weight
  - No renal AE, ketosis nor excess infections
  - Improved insulin sensitivity
- Negative
  - 1 balanitis
  - Hgb A1c deteriorated

BRIEF COMMUNICATION

Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety

Elisabeth Schwaiger[1] | Lukas Burghart[1] | Lorenzo Signorini[2] | Robin Ristl[3] | Chantal Kopecky[1] | Andrea Tura[4] | Giovanni Pacini[4] | Thomas Wrba[5] | Marlies Antlanger[1] | Sabine Schmaldienst[6] | Johannes Werzowa[7] | Marcus D. Säemann[1,8] | Manfred Hecking[1,9]

Question

- You are reviewing your transplant induction protocol and the sales representative for basiliximab just visited. You are thinking of using basiliximab (Simulect ®) for induction immunosuppression:
  - a) choice of induction agents does not affect choice of chronic immunosuppression, so you can use steroid free immunosuppression after basiliximab
  - b) Induction with Thymoglobulin ® may lead to overimmunosuppression because you must use 7 days of 1.5mg/kg/day for induction.
  - c) your protocol includes checking CD3+ cell counts. When the count is less than 50 cells/mm^3 you can stop administering Thymoglobulin because there are no more cells to kill
  - d) In the USA, most pediatric kidney transplants receive Thymoglobulin induction

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Basiliximab

- IL-2Rα blockade by receptor saturation
  - Lasts 36 days without and 59 days with mycophenolate
- Reduces incidence of acute rejection in the first 6 months compared to placebo
- No evidence of long term effect on graft nor patient survival in adults.
- No significant differences in limited pediatric studies
- Perhaps improves success of corticosteroid withdrawal

Thymoglobulin

- Polyclonal IgG from rabbits immunized with human thymus obtained at cardiac surgery
- Batch to batch variability in efficacy and adverse effects
- Comparison between studies is difficult because induction courses vary from 2 to 7 days.

Choice of induction agent may affect subsequent immunosuppressive protocol

- 106,061 received basiliximab
- 76,837 received ATG (mostly Thymoglobulin)

Clinical Nephrology, Vol. 102 – No. 1/2024 (39-50)

clinical nephrology

Original

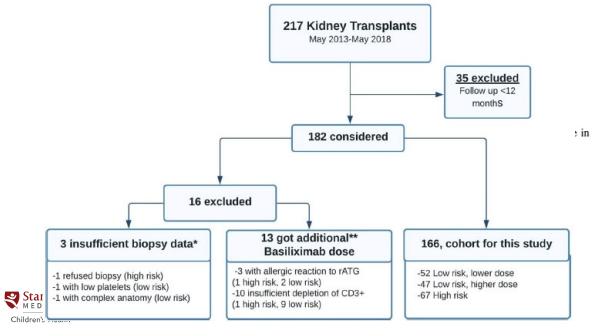
A comparative analysis of kidney allograft outcomes in steroid use versus steroid discontinuation after basiliximab and ATG induction: A UNOS database study

Pitchaphon Nissaisorakarn[1], Het Patel[2], Francesca Cardarelli[2], and Aala Amtul[2]

[1]Division of Nephrology, Department of Medicine, Massachusetts General Hosp
[2]Division of Nephrology, Department of Medicine, Beth Israel Deaconess Medi
Boston, MA, USA

Conclusion: Patients who were maintained on steroids after basiliximab induction had better 5-year allograft survival and patient survival compared to those who were not maintained on steroids. However, steroid maintenance conferred no additional benefit after ATG induction and was associated with higher mortality.

Low dose vs high dose Thymoglobulin®



Thymoglobulin Current protocol

- LOW RISK 1mg/kg/dose X 3 days= 3mg/kg total dose
- Steroids
  - Dose 1 Intraoperative solumedrol 10mg/kg max 200mg
  - Dose 2-3 0.5 mg/kg
- High RISK 1mg/kg/dose X 5 days= 5mg/kg total dose
- Steroids
  - Dose 1 Intraoperative solumedrol 10mg/kg max 200mg
  - Dose 2-5 0.5 mg/kg

Cohort Study

- 2013-2016 Simulect® n=113
- 2016-2018 Thymoglobulin® n=114

Received: 29 November 2023 | Revised: 11 January 2024 | Accepted: 28 January 2024
DOI: 10.1111/petr.14713

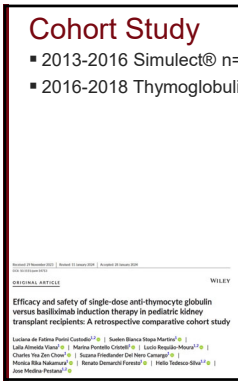
ORIGINAL ARTICLE WILEY

Efficacy and safety of single-dose anti-thymocyte globulin versus basiliximab induction therapy in pediatric kidney transplant recipients: A retrospective comparative cohort study

Luciana de Fatima Porini Custodio[1,2] | Suelen Bianca Stopa Martins[1] | Laila Almeida Viana[1] | Marina Pontello Cristelli[1] | Lucio Requião-Moura[1,2] | Charles Yea Zen Chow[1] | Suzana Friedlander Del Nero Camargo[1] | Monica Rika Nakamura[1] | Renato Demarchi Foresto[1] | Helio Tedesco-Silva[1,2] | Jose Medina-Pestana[1,2]

Cohort Study

- 2013-2016 Simulect® n=113
- 2016-2018 Thymoglobulin® n=1



Efficacy and safety of single-dose anti-thymocyte globulin versus basiliximab induction therapy in pediatric kidney transplant recipients: A retrospective comparative cohort study

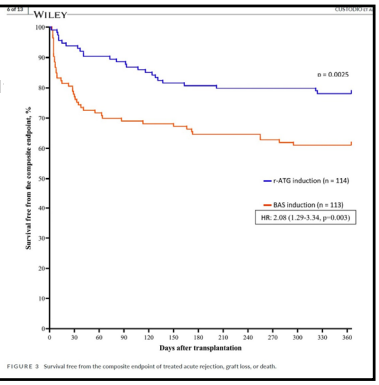
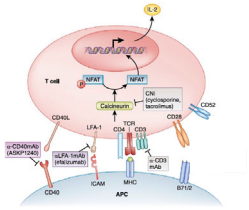


FIGURE 3 Survival free from the composite endpoint of treated acute rejection, graft loss, or death.

Campath-1h (Alemtuzumab)

- CD52
- T & B cell depletion
- Profound Immune Cell Depletion
- Long Lasting



Alemtuzumab

- First pediatric experience Bartosh 2005
  - 40% AMR, poor outcomes
- Multiple small reports as induction in pediatrics
- Some programs (Pittsburgh) embraced
- Moudgil (Ped Trans 2011) reported pediatric rejection treatment
- 14% of all transplants done in USA 2000-2010 (UNOS)

Alemtuzumab induction

- 101 consecutive living donor pediatric transplants
- 2 doses of 30mg alemtuzumab
- 3 year outcome
  - 89% graft survival
  - 93% patient survival (4 deaths due to nonvaccination)
- 84% of patients steroid free, 26% CNI free
- NO PTLD

ORIGINAL ARTICLE

WILEY

Eight-year follow-up in pediatric living donor kidney recipients receiving alemtuzumab induction

Michael M. Kaabak[1] | Nadeen N. Babenko[2] | Ron Shapiro[3] | Alexey A. Maschan[4] | Allan K. Zokoev[2] | Stanislav V. Schekaturov[2] | Julia N. Vyunkova[2] | Olga V. Dymova[5]

Abstract

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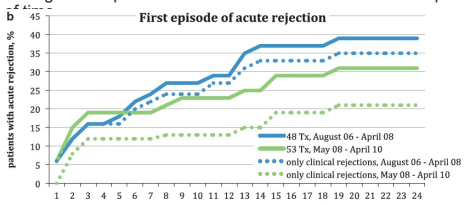
Alemtuzumab learning curve

- Mycophenolate dosing
  - During early experience, dose lowered due to neutropenia and raised slowly after bone marrow recovered
  - During later experience dose lowered less and for shorter period of time



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Indication for Steroid Free

- Infant or child, less so benefit for the older child or teen?
- Low immunologic risk of rejection
  - PRA?
  - Presence of historic or current antibody
- Underlying disease is nonimmunologic or has low risk of recurrence
- Decision to maintain a child on steroid free is continuously reassessed
  - Rejections?
  - DSA's
  - Adherence?

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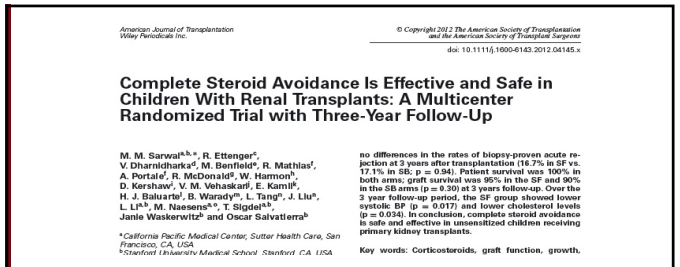

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doi: 10.1111/j.1600-6143.2012.04145.x

Complete Steroid Avoidance Is Effective and Safe in Children With Renal Transplants: A Multicenter Randomized Trial with Three-Year Follow-Up

M. M. Sarwal[a,b,*], R. Ettenger[c], V. Dharnidharka[d], M. Benfield[e], R. Mathias[f], A. Portale[g], R. McDonald[g], W. Harmon[h], D. Kershaw[i], V. M. Vehaskari, E. Kamil[k], H. J. Baluarte[l], B. Warady[m], L. Tang[n], J. Liu[n], L. Li[a,b], M. Naesens[a,o], T. Sigdel[a,b], Janie Waskerwitz[b] and Oscar Salvatierra[b]

[a]California Pacific Medical Center, Sutter Health Care, San Francisco, CA, USA
[b]Stanford University Medical School, Stanford, CA, USA

no differences in the rates of biopsy-proven acute rejection at 3 years after transplantation (16.7% in SF vs. 17.1% in SB; p = 0.94). Patient survival was 100% in both arms; graft survival was 95% in the SF and 90% in the SB arms (p = 0.30) at 3 years follow-up. Over the 3 year follow-up period, the SF group showed lower systolic BP (p = 0.017) and lower cholesterol levels (p = 0.034). In conclusion, complete steroid avoidance is safe and effective in unsensitized children receiving primary kidney transplants.

Key words: Corticosteroids, graft function, growth,

- 130 children
- Rejections 16.7% SF and 17.1% SB
- Graft survival 95% SF, 90% SB

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Steroid Avoidance RCT

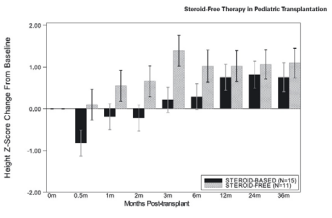

Figure 2: Change in height Z-score from baseline amongst infants and young children < 5 years of age. Change in height Z-score from baseline tended to be different between the SF and the SB arm in the first months after transplantation, but this effect was lost by 1 year after transplantation (Wilcoxon p = 0.79 at 1 year and p = 0.84 at 3 years after transplantation).

- Lower cholesterol (p=0.034)
- Lower systolic blood pressure (p=0.017

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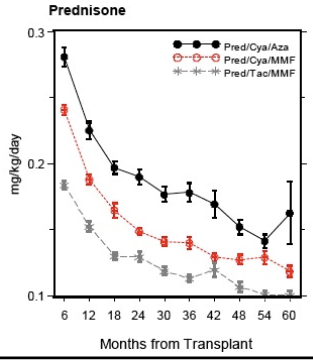
Mean Prednisone Doses by Time



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Question

- You are preparing to transplant a patient who has Systemic Lupus Erythematosus. At the time she presented, she was urgently started on dialysis and did not recover kidney function. Initial treatment of the SLE was with steroids, mycophenolate and Benlysta®. She developed severe colitis that improved once she stopped the mycophenolate. The family do not want mycophenolate to be used because of this experience. You:
  - a) encourage the family to try mycophenolate because it is less likely to cause side effects after a successful transplant
  - b) start Myfortic®, as the problem was local effects of MMF. Myfortic is enteric coated so likely to have fewer side effects
  - c) avoid mycophenolate because it is likely to cause colitis again, start azathioprine
  - d) avoid mycophenolate because it is likely to cause colitis again, start an mTOR inhibitor

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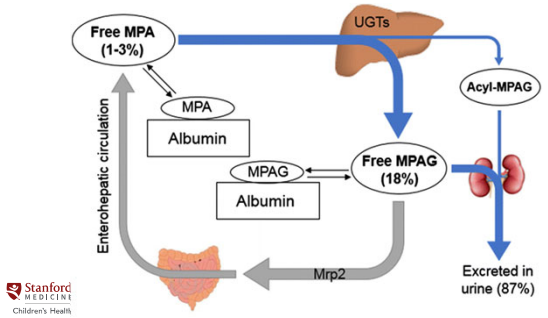
Cellcept, Myfortic, Mycophenolate, MMF



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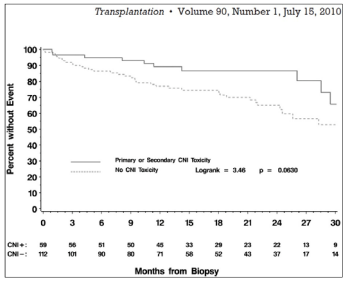
CNI Toxicity IMPROVES Long Term Graft Survival after FOR CAUSE BX

Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure

Robert S. Gaston,[1,11] I. Michael Cecka,[2] Bert L. Kasiske,[3] Ann M. Fieberg,[4] Robert Leduc,[4] Fernando C. Cosio,[5] Sita Gourishankar,[6] Joseph Grande,[6] Philip Halloran,[6] Lawrence Hunsicker,[7] Roslyn Mannon,[7] David Rush,[8] and Arthur J. Matas[10]

Transplantation • Volume 90, Number 1, July 15, 2010



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Question

- 13 year old boy, kidney transplant 11 years ago (tacrolimus/MMF/Steroid). Developed fevers, weight loss and high inflammatory markers. Lymphadenopathy. EBV PCR is negative. Got a kitten 6 months ago.
  - Choose 1
  - a) not likely to be PTLD because EBV is negative and the kidney tx was 11 years ago
  - b) a tissue biopsy is needed to differentiate PTLD from Bartonella
  - c) an empiric course of azithromycin is indicated for now
  - d) empiric lowering of immunosuppression is indicated for now

Stanford MEDICINE Children's Health

Question

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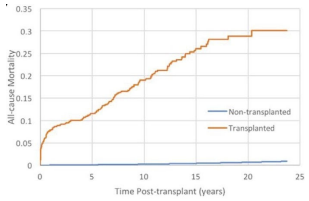
Long term outcome of Pediatric Kidney Transplant

- All SOT Hospital for Sick Children, Toronto 1991-2014, 42% kidney
- Ontario Cancer Registry does NOT include non-melanoma skin cancer



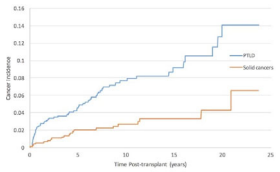


FIGURE 3. Incidence curves of solid cancers and posttransplant lymphoproliferative disorders (PTLD) among childhood transplant recipients.

Elevated Risk of Cancer After Solid Organ Transplant in Childhood: A Population-based Cohort Study

Abhijat Kitchlu, MD,[1] Stephanie Dixon, PhD,[2,3] Jade S. Dirk,[2] Rahul Chanchlani, MD,[1,4] Jovanka Vasilevska-Ristovska, MD,[5] Karlota Borges,[2] Anne I. Dipchand, MD,[1,6] Vicky L. Ng, MD,[7] Diane Hebert, MD,[1,8] Melinda Solomon, MD,[1] J. Michael Paterson,[2,9] Sumit Gupta, MD, PhD,[2,9] S. Joseph Kim, MD, PhD,[1,2,9] Paul C. Nathan, MD,[1,4] and Rulan S. Parekh, MD, FRCPC[1,4]

PROBLEM

- Immunosuppression prevents rejection
- Immunologic processes that cause rejection are the same ones that protect from **infection** and **cancer**

Since rejection is mediated by immune circuits that are important for other functions, a SPECIFIC drug is unlikely to be found

- Discover new techniques and rediscovering old ones that may REPROGRAM the immune system

Long-Term Fol
Lymphoid Irra
Heart Transpla

Clifford Chin, MD,[a] Sharon Hunt
Richard Hoppe, MD,[d] Bruce Reit

Received: 11 October 2021 | Revised: 23 November 2021 | Accepted: 10 December 2021
DOI: 10.1002/jca.21908
RESEARCH ARTICLE

Immunogenic and immuno
extracorporeal photopheres
kidney recipients. A single

Marc Xipell[1,2] | Alicia Molina-Andújar[1,2] | Gastón J. Piñeiro[1,2] | Enrique Montagud[1] | Frederic Oppenheimer[1] | Jordi Rovira[1]

ClinicalTrials.gov

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Intermediate Size Expanded Access for the Use of ExoFlo in the Treatment of Abdominal Solid Organ Transplant Patients Who Are at Risk of Worsening Allograft Function With Conventional Immunosuppressive Therapy Alone

The Clinician

- We don't know what, or why, we are doing
- We don't have definitive studies (protocol biopsies, steroid free vs steroid based, post rejection biopsies, cell free DNA, circulating or urinary transcripts, usefulness of treating DSA)
- The immune system is a fluid network that is changing in response to infections, stress, drugs, nonadherence
- We DON'T have definitive rejection diagnostics… yet.

The Clinician

- Put the whole picture together. Rely on YOUR in-depth knowledge of;
  - That patient and their unique past
  - That graft
  - Your local resources, especially your pathologist
  - Your support group "phone a friend"

I feel more like a cook in clinic

- Russian physicians

National University Hospital

Understanding Transplant Immunology

5th Primer on Paediatric Nephrology
Dr Hersharan Kaur Sran
Senior Consultant
National University Centre for Organ Transplantation

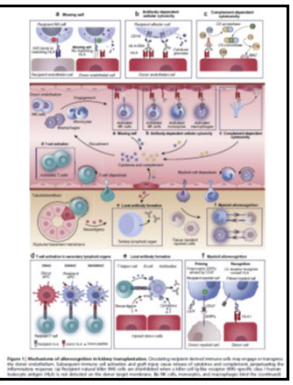
Overview

- Alloimmune response to organ transplant
- Pre-transplant evaluation of alloimmune risk
  - HLA typing
  - HLA antibody testing
    - Crossmatch tests
    - HLA-antibody identification
- Future directions

The alloimmune response

- Innate immunity
- Adaptive immunity
- Different molecular transcripts, variable patterns of immune cell infiltrates – complexity of the immune response not only explained by "T" or "antibody"-mediated rejection
- Additional mechanisms via NK cells, monocytes, myeloid cells
- Mechanisms not involving HLA antibodies

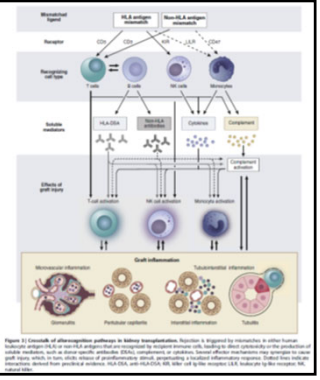
Callemeyn et al. KI 2022, 101:692.



Cross-talk of pathways

- Mismatches in HLA or non-HLA antigens
- Direct cytotoxicity
- Production of donor specific antibodies, complement, cytokines
- Synergism between several effector mechanisms to cause graft injury
- Further release of pro-inflammatory stimuli, perpetuated local inflammatory response

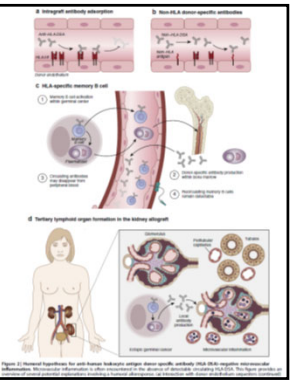
Callemeyn et al. KI 2022, 101:692.



HLA-negative ABMR

- Undetectable HLA abs – adsorption to graft
- Ab against minor histocompatibility antigens, self-epitopes e.g. angiotensin II type 1 receptors, endothelin type A, perlecan, etc..
- Memory B-cell activation, plasma cell differentiation; circulating DSA may disappear, but memory B cells persist
- Chronic inflammation, ectopic germinal centres within the allograft, local DSA production

Callemeyn et al. KI 2022, 101:692.

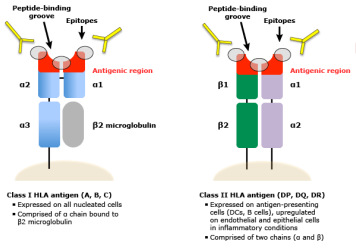


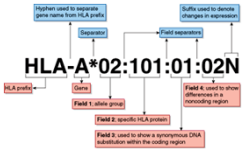
Pre-transplant assessment of risk of alloimmune response

Historical perspective

1930's	1952	1960's	1970's	1980's	1990's	2000's	current
Discovery of mouse MHC	Discovery of human MHC	HLA antibodies recognized as cause of rejection	CDC crossmatch standard protocol for renal transplant eligibility	Flow cytometry crossmatch increased sensitivity Recognition of changes in HLA antibodies – importance of current crossmatch	Advances in HLA typing (SSP, rSSOP – DNA typing of alleles) Multiplex beads for antibody identification	Facilitation of desensitization protocols to overcome positive crossmatch Paired kidney exchange programmes with virtual crossmatch	Multiple developments in technology, assay understanding interpretation standardization Future research avenues

HLA molecule and typing





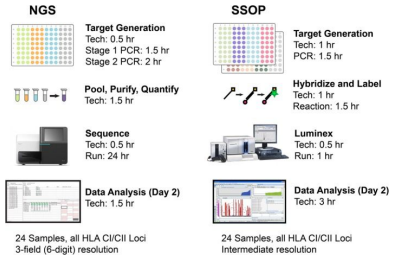
Typing techniques:

- Serologic
- Molecular (SSP, SSOP, RT-PCR, SBT)
- Next generation sequencing

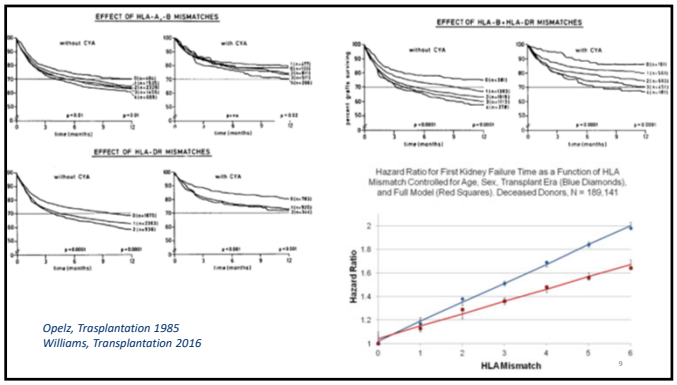
11 loci typing: HLA A, B, C, DRB1, DRB3/4/5, DQA, DQB, DPA, DPB

NGS vs SSOP procedure

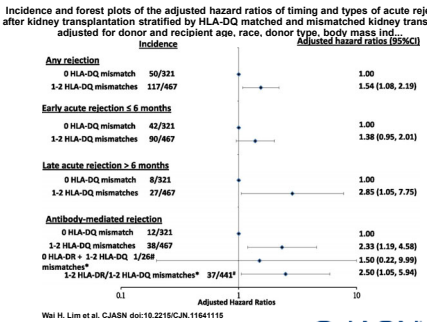
- NGS provides more accurate high resolution typing at least 3 fields, can identify novel sequences
- SSOP prone to ambiguities at high resolution especially at highly polymorphic antigens
- SSOP may take longer to resolve ambiguities, may require additional testing



Smith et al. HLA 2019, 94: 296.



Opelz, Trasplantation 1985
Williams, Transplantation 2016

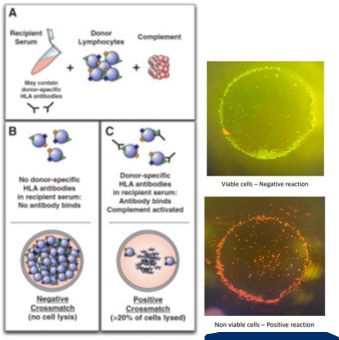


Wai H. Lim et al. CJASN doi:10.2215/CJN.11641115

CDC crossmatch

- Recipient serum centrifuged, lymphocyte suspension
- Add donor lymphocytes (time sensitive) (T + B cells separately)
- Add rabbit complement, incubate, add dye
- Read under microscope

- DTT to break disulphide bonds (IgM)
- AHG to enhance binding
- Titration to dilute serum to determine "strength" of antibody



Interpretation of CDC XM

- Caveats in interpretation:
- Subjective (visual analysis)
- Auto-antibodies
- ➢ Perform auto-crossmatch
- Rituximab effect – false +ve BCXM
- Low level class I abs
- ➢ B cells have higher class I expression than T cells
- BCXM should be interpreted with SAB assay as 50% "false positive"

Table 3 Interpretation of Crossmatch result

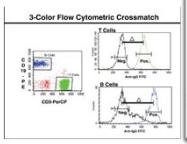
T-Cell XM	B-Cell XM	Interpretation
–ve	–ve	No DSAb to HLA class I or II OR DSAb titre too low to cause positive reaction OR (DSAb that is not complement-fixing – relevance unclear)
+ve	+ve	DSAb/s to HLA class I OR Multiple DSAbs to HLA class I +/– II
–ve	+ve	DSAb/s to HLA class II OR Low level DSAb/s to HLA class I
+ve	–ve	Technical error (possibly related to B-cell viability). The test should be repeated

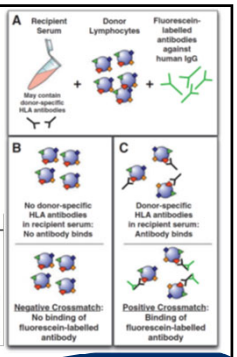
+ve, positive; –ve, negative, DSAb: donor-specific anti-HLA antibody; HLA, human leucocyte antigen, XM: crossmatch.

Mulley, Kanellis. Nephrology 2011, 16: 125.

Flow cytometry crossmatch

- Recipient serum mixed with donor lymphocytes + fluorescent antihuman-IgG antibody
- T & B cells distinguished with different fluorochrome labels
- Can identify IgG subtypes
- Intensity of fluorescence above control, measured as mean channel shift, or by serial dilutions
- Lab-defined cutoff for positive response





13

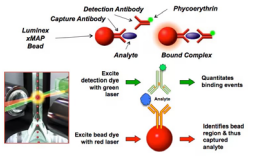
Flow XM interpretation

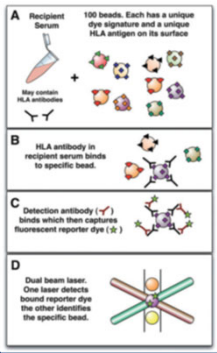
- IgG antibody present, more sensitive than CDC XM
  - Dependent on cut-off level – lab variation
- Class I ab bind T cells + B cells, class II bind B cells
  - But some activated T cells may express class II antigen..
- May not be HLA antibody, may not be complement binding, may be due to "auto-antibodies"
- Rituximab > false positive tests
  - Pronase treatment – peptidase to cleave Fc receptors from T/B cells, reduce false- positive results, but can interfere with donor HLA expression so may be unreliable

14

Single-antigen bead assay

- Microspheres coated with single HLA antigen mixed with recipient serum
- Fluorescent labeled IgG antibodies bind to anti-HLA antibody bound to bead
- Laser beams detect bound IgG fluorescence and identify the bead specificity





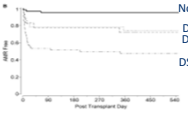
Interpretation of HLA antibodies

- Caveats
  - semiquantitative
  - interference by IgM, complement, "background", lab factors
  - bead saturation "prozone effect"
  - variations in HLA density on beads
  - incomplete representation of antigens on beads ("missing antigens")
  - shared epitopes represented on several HLA antigens, beads – "diluted" strength
  - denatured antigens > not clinically relevant
- Add C1q to assess complement binding .. But binding may be related to antibody strength
- In context of ABMR
  - low level (<1400 or 1000 MFI) HLA DSA ? Causal in AMR
  - Memory B cells in sensitized recipients – absent circulating DSA until re-challenge with antigen – antibodies may come & go
  - adsorption to graft?
  - Local DSA production, ectopic germinal centres within the allograft

16

Relevance of histocompatibility testing

- Increasing risk of graft loss
  - ➢ Positive Luminex / negative FXM
  - ➢ Positive FXM / negative CDC XM
  - ➢ Positive CDC XM
  - ➢ Strength of DSA



Orandi AJT 2014
Gloor et al AJT 2010

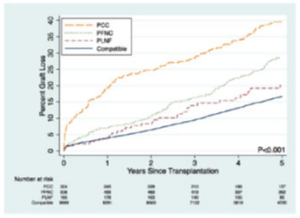
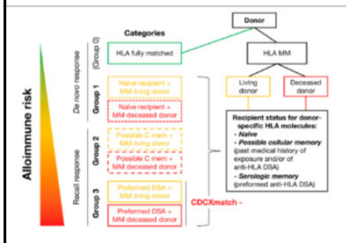
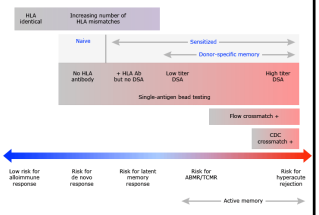


Figure 1: All-cause graft loss, by antibody strength. PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

Spectrum of risk for alloimmune response





Bestard et al. Transpl Intl, May 2022.

18

Interpretation of histocompatibility testing

Assay					Interpretation
DSA	FXM		CDC		
	T	B	T	B	
+	+	+/-	+	+/-	High burden of DSA likely complement fixing, high risk hyperacute rejection, contraindication to transplantation
+	+	+/-	-	-	Moderate burden of DSA, non-complement fixing Active memory, at risk for ABMR / TCMR
+	-	+	-	+	Class II ab (or low titre Class I Ab), moderate risk of ABMR False positive from monoclonal/polyclonal abs e.g. Rituximab
+	-	-	-	-	Lowest burden of DSA, active memory and at risk of ABMR/TCMR DSA sample different from XM (historical DSA) False positive DSA - overcalling (MFI threshold too low) - high background due to binding of serum factors - binding to denatured antigens

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Assay					Interpretation
DSA	FXM		CDC		
	T	B	T	B	
-	+	+/-	+	+/-	Non-HLA IgG binding to lymphocyte cell surface antigens Drug interference (e.g. rituximab, IVIG, ATG, Alemtuzumab) Missing antigens on SAB assay Temporally disparate samples – new DSA after sensitizing event, historical sample used for DSA testing False negative SAB - donor Ag not represented on bead panel - prozone effect, presence of inhibitors in serum - IgM/IVIG binding to beads interfering with detection of IgG - complement components binding to HLA ab preventing detection - shared epitopes diluting MFI strength
-	+	+/-	-	+/-	Moderate risk Non-complement fixing HLA ab Low level IgG non-HLA ab False negative SAB
-	-	-	+	+/-	IgM antibody

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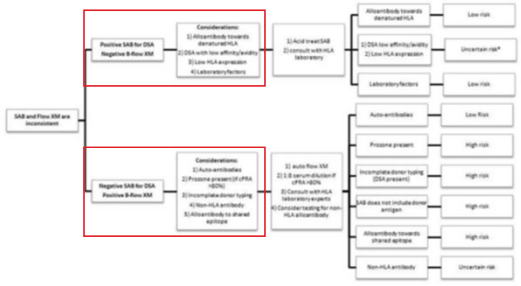

Figure 4. Evaluation when the Single Antigen Beads and Flow Crossmatch are Inconsistent

Schinstock et al. Transplantation 2016, 100: 1619

21

Case Mrs V

56 year old woman

Married with 4 daughters

CKD due to presumed chronic glomerulonephritis, initially presented with haematuria >25 years ago

Subsquent proteinuria, declining eGFR – currently 10ml/min/1.73m^2

Keen for pre-emptive living kidney transplant from her husband

No history of blood transfusions

Underwent initial CDC crossmatch

CDC Crossmatch	
Normal T-cell crossmatch	Negative
Normal B-cell crossmatch	Negative

22

MCQ 1

Case Mrs V

56 year old woman
Married with 4 daughters
CKD due to presumed chronic glomerulonephritis, initially presented with haematuria >25 years ago
Subsquent proteinuria, declining eGFR – currently 10ml/min/1.73m^2
Keen for pre-emptive living kidney transplant from her husband
No history of blood transfusions
Underwent initial CDC crossmatch

CDC Crossmatch	
Normal T-cell crossmatch	Negative
Normal B-cell crossmatch	Negative

How would you characterise her immunological risk?

a) **Low risk**

b) **Moderate risk**

c) **High risk**

d) **Unable to comment**

Polling will open on the next slide

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Q1: How would you characterise her immunological risk? 124

A. Low risk

B. Moderate risk

C. High risk

D. Unable to comment

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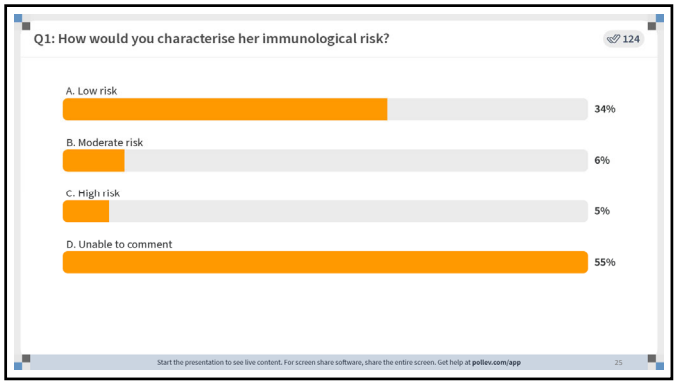

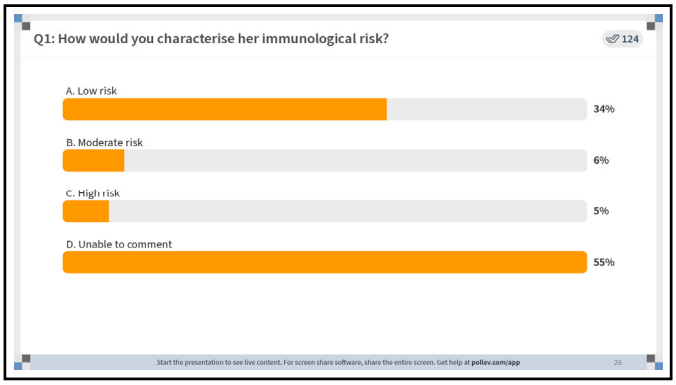

Case Mrs V

56 yo woman

Married with 4 daughters

CKD due to presumed chronic glomerulonephritis, initially presented with haematuria >25 years ago

Subsquent proteinuria, declining eGFR – currently 10ml/min/1.73m²

Keen for pre-emptive living kidney transplant from her husband

No history of blood transfusions

CDC Crossmatch	
Normal T-cell crossmatch	Negative
Normal B-cell crossmatch	Negative
DTT-treated T-cell crossmatch	Negative
DTT-treated B-cell crossmatch	Negative
AHG DTT-treated T-cell crossmatch	Negative
AHG DTT-treated B-cell crossmatch	Negative

HLA antibody screen	
Class I % PRA	6%
Class II % PRA	44%

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MCQ 2

Case Mrs V

56 yo woman

Married with 4 daughters

CKD due to presumed chronic glomerulonephritis, initially presented with haematuria >25 years ago

Subsquent proteinuria, declining eGFR – currently 10ml/min/1.73m²

Keen for pre-emptive living kidney transplant from her husband

No history of blood transfusions

CDC Crossmatch	
Normal T-cell crossmatch	Negative
Normal B-cell crossmatch	Negative
DTT-treated T-cell crossmatch	Negative
DTT-treated B-cell crossmatch	Negative
AHG DTT-treated T-cell crossmatch	Negative
AHG DTT-treated B-cell crossmatch	Negative

HLA antibody screen	
Class I % PRA	6%
Class II % PRA	44%

What is a possible explanation for these results?

a) **False negative CDC crossmatch**

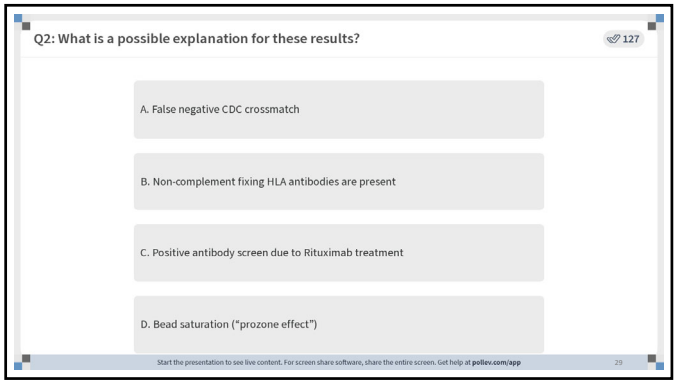
b) **Non-complement fixing HLA antibodies are present**

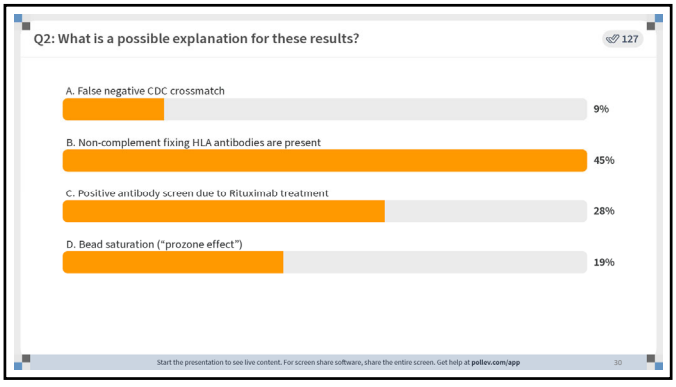
c) **Positive antibody screen due to Rituximab treatment**

d) **Bead saturation ("prozone effect")**

Polling will open on the next slide

28





Q2: What is a possible explanation for these results?

127

A. False negative CDC crossmatch 9%

B. Non-complement fixing HLA antibodies are present 45%

C. Positive antibody screen due to Rituximab treatment 28%

D. Bead saturation ("prozone effect") 19%

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Case Mrs V

56 yo woman

Married with 4 daughters

CKD due to presumed chronic glomerulonephritis, initially presented with haematuria >25 years ago

Subsquent proteinuria, declining eGFR – currently 10ml/min/1.73m²

Keen for pre-emptive living kidney transplant from her husband

No history of blood transfusions

Flow Crossmatch		
IgG T-cell crossmatch	Positive Channel shift 113	*Cut-off for T cell 60*
IgG B-cell crossmatch	Positive Channel shift 193	*Cut-off for B-cell 90*

ANTIGEN	ALLELES	MFI	DSA/CREG
B13	B*13:02	10668	DSA at antigen level
B13	B*13:01	9398	DSA
DP13	DP81*13:01	2048	NO
N5 , DP13	DPA1*02:02, DP81*13:01	1963	DSA, NO
DP14	DP81*14:01	1231	NO
DP5	DP81*05:01	1427	DSA
N5 , DP5	DPA1*02:02, DP81*05:01	1401	DSA, DSA
N5 , DQ7	DQA1*06:01, DQB1*03:01	16670	DSA, DSA
N5 , DQ7	DQA1*05:03, DQB1*03:01	16414	NO , DSA
N5 , DQ7	DQA1*05:05, DQB1*03:19	16349	NO , DSA at antigen level
N5 , DQ7	DQA1*02:01, DQB1*03:01	12603	NO , DSA
N5 , DQ7	DQA1*03:01, DQB1*03:01	7775	NO , DSA
N5 , DQ8	DQA1*03:02, DQB1*03:02	16389	NO , CREG
N5 , DQ8	DQA1*03:01, DQB1*03:02	13689	NO , CREG
N5 , DQ8	DQA1*02:01, DQB1*03:02	13182	NO , CREG
N5 , DQ9	DQA1*03:02, DQB1*03:03	14406	NO , CREG
N5 , DQ9	DQA1*02:01, DQB1*03:03	13887	NO , CREG
N5 , DQ9	DQA1*03:01, DQB1*03:03	12101	NO , CREG
DR12	DR81*12:02	903	DSA
DR12	DR81*12:01	701	DSA at antigen level
DR51	DR85*01:01	976	DSA

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MCQ 3

Case Mrs V

56 yo woman

Married with 4 daughters

CKD due to presumed chronic glomerulonephritis, initially presented with haematuria >25 years ago

Subsquent proteinuria, declining eGFR – currently 10ml/min/1.73m²

Keen for pre-emptive living kidney transplant from her husband

No history of blood transfusions

Which of the following BEST decribes the immunological risk?

a) **High risk for hyperacute rejection**

b) **At risk for latent memory with recall B and T cell response**

c) **Active memory and at risk for TCMR / ABMR**

d) **Increased risk for de novo alloimmune response**

Polling will open on the next slide

33

Q3: Which of the following BEST decribes the immunological risk?

127

A. High risk for hyperacute rejection

B. At risk for latent memory with recall B and T cell response

C. Active memory and at risk for TCMR / ABMR

D. Increased risk for de novo alloimmune response

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34

Q3: Which of the following BEST decribes the immunological risk?

127

A. High risk for hyperacute rejection 6%

B. At risk for latent memory with recall B and T cell response 14%

C. Active memory and at risk for TCMR / ABMR 80%

D. Increased risk for de novo alloimmune response 1%

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35

Q3: Which of the following BEST decribes the immunological risk?

127

A. High risk for hyperacute rejection 6%

B. At risk for latent memory with recall B and T cell response 14%

C. Active memory and at risk for TCMR / ABMR 80%

D. Increased risk for de novo alloimmune response 1%

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MCQ 4

50 year old woman, single

ESKD due to lupus nephritis

Planned for pre-emptive kidney transplant from her sister

History of blood transfusion

These are the CDC crossmatch results

RELATIONSHIP	: SISTER
CROSSMATCH RESULTS:	
NORMAL T-CELL CROSSMATCH	: POSITIVE (1:1)
NORMAL B-CELL CROSSMATCH	: POSITIVE (1:1)
DTT-TREATED T-CELL CROSSMATCH	: NEGATIVE
DTT-TREATED B-CELL CROSSMATCH	: NEGATIVE
AHG DTT-TREATED T-CELL CROSSMATCH	: NEGATIVE
AHG DTT-TREATED B-CELL CROSSMATCH	: NEGATIVE

How would you interpret the crossmatch results?

a) **Low level class I and II antibodies present**

b) **Low level class II antibodies present**

c) **Presence of non-complement fixing antibodies**

d) **Presence of IgM antibodies**

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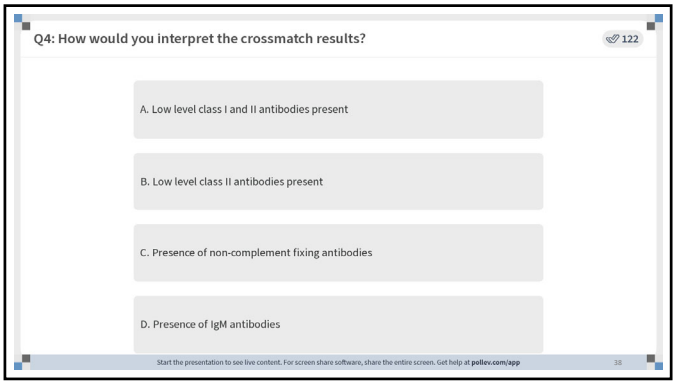

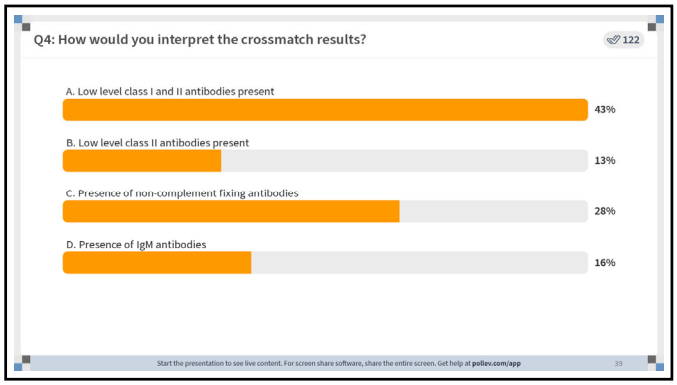

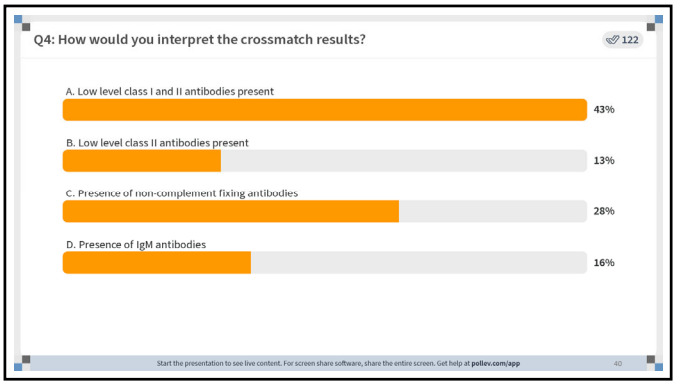

MCQ 5

21 year old male

ESKD due to IgA nephropathy

No history of transfusions or transplants

Planned for ABO incompatible transplant from father

Initial crossmatch result:

CROSSMATCH RESULTS:		Channel Shift
IgG T-CELL CROSSMATCH	: NEGATIVE	-15
IgG B-CELL CROSSMATCH	: NEGATIVE	22
PRONASE IgG T-CELL CROSSMATCH	: NEGATIVE	-17
PRONASE IgG B-CELL CROSSMATCH	: NEGATIVE	-39

Repeated 1 week before transplant

CROSSMATCH RESULTS:		Channel Shift
IgG T-CELL CROSSMATCH	: NEGATIVE	0
IgG B-CELL CROSSMATCH	: POSITIVE	498

HLA ANTIBODY IDENTIFICATION	
HLA CLASS I SPECIFICITY ANTIBODY	: NOT DETECTED
HLA CLASS II SPECIFICITY ANTIBODY	: NOT DETECTED

What is the likely explanation for these results?

a) **Mix-up in patient samples**

b) **Recent sensitising event**

c) **Rituximab treatment**

d) **Thymoglobulin treatment**

Polling will open on the next slide

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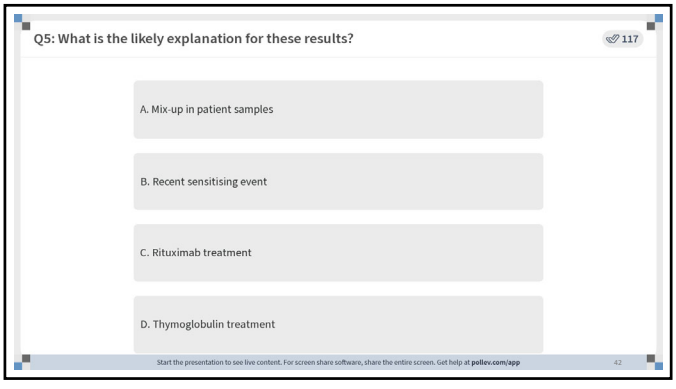

Q5: What is the likely explanation for these results? 117

A. Mix-up in patient samples 3%

B. Recent sensitising event 41%

C. Rituximab treatment 47%

D. Thymoglobulin treatment 9%

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Q5: What is the likely explanation for these results? 117

A. Mix-up in patient samples 3%

B. Recent sensitising event 41%

C. Rituximab treatment 47%

D. Thymoglobulin treatment 9%

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MCQ 6

43yo man

ESKD due to presumed diabetic nephropathy

No history of transfusions or transplants

What is a possible explanation for presence of HLA antibodies on the single antigen bead panel?

a) **Missing antigen on Luminex panel**
b) **Prozone effect is present**
c) **Denatured antigen on Luminex panel**
d) **Presence of autoantibodies**

Polling will open on the next slide

HLA ANTIBODY SCREEN

CLASS I : ANTI-HLA ANTIBODY (IgG) NOT DETECTED
% PRA <3

CLASS II : ANTI-HLA ANTIBODY (IgG) NOT DETECTED
% PRA <3

CROSSMATCH RESULTS:

		Channel Shift
IgG T-CELL CROSSMATCH	: NEGATIVE	5
IgG B-CELL CROSSMATCH	: NEGATIVE	20

ANTIGEN	ALLELES	MFI	DSA/CREG
B13	B*13:02	1315	CREG
Cw17	C*17:01	1278	CREG
Cw18	C*18:02	1073	CREG

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Q6: What is a possible explanation for presence of HLA antibodies on the single antigen bead panel? 120

A. Missing antigen on Luminex panel

B. Prozone effect is present

C. Denatured antigen on Luminex panel

D. Presence of autoantibodies

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Q6: What is a possible explanation for presence of HLA antibodies on the single antigen bead panel? 120

A. Missing antigen on Luminex panel 13%

B. Prozone effect is present 32%

C. Denatured antigen on Luminex panel 24%

D. Presence of autoantibodies 32%

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Q6: What is a possible explanation for presence of HLA antibodies on the single antigen bead panel? 120

A. Missing antigen on Luminex panel 13%

B. Prozone effect is present 32%

C. Denatured antigen on Luminex panel 24%

D. Presence of autoantibodies 32%

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Summary & future directions

- The age of precision medicine in transplantation
- Improved technology in histocompatibility testing, differentiation of immunological risk
- Greater understanding of the mechanisms of the alloimmune response
- Allow tailored strategies for induction & maintenance immunosuppression, treatment of rejection
- Overall aim of improving allograft survival

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Summary & future directions

- Refinements in current histocompatibility testing
  - Validation and standardization of assays
- Development of assays to measure immune memory
- Better predictors of de novo alloimmune response
  - Molecular mismatch
- Better understanding of the role of non-HLA antibodies
  - Genetic testing
- Cost concerns

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Thank you.
Any Questions?

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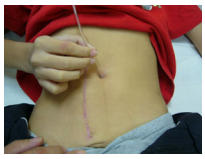
Challenges in Paediatric Kidney Transplantation -The Surgeon's Perspective

A/Prof Mali Vidyadhar
Surgical Director, Paediatric Transplantation
National University Hospital
Singapore

Preoperative

Recipient preoperative evaluation

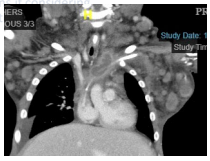
- The 'urological' bladder
- Vascular access issues- evaluate for thrombosis of intra-abdominal vessels
- Previous abdominal operations if considering intraperitoneal placement of transplant kidney
- Need an adequate functional or low-pressure reservoir
- Bladder dysfunction requiring bladder augmentation and continent stoma creation for clean intermittent catheterisation
- Mitrofanoff and augmentation cystoplasty should be performed ~ 3-6 months before transplant

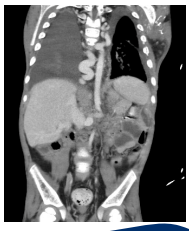


Preoperative

Recipient preoperative evaluation

- The 'urological' bladder
- Vascular access issues- evaluate for thrombosis of neck and intra-abdominal vessels
- Previous abdominal operations if considering intraperitoneal placement of t
- Recipient size

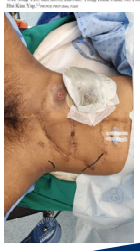




Preoperative

Recipient preoperative evaluation

- The 'urological' bladder
- Vascular access issues- evaluate for thrombosis of intra-abdominal vessels
- Previous abdominal operations (CAKUT) (considerations for siting the transplant kidney)
- Recipient size



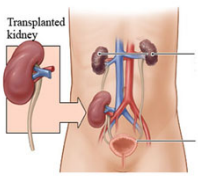
Preoperative

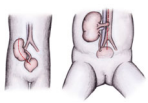
Recipient size-Transplant operation

Children > 30kg
- Technical details are generally similar to adult kidney transplants
- Retroperitoneal exposure
- Anastomoses to external iliac vessels

Children 10-30kg
- Retroperitoneal vs intraperitoneal approach
- Common iliac vessels

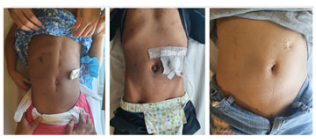
Children < 10kg
- Midline laparotomy
- Anastomoses to inferior vena cava and aorta



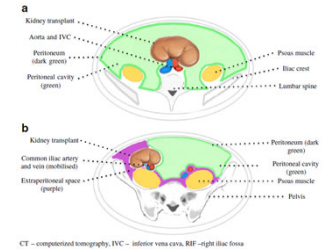


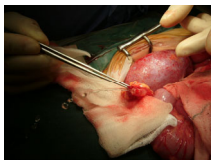
Preoperative

Transplantation of an adult-size kidney into a small child



Pre/intraoperative

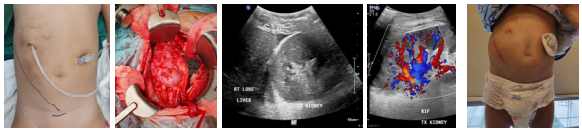




Pediatr Nephrol (2018) 33:947–955

Pre/intraoperative

- Extraperitoneal renal transplantation is technically feasible in children who weigh less than 15 kg
- Limits potential gastrointestinal complications
- Allows the confinement of potential surgical complications, such as bleeding and urinary leakage
- Preserves the peritoneal cavity
- Provides complete access to the retroperitoneum to enable concurrent retroperitoneal surgery, such as nephrectomy, to be performed safely.



NUH Children's Kidney Centre experience

- Study period 1989-2023
- N=12 (10 living-related donors)
- Median age at transplant 62 months (IQR 43-68)
- Median weight at transplant 13.8kg (IQR 10-14.2)
- Median follow-up 8 years (IQR 0.75-33)
- Transperitoneal=6 (early era until 2008)
- Retroperitoneal=6
- Graft loss=2 (vascular thrombosis, BK nephropathy)

Excellent outcomes in living-related kidney transplantation in children 15 kg or less: experience from a tertiary pediatric referral center in Singapore

Korean J Transplant 2022;36 Suppl 1:S252
https://doi.org/10.4285/kjtx2022.F-2021

	1-year graft survival (%)	3-year graft survival (%)
Paediatric Kidney Transplantation in NUH[a]		
(a) Living-donor	98.1	93.9
(b) Deceased donor	90.3	76.7
(c) Living donor–recipient < 15kg (n=10)	100	90
NAPRTCS[b]		
(a) Living donor	94.0	88.0
(b) Deceased donor	88.0	78.0

Preoperative

Donor selection

Living donor kidneys

- Reduced waiting time-may limit dialysis related complications
- Allows for pre-emptive transplantation- avoid dialysis
- Superior outcomes for paediatric recipients-long-term graft survival longer
- Gold-standard- HLA-identical adult siblings aged 19-45 years- 23.3 yrs gra survival
- Projected half-lives of living donor kidneys in young recipients (after 1st y post-tx)
- 26.3 years for recipients aged 0-2.5 years
- 29.3 years for recipients aged 2.5-5years
- Transplantation of a pediatric recipient, with an excellent quality adult-sized kidney, without acute tubular necrosis--distinct and significant survival advantage, particularly for the young recipient less than 6 years old.[a]

Nineteen-Year Experience of Paediatric Renal Transplantation in Singapore

Ann Acad Med Singapore 2009;38:300-8

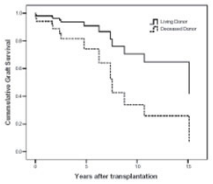


Fig. 2. Cumulative graft survival by donor type, adjusted for gender, race, waiting time, recipient age at time of transplant, immunosuppression era, and adherence.

Sarwal MM, Cecka JM, Millan MT, et al. Adult-size kidneys without acute tubular necrosis provide exceedingly superior long-term graft outcomes for infants and small children: a single center and UNOS analysis. United Network for Organ Sharing. Transplantation 2000;70:1728–36.

Preoperative

Donor selection

Living donor	Deceased donor
Shorter ischaemia times	Longer ischaemia times
Shorter blood vessels on the graft	Longer blood vessels
Planned	"Emergency"

Nineteen-Year Experience of Paediatric Renal Transplantation in Singapore

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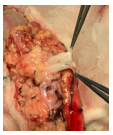

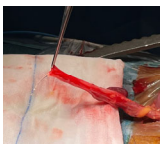

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Post-operative

Doppler ultrasound for post-transplant surgical monitoring and complications

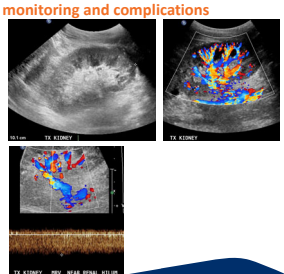
- Doppler USG allows rapid visualization of the kidney, the collecting system, and the vessels.

Vascular complications

- Vascular thrombosis – hypercoagulable states, intraoperative hypotension, multiple arteries
- Graft loss- especially younger recipients
- Surgical re-exploration, thrombectomy and revascularisation

Other surgical complications

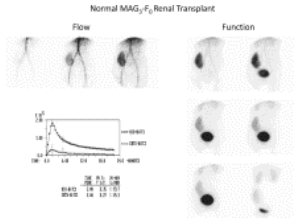
- It also aids in the detection of obstruction (hydronephrosis), lymphocele and urine leakage (perinephric fluid collection) –may need intervention/ re-exploration



Post-operative

MAG3 scans in the early period following kidney transplantation

- Although ultrasonography can be useful, it provides no indication of renal function.
- Nuclear renography provides an accurate representation of perfusion, tubular function, and drainage of the kidney transplant.
- Mercaptotriglycylglycine (MAG-3), demonstrates both glomerular filtration and tubular excretion
- Delayed or decreased perfusion to the kidney may indicate acute rejection or compromise of arterial inflow
- Decreased tubular excretion may be due to acute or chronic rejection or acute tubular necrosis (ATN)
- Perinephric urine leak



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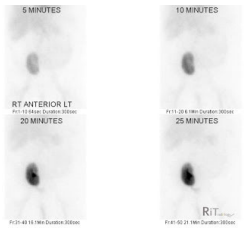

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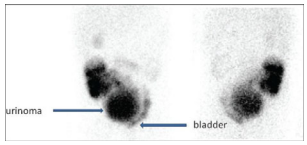

Question 1: Abrupt drop in urine output post-kidney transplant

A 6 year old child received a kidney transplant from a brain-deceased donor. The transplant operation went well with prompt perfusion of the transplant kidney. There is good urine output as the child leaves OT and arrives in the ICU.. On the 1st postoperative night, you are called for an abrupt drop in urine output.

Initial treatment strategy should be:

A. Flush the urine catheter to ensure that it is patent

B. Evaluate the fluid status and volume resuscitate as necessary

C. Arrange for an urgent doppler ultrasound to evaluate the renal blood vessels

D. All of the above

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Question 2: Abrupt increase in drain output – mainly clear

A 10-year-old 22 kg child received a living-donor kidney transplant. The transplant operation went well with prompt perfusion of the transplant kidney. On postoperative day 2, the child develops a fever. The output from the drain adjacent to the transplant operation increases suddenly to 200ml over a few hours. The urine output which has been good so far drops to less than 1ml/kg/h. The drain fluid was sampled, demonstrating a creatinine of 700umol/L. The serum creatinine is 240umol/L.

Management strategy should include:

A. Prepare for re-exploration for vascular thrombosis.

B. Initiation of broad-spectrum antibiotics

C. Continued Foley bladder decompression

D. Ultrasound to evaluate presence of fluid collection adjacent to the transplant kidney or hydronephrosis

E. B, C and D

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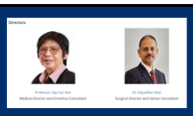
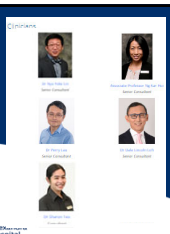
Thank you for your attention!





NUHS National University Health System

National University Hospital | Ng Teng Fong General Hospital | Alexandra Hospital

Jurong Community Hospital | National University Polyclinics | Jurong Medical Centre

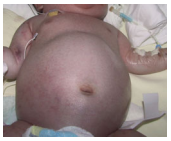
National University Cancer Institute Singapore | National University Heart Centre Singapore | National University Centre for Oral Health Singapore

NUS Yong Loo Lin School of Medicine | NUS Faculty of Dentistry | NUS Saw Swee Hock School of Public Health

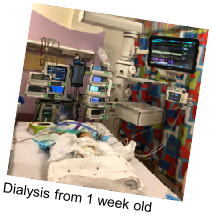
Challenges in Dialysing Infants

Ng Kar Hui
Associate Professor
Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

Senior Consultant
Division of Paediatric Nephrology, Dialysis and Renal Transplantation
Khoo Teck Puat – National University Children's Medical Institute
National University Hospital



Nephrotic syndrome from birth



Dialysis from 1 week old

How common in infant dialysis?

11-13% of children started in dialysis were infants

NAPRTCS 2022
ESPN/ERA-EDTA 1991-2013

What's in this talk?

Walk through the journey of a patient

Peritoneal Dialysis
Continuous Renal Replacement Therapy
Intermittent haemodialysis

Nutrition
Psycho-socio-emotional development

"Can you see this lady urgently?"

Antenatal counselling

- Etiology
- What to expect: antenatal, **postnatal**
- **Types of treatment**

- Financial counselling
- Genetics referral
- Palliative referral; peer family support

Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period

Karlijn J. van Stralen[1], Dagmara Borzych-Dużalka[2,3], Hiroshi Hataya[4], Sean E. Kennedy[5], Kitty J. Jager[1], Enrico Verrina[6], Carol Inward[7], Kai Rönnholm[8], Karel Vondrak[9], Bradley A. Warady[10], Aleksandra M. Zurowska[2], Franz Schaefer[3,12] and Pierre Cochat[11,12]; for the ESPN/ERA-EDTA, IPPN, ANZDATA and Japanese RRT registries

264 patients from 32 countries (ESPN/IPPN/Japan/ANZDATA)
Between 2000 and 2011
53% started in first week of life

Survival: 2-year 81%, 5-year 76%
After 2 years:
- Growth retardation (63%)
- Anemia (55%)
- Hypertension (57%)

Stralen, KI, 2014: 168

Outcomes of infants receiving chronic peritoneal dialysis: an analysis of the USRDS registry

Keia R. Sanderson[1], Yichun Yu[1], Hongying Dai[2], Laurel K. Willig[2], and Bradley A. Warady[2]
[1]University of North Carolina Department of Medicine-Nephrology, 7024 Burnett-Womack, CB 7155, Chapel Hill, NC 27599, USA
[2]Children's Mercy Hospitals and Clinics, Kansas City, Kansas City, MO, USA

1723 infants initiated chronic dialysis between 1990 to 2014.

Patient survival:
1 year 87% ; 5 years 74.6% (initiated as neonates)
1 year 89.6%; 5 years 79.3% (initiated as infants)
No difference

Common causes of death:
"Cardiac arrest" (congestive heart failure or electrolyte imbalance) (26%)
Infection (23%)

Pediatr Nephrol. 2019:155

Planning before delivery

- Obstetrician
- Neonatologist
- Surgeon
- Nephrologist
- NICU/ PICU team
- Palliative care physician

- PD / HD catheters
- Y connectors / other consumables
- Dialyzers
- Machines

Lungs

- Stabilise the baby
- Wait for 1-2 days

- FiO2
- PIP/PEEP
- Chest X ray

"How are the lungs?"

Kidneys

- Correct electrolytes
- Judicious fluids / IV frusemide
- BP control

- Urine output vs fluid requirements
- Serum creatinine
- Serum potassium/ acidosis

Should we dialyse this baby?

Beneficence
- Needed for survival. 8-10% can resolve *(CJASN 2018:1510)*
- Bridge to transplant

Nonmaleficence
- Risks of hypotension, electrolyte anomalies
- Multiple procedures
- Infections
- Financial burden
- Psychological burden

Local resources
Co-morbidities
Expected survival and QOL
Family's values

Autonomy

Distributive justice

Is it a physician's or family's decision?

When do we start dialysis?

eGFR?

- Anhydramnios, agenesis, anuria
- Acid-base electrolyte imbalance
- Fluid overload state
- Fluid requirement: Nutrition, blood products

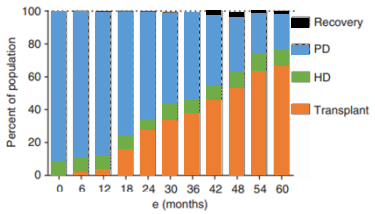
Kidney's trajectory
Patient's trajectory

Line access will be a problem

Plan early

Which modality should we choose?

264 patients from 32 countries (ESPN/IPPN/Japan/ANZDATA)
Dialysis in the neonatal period



HD/CRRT
Hyperoxaluria
Hyperammonemia
Abdominal surgery

Stralen, KI, 2014: 168

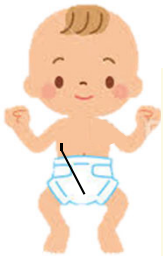
Why PD first?

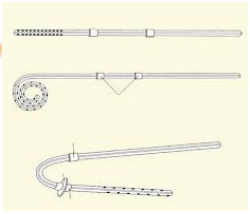
- Preserves vascular access
- Preserves residual kidney function

Less UF control

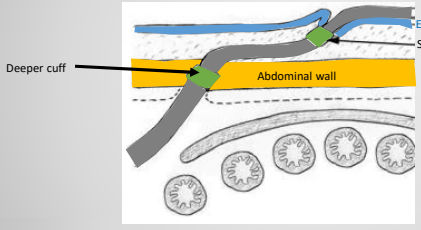
Talk to the surgeon!

Measure and plan cuffs and holes!





Exit above diaper line, away from stomas
Downward and lateral exit



Skin puncture, not incision

Tissue glue

Image source: Medscape Reference

Work processes in your programme

- Dedicated surgeon
- Nurse in operating theatre

Who handles the catheter?
- Immobilise
- Dressing

Prescribing the manual PD

- Set up Y connector
- 1.5% and 2.5%

- 10-15 ml/kg dwell

Half hourly cycles
- Inflow 1min
- Dwell 20-25min
- Drain 5-10min

Hourly cycles
- Inflow 1min
- Dwell 30-50min
- Drain 15-20min

Trial and error
Adjust accordingly

Tips

- IP Heparin 250-1000U/L
- IP Potassium 2-4 mmol/L
- Warming the dialysate

Leak = game over

Fill volume- go easy

If exit site is wet…
If leak happens- stop PD. Put tissue glue. Antibiotics

Question

Baby X is having PD for the second day.
Your nurse noted the gauze at exit site is wet.
You did a dipstick on the fluid- glucose +++

What is the *ideal* next step?
1) Decrease the fill volume
2) Start IP antibiotics
3) Decrease fill volume and start IP antibiotics
4) Stop PD, convert to CRRT / HD

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4) **Stop PD, convert to CRRT / HD**

Transiting to chronic PD

Fill volumes
- Age <2y: 800ml/m2
- Age >2y: 1100-1400ml/m2

Raised intraperitoneal pressures:
GERD, hernias

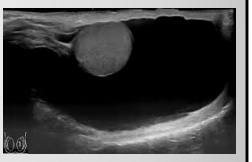


Image: wikipedia

Automated PD

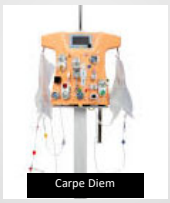
When fill volumes >60ml

Transiting to chronic PD

- Fluid balance, parental empowerment
  - Hypotension is common and dangerous.
  - Salt supplements

Continuous kidney replacement therapy
Haemodialysis


Conventional


Carpe Diem


Aquadex

Filters	Surface area (m2)	ECV (ml)	Blood flow (ml/min)	UF (ml/h)	Accuracy
Prismaflex HF20 (PAES) M60 (AN69)	 0.2 0.6	 60 93	 10-100 (+2) 50-200 (+10)	 0-500 (+10)	 10% of set UF
Aquadex	0.12	33	10-40 (+5)	0-500 (+10)	10%
Carpediem	0.075 0.15 0.25	27 33 41	2-50 (+1)	0-150 0-240 0-600	1g/h

Question

You are starting CRRT for a 3kg baby. You have this dialyzer in your centre.

Dialyzer	Material	SA (m^2)	Fill volume (ml)	
			Dialyzer	Dialyzer + Tubing
Prismaflex HF20	PAES	0.2	17	60

What percentage of the patient's blood volume is the extracorporeal volume?

1) 5%
2) 14%
3) 20%
4) 25%

Hint: Patient's blood volume = 80ml/kg

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Priming fluid

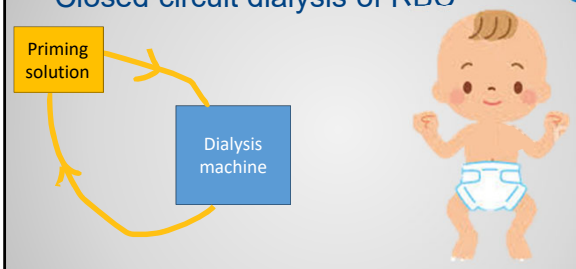
i. ECV <10% of blood volume: 0.9% saline.
ii. ECV 10-15% of blood volume:
- Normal Hb and BP/HR ok: **0.9% saline or 5% albumin.**
- Low Hb (<7 g/dL) or BP/HR ok: **diluted packed cells or whole blood.**

iii. ECV >15% of blood volume: **diluted packed cells or whole blood.**

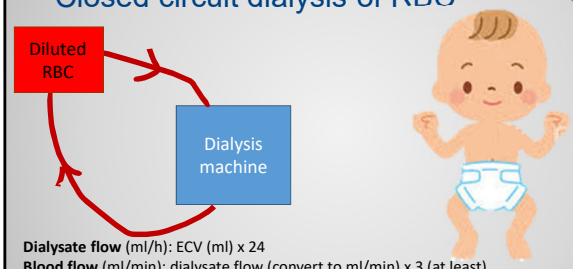
Diluting packed red cells 1: 1
- Sodium bicarbonate solution 140mmol/L
- Normal saline → Dialyse RBC

Give calcium!
AN69!

Closed circuit dialysis of RBC

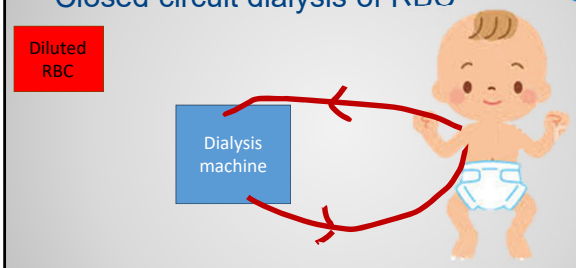


Closed circuit dialysis of RBC



Dialysate flow (ml/h): ECV (ml) x 24
Blood flow (ml/min): dialysate flow (convert to ml/min) x 3 (at least) 5-10min
Bolus heparin at 2U/ml of ECV , deduct from bolus at CRRT initiation

Closed circuit dialysis of RBC



Tips at starting CRRT / HD

- Start at low blood flow

Recommended target blood flow	Blood flow rate (Q_b) (ml/kg/min)	Typical blood flow (Qb) ranges (ml/min)
Neonates and infants	10-12	<8 kg: 30-80 ≥8 kg: 50-100

Adjust blood flow to achieve pressures:
- Access pressure: 0 to -150 mmHg (ideally near 0)
- Venous return pressure: 0 to +150 mmHg (ideally near 0)

Avoiding hypotension at CRRT initiation

- Ionised calcium level >1.1 mmol/L
- Fluid flushes, inotropes

- Blood, dialysate or replacement flow

- Check microelectrolytes early

Avoiding clotting of circuit

- CVVHDF pre-filter if possible
- Post-filter replacement of 50ml/h

- Heparin adjustments
- Trial and error, use previous doses

Ultrafiltration tips

- Hourly UF based on hourly continuous infusion rates
- Ad hoc fluids like antibiotics

- Net UF: Target <5% of body weight loss a day; max 10%

Is everyone on the same page?

Vascular catheters

4 chances only

Strategise and preserve vessels for future AVF and transplants

Body Weight	Catheters
<4 kg	6.5-7 F
4-10 kg	8 F
10-20 kg	9-10 F

Preferred: Right internal jugular vein
Avoid: Right femoral vein

Catheter: Fattest and shortest possible
Puncture, not cut-down

Citrate lock if possible

Ending the circuit

- RBC prime: do not return blood- why?

- If saline prime: return blood up to dialyzer (~2/3)- why?
Slow blood flow rate

Filters	Surface area (m2)	ECV (ml)	Blood flow (ml/min)	UF (ml/h)	Accuracy
Prismaflex					
HF20 (PAES)	0.2	60	10-100 (+2)	0-500 (+10)	10% of set UF
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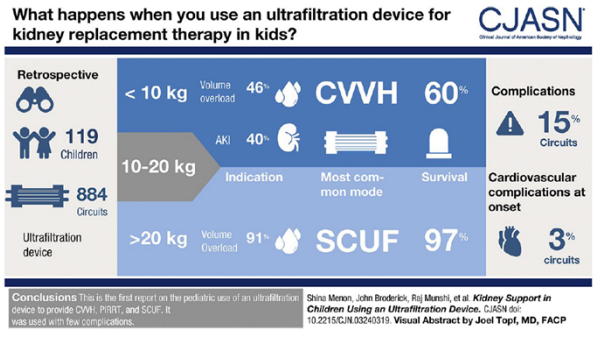
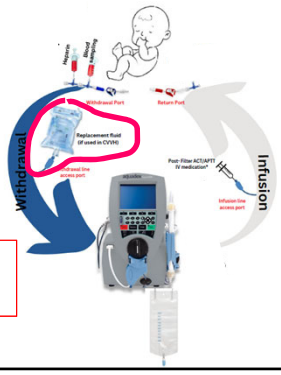
	0.15	33		0-240	
	0.25	41		0-600	

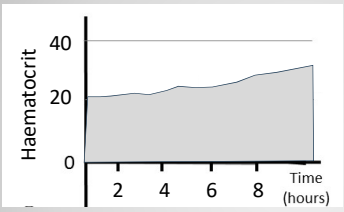


Replacement fluid volume is not included in UF



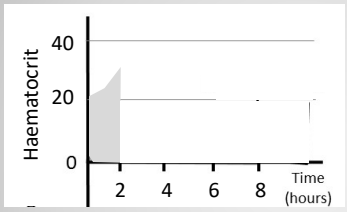
UF is stopped when haematocrit reaches target

Courtesy of transmedic



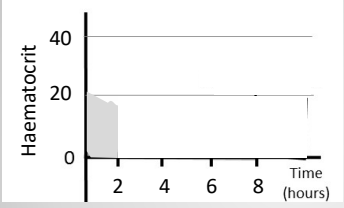
Baseline hematocrit
Set upper limit: 4-10% above baseline
UF is stopped when hematocrit reaches upper limit

Ideal: 1% rise per hour (patient specific)



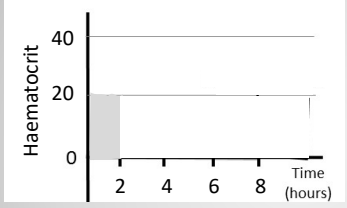
Rapidly rising hematocrit

- UF is too fast
- Packed cell transfusion



Decreasing hematocrit

- UF is too slow
- Ongoing blood loss



Flat hematocrit

- UF can be optimised further

Question

You are providing CVVH using Aquadex, an ultrafiltration device for a 3kg baby.

Blood flow: 30ml/min

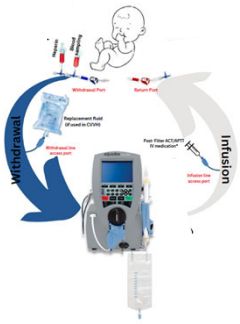
Replacement flow: 80ml/h

UF: 85ml/h

Your resident has stopped the UF because BP has become 68/30 mmHg. She is giving normal saline flush at 10ml/kg over 10min.

What should you do now?

1) Watch for patient's response
2) Stop replacement fluid
3) Decrease blood flow
4) Check vascular access



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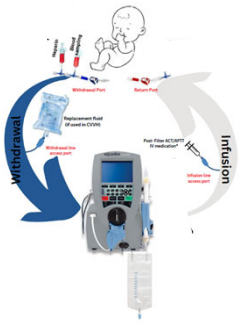
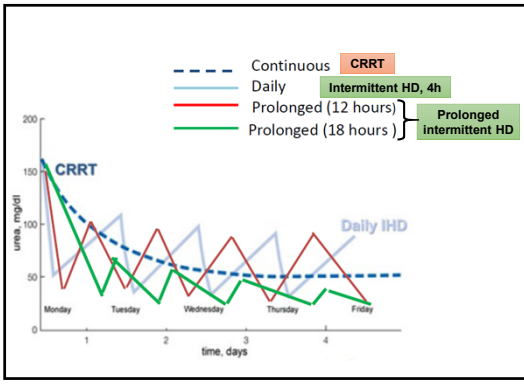


Transiting to chronic HD

Nutritional needs

- Gastrostomy
- Caloric density
- Timing/amount of feeds with dialysis



Balancing HD burden with nutritional needs

Frequent long dialysis

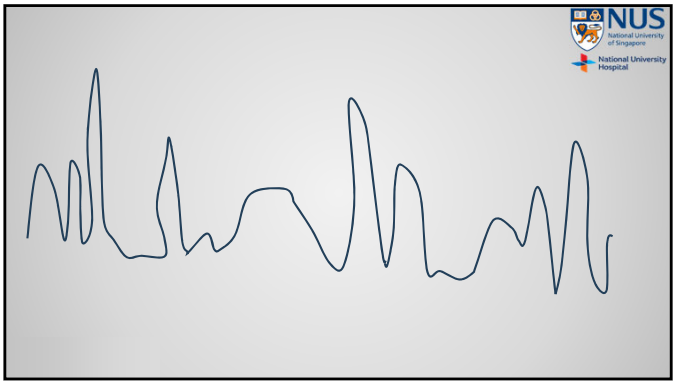
Nutritional needs

Psychological burden

Costs

Taking care of the family

Image from https://www.beautifulgatesouthafrica.org/



Take home messages

Peritoneal dialysis is the preferred mode of dialysis in infants
Preservation of vascular access is important

Conventional HD/CRRT machines are not designed for babies.
Aquadex is a promising mode of modality but there are many pitfalls.

Having standardised protocols and work processes are paramount for good outcomes

Thank you

Causes of kidney failure in neonates

Neonates

- Congenital anomalies of kidneys and urinary tract
- Autosomal recessive polycystic kidney disease
- Bilateral renal vein thrombosis
- Congenital nephrotic syndrome
- Inherited renal tubular dysgenesis
- Primary hyperoxaluria

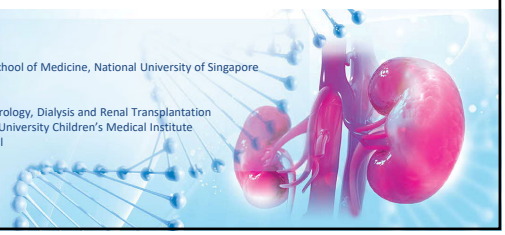
Others

- Cortical necrosis
- Other genetic causes

Genetics for the Practising Nephrologist

Ng Kar Hui
Associate Professor
Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

Senior Consultant
Division of Paediatric Nephrology, Dialysis and Renal Transplantation
Khoo Teck Puat – National University Children's Medical Institute
National University Hospital



Practising Nephrologist

Kidney biopsy

Knows how and when it can guide management
Understands the use of LM, IMF, EM
Reads the biopsy report /histology images with confidence
Calls the pathologist to discuss complex cases

Practising Nephrologist

Genetics testing

Knows how and when genetic tests can guide management
Understands the use of panels, WES, WGS, CMA
Reads the genetics report /genetics details with confidence
Calls the geneticists to discuss complex cases

Genetics for the Practising Nephrologist

Nephrologists don't understand Genetics very well

How do I make sense of Genetics to survive

I am assuming you know

DNA → RNA → protein

What's in this talk?

Spectrum of genetic kidney disease

Utility of genetic testing

Types of genetic tests

Basic reading of a genetics report

Spectrum of genetic kidney diseases

Diagnostic yield with genetic testing in patients

Category	Childhood onset CKD <18 years	Adult onset CKD ≥ 18 years	Number of genes
Kidney tubulopathies	70%	83%	50
Chronic glomerulonephritis	67%	79%	20
AD tubulointerstitial disease	NA	45%	5
CKD of unknown cause	-	40%	NA
Cystic kidney disease	50%	17%	92
Congenital anomalies of kidney and urinary tract (CAKUT)	17%	22%	40 isolated 153 syndromic
Steroid resistant nephrotic synd	26%	14%	59
Nephrolithiasis / calcinosis	25%	11%	38
Overall diagnostic yield	**30%**	**5-30%** (enriched for familial cases)	**457**

Panel / ES

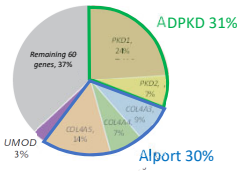
Connaughton, Hildebrandt. NDT (2020) 35: 390

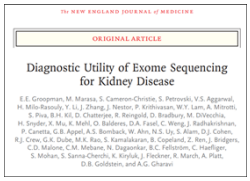
3315 patients with chronic kidney disease
Mostly adults (92%)
Mostly with no family history (72%)

1 in 10 had a *monogenic* disorder.

ADPKD and Alport is commonest genetic cause

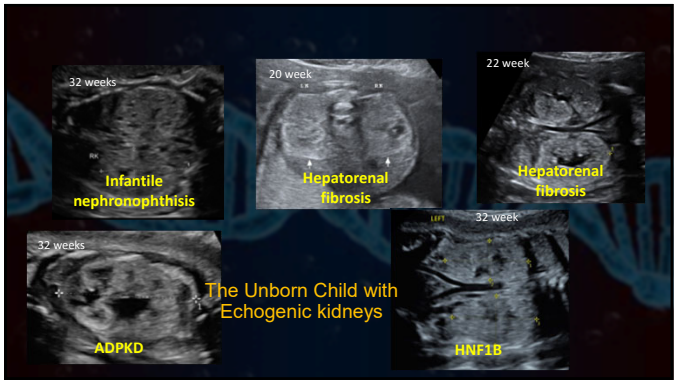
N=307 patients with genetic diagnosis




The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Diagnostic Utility of Exome Sequencing for Kidney Disease

Groopman, N Engl J Med

Utility of genetic tests

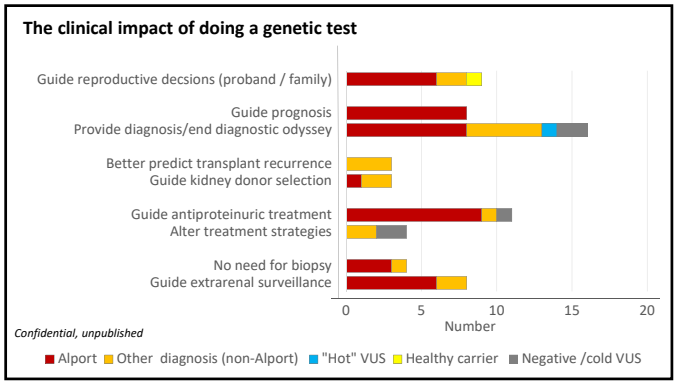


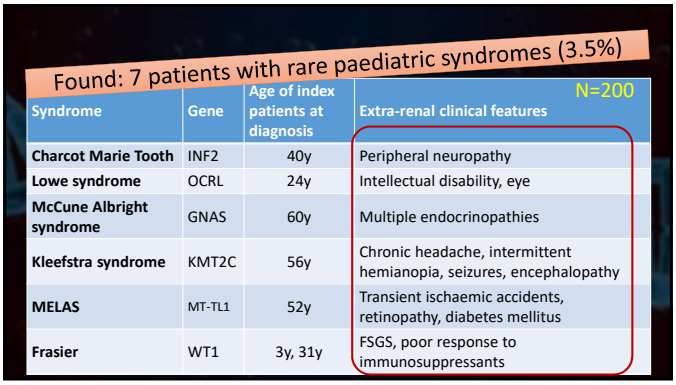
Diagnostic Utility and Clinical Implications of a Genetic Diagnosis

N=167 diagnosed patients

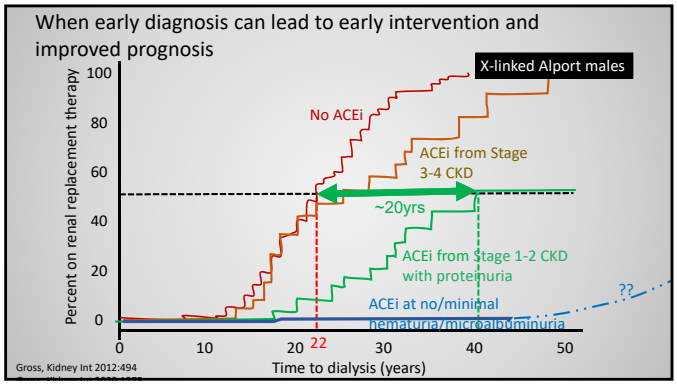
Diagnostic Utility of Genetic Findings	Patients	Genetic Diagnosis with Implications for Clinical Management* number (percent)
Confirmed suspected hereditary cause	45	34 (76)
Discerned specific subcategory of condition within broader clinical disease category	65	58 (89)
Reclassified disease	18	18 (100)
Identified molecular cause for undiagnosed condition	39	39 (100)
Total	167	149 (89)

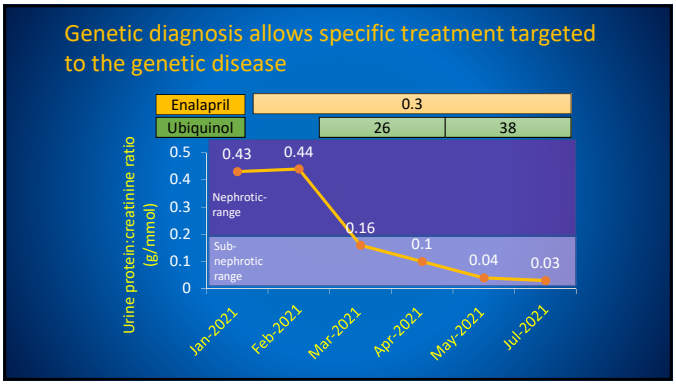
Groopman, NEJM, 2019

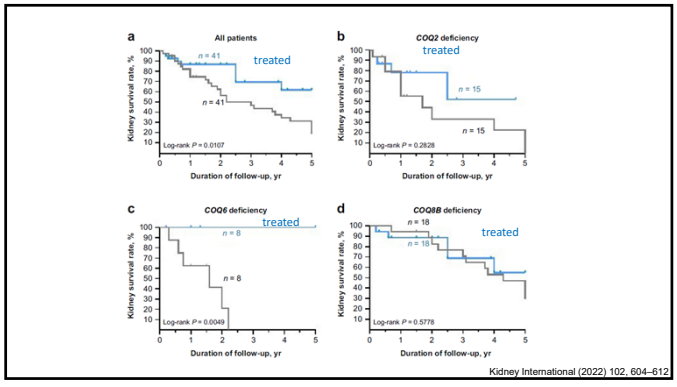


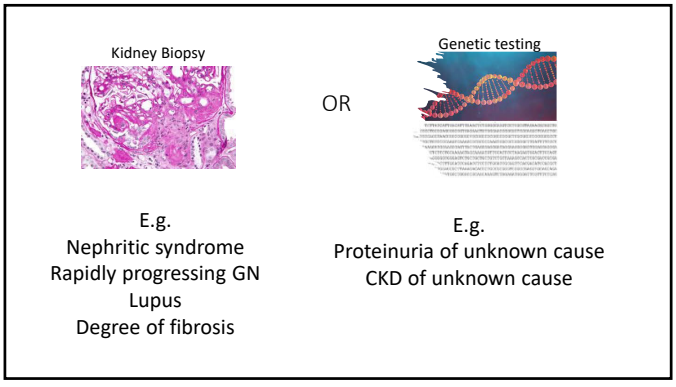


Syndrome	Gene	Age of index patients at diagnosis	Extra-renal clinical features
Charcot Marie Tooth	INF2	40y	Peripheral neuropathy
Lowe syndrome	OCRL	24y	Intellectual disability, eye
McCune Albright syndrome	GNAS	60y	Multiple endocrinopathies
Kleefstra syndrome	KMT2C	56y	Chronic headache, intermittent hemianopia, seizures, encephalopathy
MELAS	MT-TL1	52y	Transient ischaemic accidents, retinopathy, diabetes mellitus
Frasier	WT1	3y, 31y	FSGS, poor response to immunosuppressants



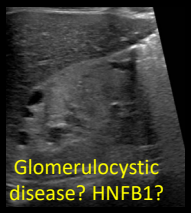




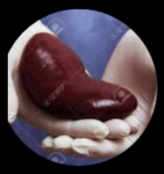


Guided decisions

Extrarenal surveillance

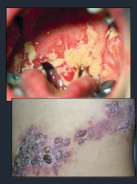


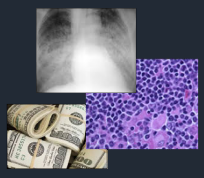
Kidney donor



Even a negative genetic report is helpful!

Immunosuppression

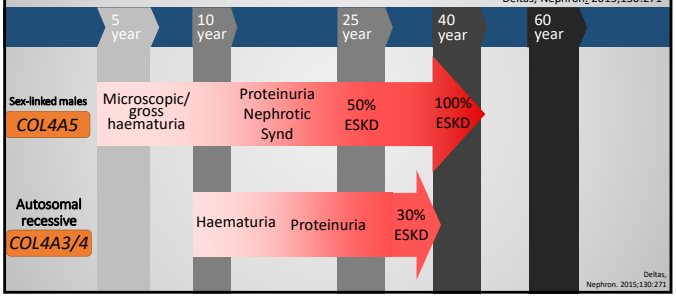




Informing disease trajectory

NATURAL HISTORY OF ALPORT SYNDROME

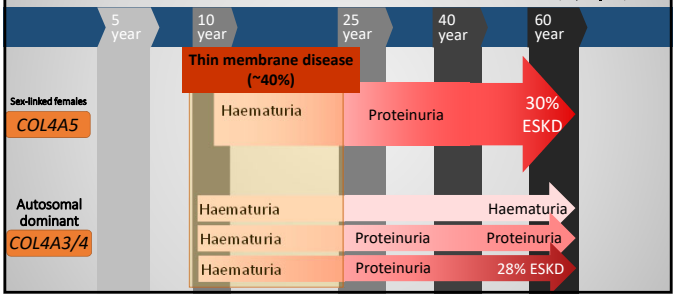
Deltas, Nephron. 2015;130:271



Informing disease trajectory

NATURAL HISTORY OF ALPORT SYNDROME

Hirabayashi Y. Genes (basel). 2022):1779.
Savige J. Kidney int. 2003:1169
Deltas, Nephron. 2015;130:271



A 15-year-old girl has microscopic haematuria and subnephrotic proteinuria. Normal kidney function.

Hearing test normal
No family history: Well 6-year-old brother. All first-degree family members were recently tested with urine dipstick.

Initial evaluation: no apparent cause.
Biopsy diagnosis: Alport syndrome- lamination and scalloping of GBM.

Should a genetic test be performed?
1) Yes
2) No

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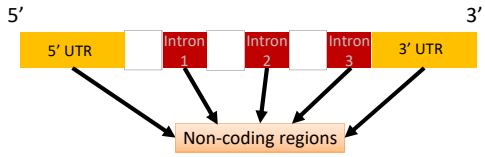
Should a genetic test be performed?
1) Yes
2) No

Types of genetic tests

Basic structure of a gene

Can variants in non-coding areas cause disease?

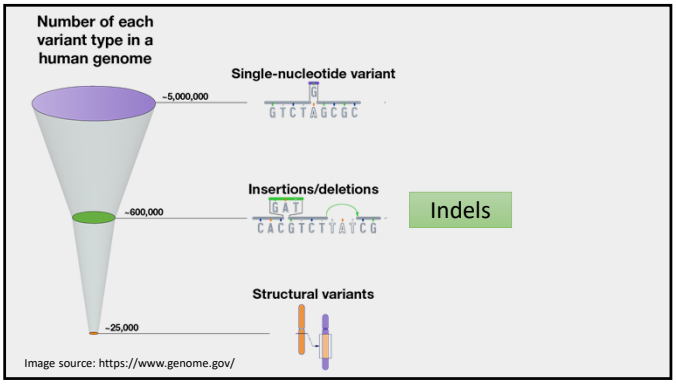


Does not affect sequence of the amino acids

May alter protein function through other ways:
- altering the level of gene expression
- splicing

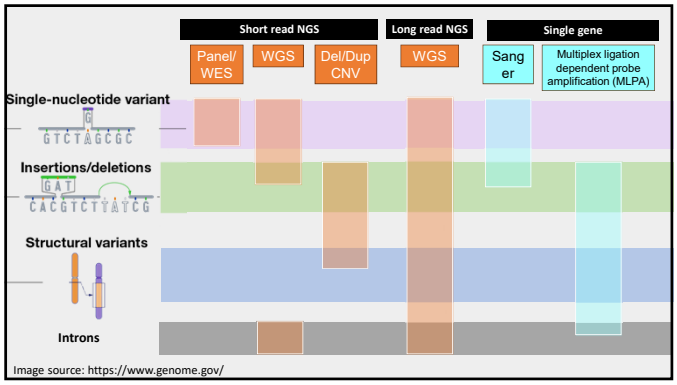
6 billion nucleotides
>25 million nucleotides (0.4%) are different

All of us have >5 million genetic variants



THE OWL HIT THE RAT BUT THE RAT DID NOT RUN OUT

THE OWL BIT THE RAT BUT THE RAT DID NOT RUN OUT.	Missense
THE OWL HHI TTH ERA TBU TTH ERA TDI DNO TRU NOU	Insertion
THE OWL ITT HER ATB UTT HER ATD IDN OTR UNO UT	Deletion
THE ~~OWL HIT THE RAT BUT THE~~ RAT DID NOT RUN OUT.	Inframe
THE OWL HIT THE RAT BUT BUT THE RAT DID NOT RUN OUT.	Inframe
THE OUT. ~~THE RAT DID NOT RUN OUT~~	Frameshift (nonsense)
THE OOO WLH ITT HER ATB UTT HER ATD IDN OTR UNO	Frameshift
THE RAT DID NOT RUN OUT. THE OWL HIT THE RAT BUT	Translocation
TUO NUR TON DID TAR EHT TUB TAR EHT TIH LWO EHT	Inversion



Comparing panel / WES / WGS

Less Panel — **More** WES — **All genes** WGS

Breadth

Depth (coverage)

Notorious genes
PKD1
HNFB1
MUC1

Ambiguous phenotype

Incidental findings

46-year-old lady
Presented at 40years old with A2 albuminuria and microscopic haematuria
Hypertension, preeclampsia
eGFR normal
Very strong family history

Mother (66y): Alport and CKD stage 4, hearing loss
Brother (29y): Hematuria since 22y
Maternal grandma: Hematuria and proteinuria since 70y+, dialysis since 80y+, neurosensory hearing loss
Maternal aunt (71y): Hematuria and proteinuria, nephrotic syndrome, impaired kidney, hearing loss
Mother's mother's father: high bp/DM/gout <40y, hematuria and proteinuria since ?age, impaired kidney no RRT, d. 50y+ kidney issues
Maternal cousin (43y): Hematuria, proteinuria and nephrotic syndrome since 8y
Maternal aunt (70y): Hematuria since 20y+, recent hearing loss
Maternal uncle (68y): Hematuria since 20y+, recent hearing loss

Panel of glomerular and cystic genes was done

Result: No genetic variant found

This patient may still have genetic kidney disease. Why?
1) Gene causing kidney disease has not been discovered.
2) Pathogenicity determination was inaccurate.
3) Genetic variant is in the intron.
4) Genetic variant cannot be picked up by the technique used.
5) All of the above.

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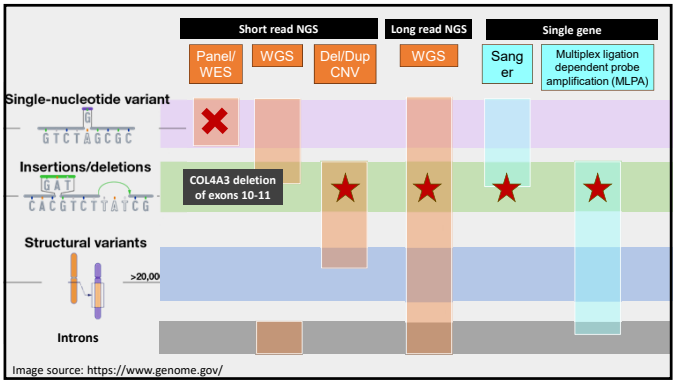


Basic reading of genetic reports

Modern terminology

5 categories

Genetic variants

1. Pathogenic
2. Likely pathogenic
3. Uncertain significance
4. Likely benign
5. Benign

based on a set of criteria

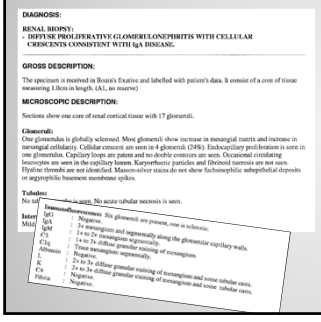
The ACMG matrix for classification

https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/

Is the variant causing the disease?

- Gene-phenotype
- Mode of inheritance
- Population frequency
- In silico tools
- Nature of variant
- Hot spot
- Nearby variants
- Functional studies
- Family segregation
- De novo
- Phenotype specificity
- Previous reported cases

Biopsy report



DIAGNOSIS:

RENAL BIOPSY:
- DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS WITH CELLULAR CRESCENTS CONSISTENT WITH IgA DISEASE.

GROSS DESCRIPTION:

The specimen is received in Bouin's fixative and labelled with patient's data. It consist of a core of tissue measuring 1.0cm in length. (A1, no reserve)

MICROSCOPIC DESCRIPTION:

Sections show one core of renal cortical tissue with 17 glomeruli.

Glomeruli:
One glomerulus is globally sclerosed. Most glomeruli show increase in mesangial matrix and increase in mesangial cellularity. Cellular crescent are seen in 4 glomeruli. (24%). Endocapillary proliferation is seen in one glomerulus. Capillary loops are patent and no double contours are seen. Occasional circulating leucocytes are seen in the capillary lumen. Karyorrhectic particles and fibrinoid necrosis are not seen. Hyaline thrombi are not identified. Masson-silver stains do not show fuchsinophilic subepithelial deposits or argyrophilic basement membrane spikes.

Tubules:
No tubular necrosis is seen. No acute tubular necrosis is seen.

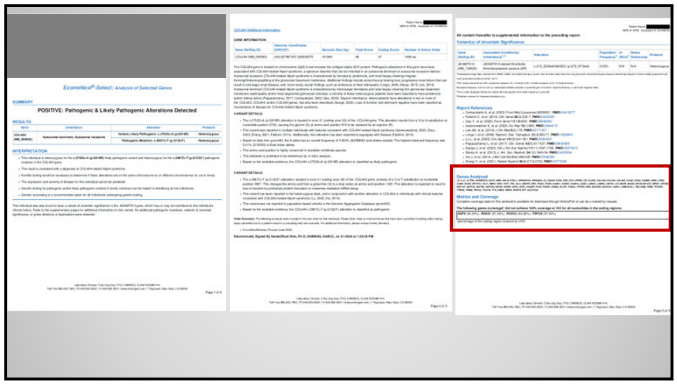
Immunofluorescence: Six glomeruli are present, one is sclerotic.
IgG : Negative.
IgA : 3+ mesangium and segmentally along the glomerular capillary walls.
IgM : 1+ to 2+ mesangium segmentally.
C3 : 1+ to 2+ diffuse granular staining of mesangium.
Albumin : Trace mesangium segmentally.
L : Negative.
K : 2+ to 3+ diffuse granular staining of mesangium and some tubular casts.
C4 : 2+ to 3+ diffuse granular staining of mesangium and some tubular casts.
Fibrin : Negative.

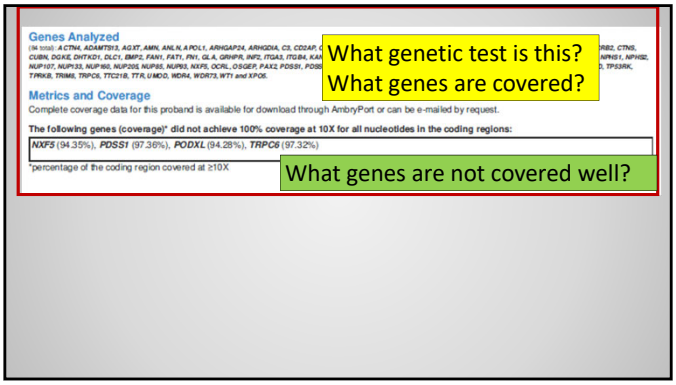
Genetics report

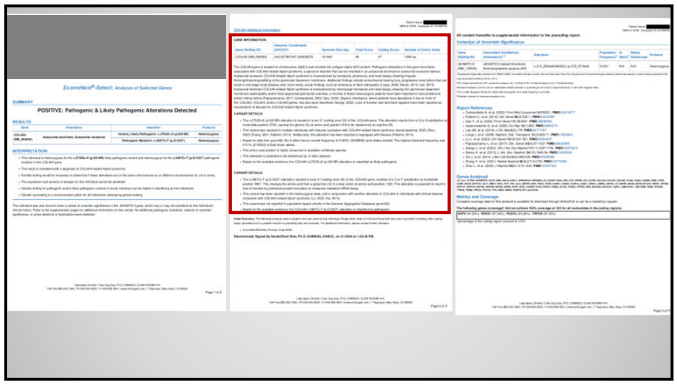
Variant(s) of Uncertain Significance

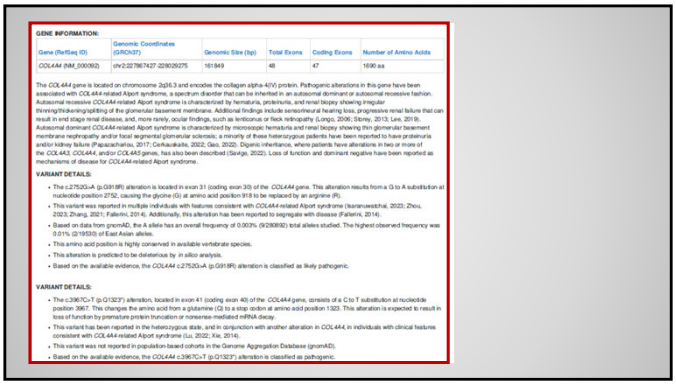
Biopsy report

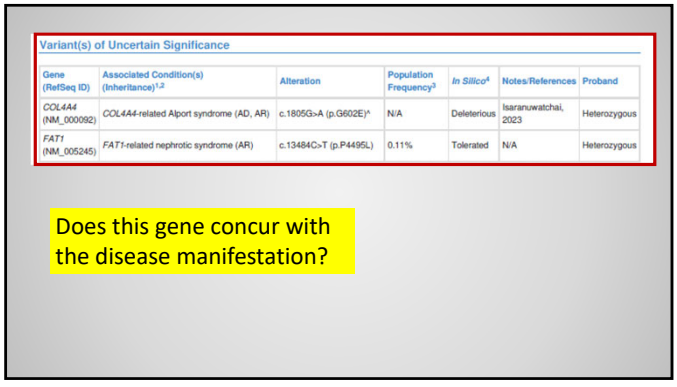
- 3 year old boy
- Microscopic haematuria and subnephrotic proteinuria
- Normal eGFR
- No extrarenal manifestation
- No family history







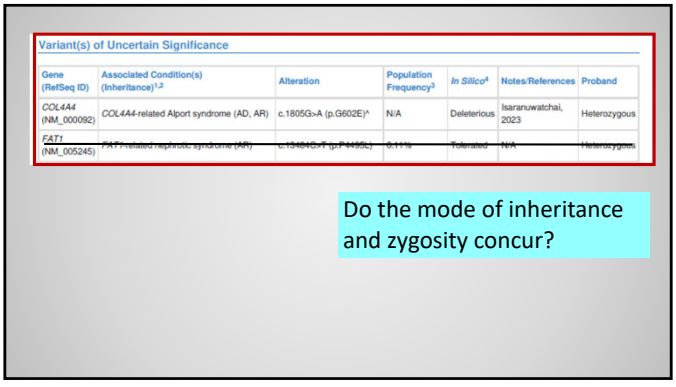




Variant(s) of Uncertain Significance

Gene (RefSeq ID)	Associated Condition(s) (Inheritance)[1,2]	Alteration	Population Frequency[3]	*In Silico*[4]	Notes/References	Proband
COL4A4 (NM_000092)	*COL4A4*-related Alport syndrome (AD, AR)	c.1805G>A (p.G602E)^	N/A	Deleterious	Isaranuwatchai, 2023	Heterozygous
FAT1 (NM_005245)	*FAT1*-related nephrotic syndrome (AR)	c.13484C>T (p.P4495L)	0.11%	Tolerated	N/A	Heterozygous

Does this gene concur with the disease manifestation?



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Do the mode of inheritance and zygosity concur?

GnomAD = Genome Aggregation Database https://gnomad.broadinstitute.org/

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Gene (RefSeq ID)	Associated Condition(s) (Inheritance)[1,2]	Alteration	Population Frequency[3]
COL4A4 (NM_000092)	*COL4A4*-related Alport syndrome (AD, AR)	c.1805G>A (p.G602E)^	N/A
FAT1 (NM_005245)	*FAT1*-related nephrotic syndrome (AR)	c.13484C>T (p.P4495L)	0.11%

Gene-specific
In general,
Recessive: Absent ≤0.00007 (0.007%)

Dominant ≤0.00002 (0.002%)

VARIANT DETAILS:

- The c.2752G>A (p.G918R) alteration is located in exon 31 (coding exon 30) of the *COL4A4* gene. This alteration results from a G to A substitution at nucleotide position 2752, causing the glycine (G) at amino acid position 918 to be replaced by an arginine (R).
- This variant was reported in multiple individuals with features consistent with *COL4A4*-related Alport syndrome (Isaranuwatchai, 2023; Zhou, 2023; Zhang, 2021; Fallerini, 2014). Additionally, this alteration has been reported to segregate with disease (Fallerini, 2014).
- Based on data from gnomAD, the A allele has an overall frequency of 0.003% (9/280892) total alleles studied. The highest observed frequency was 0.01% (2/19530) of East Asian alleles.
- This amino acid position is highly conserved in available vertebrate species.
- This alteration is predicted to be deleterious by *in silico* analysis.
- Based on the available evidence, the *COL4A4* c.2752G>A (p.G918R) alteration is classified as likely pathogenic.

In silico tools

Variant(s) of Uncertain Significance

Gene (RefSeq ID)	Associated Condition(s) (Inheritance)[1,2]	Alteration	Population Frequency[3]	*In Silico*[4]	Notes/References	Proband
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FAT1 (NM_005245)	*FAT1*-related nephrotic syndrome (AR)	c.13484C>T (p.P4495L)	0.11%	Tolerated	N/A	Heterozygous

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Is the variant causing the disease?

- Rule out
  - Gene-phenotype
  - Mode of inheritance
  - Population frequency
  - In silico tools
- Nature of variant
  - Hot spot
  - Nearby variants
  - Functional studies
- Family segregation
  - De novo
  - Phenotype specificity
- Rule in
  - Previous reported cases

- 15 years old, Chinese boy
- Persistent isolated haematuria with no albuminuria
- Mother has microscopic haematuria

Variant(s) of Uncertain Significance

Gene (RefSeq ID)	Associated Condition(s) (Inheritance)[1,2]	Alteration	Population Frequency[3]	*In Silico*[4]	Notes/References	Proband
ADAMTS13 (NM_139025)	*ADAMTS13*-related thrombotic thrombocytopenic purpura (AR)	c.392T>C (p.M131T)	N/A	Inconclusive	N/A	Heterozygous

[1]Disease/phenotype data collected from OMIM, HGMD, the medical literature, and/or internal Ambry data. Note that only genes with characterized gene-disease relationships based on clinical validity assessment will have associated conditions (Smith, 2017).
[2]AD= autosomal dominant, AR= autosomal recessive, XL= X-linked, XLR= X-linked recessive, XLD= X-linked dominant.
Recessive Diseases: Cannot rule out undetectable biallelic alteration or potential gain-of-function, haploinsufficiency, or dominant-negative effect.
[3]The number displayed reflects the highest ethnicity-specific minor allele frequency in gnomAD.
[4]Prediction relevant for missense alterations only.

Is this variant explaining the disease of the patient?

1) Yes
2) No
3) Maybe, needs further evaluation

- 15 years old, Chinese boy
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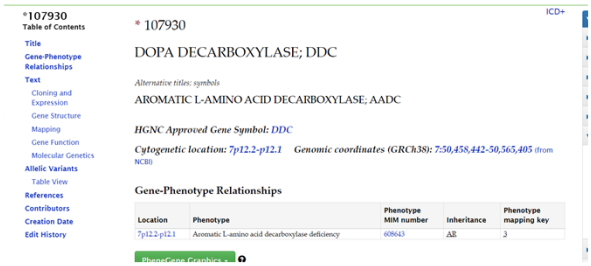
7 month old girl with mild edema and nephrotic range proteinuria.

SEQUENCE VARIANTS

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES **	TYPE AND CLASSIFICATION ***
DDC	NM_000790.3:c.1234C>T	p.(Arg412Trp)	rs542063660	Heterozygous	PolyPhen: - Align-GVGD: C0 SIFT: - MutationTaster: Disease causing Conservation_nt: moderate Conservation_aa: high	gnomAD: 0.000012 ESP: - 1000 G: 0.00020 CentoMD: -	Missense Pathogenic (class 1)

Variant annotation based on OTFA (using VEP v94). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

Search : DDC gene OMIM



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Dopa decarboxylase (DDC)
Autosomal recessive
Aromatic L-amino acid decarboxylase deficiency

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Gene-specific allele frequencies
In general,
Recessive: Absent ≤0.00007 (0.007%)

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WT1	NM_024426.4:c.1316G>A	p.(Arg439His)	rs121907901	Heterozygous	PolyPhen: - Align-GVDG: C25 SIFT: Deleterious MutationTaster: Disease causing Conservation_nt: high Conservation_aa: weak	gnomAD: - ESP: - 1000 G: 0.000026 CentoMD: 0.000022	

Variant annotation based on OTFA (using VEP v94). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

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Variant annotation based on OTFA (using VEP v94). * AlignGVD: C0: least likely to interfere with function, C65: most

Gene-specific
In general,

Dominant ≤0.00002 (0.002%)

RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (10

Take home messages

Nephrologists need to believe the utility of genetic testing, and then articulate it well.

Appreciating the pros and cons of different genetic tests (Panels, WES, WGS) allows one to know which tests to order, and appreciate false negatives.

Nephrologists can read genetic reports at a very basic level.
But the provision of genetic services requires multiple stakeholders.

Thank you

Nocturnal Enuresis: Evaluation and Management

Ng Yong Hong
Nephrology Service, Department of Paediatrics
22 August 2024

Objectives

1. Nocturnal enuresis (NE): definition and epidemiology
2. Pathogenesis
3. Evaluation of a child with nocturnal enuresis
4. Treatment strategy and options

Nocturnal Enuresis: Definition

- Enuresis is both a symptom and a condition of intermittent incontinence that occurs during sleep
- Symptom of incontinence requires a minimum
  - Age of 5 years
  - Frequency of 1 episode per month and
  - Duration of 3 months, to be termed a condition

Austin PF et al. The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Update Report From the Standardization Committee of the International Children's Continence Society. Neurourology and Urodynamics 35:471–481 (2016)

Nocturnal Enuresis: Definition

Term	Definitions	Notes
Primary nocturnal enuresis (PNE)	Wetting while asleep beyond 5 years, >1 episode per month for at least 3 months and never been dry for more than 6 months	Frequent enuresis if frequency >4 per week or infrequent if <4 per week ~75% have PNE
Secondary nocturnal enuresis	Bedwetting that recurred after extended period of dryness of more than 6 months	May be associated with stress, UTI and polyuric states ~25% have secondary NE
Primary monosymptomatic nocturnal enuresis (PMNE)	Bedwetting not complicated by daytime symptoms and absence of physical disease	~75% have PMNE
Non-monosymptomatic Nocturnal Enuresis (NMNE)	Bedwetting complicated by daytime symptoms of urgency with/without urge incontinence	~25% have NMNE

Non-Monosymptomatic Nocturnal Enuresis (NMNE)

- Children who, in addition to NE, have any of the following daytime lower urinary tract symptoms (LUTS)
  - Daytime incontinence
  - Urgency (sudden, unexpected and imperative urge to void)
  - Voiding difficulties (poor stream, hesitancy, need to strain to void)
  - Abnormally low or high daytime voiding frequency (voiding <4 or >7 times per day)
- Management of children with NMNE may differ from those with MNE

Useful Terms

- Bladder capacity
  - Estimated bladder capacity (EBC): ([age in years] X 30) + 30 (ml)
    - Formula applicable until early adolescence when adult capacity of 400 ml is reached
  - Can be evaluated through voided volumes via a voiding diary or a uroflow
- Nocturnal polyuria
  - Nocturnal urine production (weight of urine in sheet covers or diapers + 1st morning void) on a night with enuresis, of at least 130% of the EBC for the child's age

Nocturnal Enuresis: Epidemiology

- Higher incidence in males (male: female ratio 3:1)
- Estimated prevalence of ~15% of children at age of 5 years
- Typically resolves spontaneously at a rate of 15% per year with persistence at higher ages
- ~15% with nocturnal enuresis may experience encopresis
- Less than 3% of children referred to an enuresis clinic have an identifiable "organic" disorder

Age (years)	Prevalence
5	~15%
6	13%
7	10%
8	7%
10	5%
12-14	2-3%

Pathogenesis: Nocturnal Enuresis

- A complex problem!
- Likely multifactorial in origin:
  - Genetic factors
  - Physiological factors
    - Role of the bladder
    - Nocturnal polyuria
    - Role of central nervous system
  - Psychiatry and psychology factors

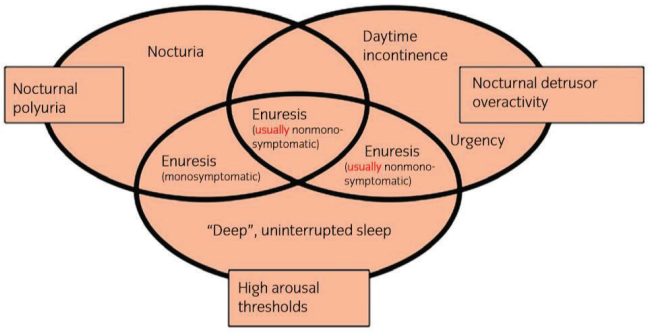
Genetic Factors

- Up to 75% of affected children have an affected 1st degree relative
  - 44% incidence when one parent is affected
  - 77% incidence when both parents have NE
- Greater concordance for bedwetting in monozygotic compared to dizygotic twins (twice the risk)
- Associated genetic loci on chromosomes 8q, 12q (ENUR 2), 13q (ENUR 1) and 22q11 identified on linkage analysis

Arnell H et al. The genetics of primary nocturnal enuresis: inheritance and suggestion of a second major gene on chromosome 12q. J Med Genet 1997; 34: 360-365
Wolfish NM et al. Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Paediatr 1997; 86: 381-384

Physiological Factors

- Role of the bladder
  - Small functional bladder capacity
  - Nocturnal detrusor overactivity
- Nocturnal polyuria
- Central nervous system
  - Associated sleep arousal disturbance
  - Bladder brain connection dysfunction
  - Global maturation delay



The three system model of enuresis pathogenesis

Pathogenesis of enuresis: Towards a new understanding. Tryggve Neveus. International Journal of Urology (2017) 24, 174--182

One Defect to Explain Them All?

- All 3 mechanisms may be due to underlying brainstem disturbance at the locus coeruleus (LC)
- Locus coeruleus: a noradrenergic neuron group in the upper pons
  - Crucial for sleep arousal
  - Overlaps both anatomically and functionally with the pontine micturition center (coordinates micturition reflex)
  - Has axonal connections with hypothalamic cells that produce ADH

Comorbidities in Nocturnal Enuresis

1. Behavioural issues
   - Low self esteem
   - NE and daytime voiding dysfunction more common among children with neuropsychiatric disturbances such as ADHD
     - 15% of children with ADHD have enuresis and vice versa
2. Constipation
3. Asymptomatic bacteriuria (does not require treatment)
4. Sleep disordered breathing

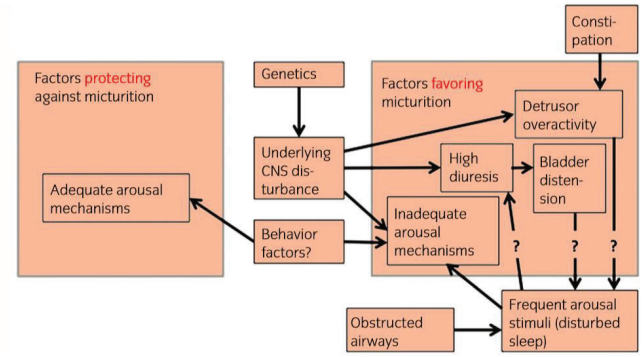
Requires consideration as they may influence prognosis &/or response to therapy

NE & Sleep Disordered Breathing

- 2 possible non-exclusive mechanisms
  1. Constant stimuli from obstructed airway causes paradoxically high arousal threshold
  2. Negative intrathoracic pressure causes polyuria via increased secretion of atrial natriuretic peptide

Psychiatry and Psychology

- Enuretic children suffer from subtle cognitive problems linked to sleep disturbance and that disappear when sleep is improved, regardless of outcome of NE treatment
- Psychiatric comorbidity observed to be more common among children with secondary enuresis
- Role of psychological stress or trauma



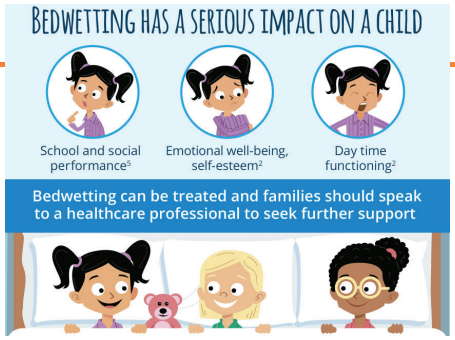
A hypothetic diagram of enuresis pathogenesis

Pathogenesis of enuresis: Towards a new understanding. Tryggve Neveus. International Journal of Urology (2017) 24, 174–182

	Evidence Status	Importance	Caveats and Comments
Renal mechanisms			
▪ Vasopressin deficiency (water diuresis)	Established	Major subgroup	Explanation for not waking up still needed. Might in some cases be consequence, as opposed to cause, of enuresis
▪ Non-free water polyuria (solute diuresis)	Established	Minor subgroup	
▪ Hypercalciuria	Poor	Unknown	Not causative per se, but possibly a by-product of polyuria
Urodynamic mechanisms			
▪ Detrusor overactivity	Established	Major subgroup	Could, in turn, have causes related to the bladder, bowel &/or the CNS
▪ Constipation	Decent evidence	Minor subgroup?	Causes enuresis via detrusor overactivity
Sleep and arousal			
▪ Low arousability	Decent evidence	Majority	Could possibly be consequence, as opposed to cause, of enuresis
▪ Sleep disruption		Major subgroup?	Could cause low arousability. Could, in turn, be caused by arousal stimuli from the bladder or the airways
▪ Airway obstruction		Minor subgroup	Causes enuresis via sleep disruption &/or polyuria
Psychology/psychiatry			
▪ Stress or trauma	Decent evidence	Minor subgroup	May be causative in a small minority and determine the occurrence of individual wet/dry nights in a larger group, acting via CNS effects on arousal or micturition reflex thresholds
CNS disturbance			
▪ Primary pontine lesion	Hypothetical	Unknown	Could, in turn, cause detrusor overactivity, low arousability, autonomous imbalance &/or polyuria
▪ Autonomous imbalance			More research needed
Anatomy			
▪ Urethral obstruction	Hypothetical	Unknown	More research needed

Proposed mechanisms linked to enuresis pathogenesis, their evidence status and relative importance in the enuretic population

Pathogenesis of enuresis: Towards a new understanding. Tryggve Neveus. International Journal of Urology (2017) 24, 174–182



World Bedwetting Day is held every last Tuesday in May to raise awareness among the public and healthcare professionals that bedwetting is a common medical condition that can and should be treated.

Source: WBD_2021_Flyer_1.pdf (worldbedwettingweek.com)

Effects of Prolonged Untreated NE

- Not all children outgrow NE with risk for persistence into adulthood highest among those with daily NE
- Adverse outcome on psychological development causing low self esteem, emotional well-being and poor social adjustment
- High risk groups
  - Non-monosymptomatic secondary enuresis
  - Therapy resistant nocturnal enuresis

Hagglof B et al. Self esteem before and after treatment in children with nocturnal enuresis and urinary incontinence. 1997. Scand J Urol Nephrol;31:79-82
Duel BP et al. A survey of voiding dysfunction in children with attention deficit hyperactivity disorder. J Urol 170: 1521-1524
Yeung CK et al. Characteristics of primary nocturnal enuresis in adults: an epidemiological study. 2006. BJU Int 97:1069-1073
Joinson C et al. A United Kingdom population-based study of intellectual capacities in children with and without soiling, daytime wetting and bed-wetting. Pediatrics 2007;120:e308-316
Iscan B et al. Evaluation of health-related quality of life and affecting factors in child with enuresis. J Pediatr Urol. 2020 Apr;16(2):195.e1-195

Who Should Be Treated?

- A child should be offered active treatment if
  - Above age of 6 years
  - The condition affects the child's normal social and emotional development
  - The condition affects the child's schoolwork

Evaluation of a Child with NE: Goals

1. Confirm the diagnosis
2. Identify the different subtypes
3. Identify early warning signs of organic pathologies
4. Assess for precipitating psychosocial dysfunction especially in a child with secondary NE
5. Formulate a treatment plan

A thorough medical history and examination forms the cornerstone for evaluation

Evaluation of a Child with NE: History

- Always engage the child and not just the parents / caregiver during history taking
  - It is the child's problems that requires intervention
  - The child needs to be involved in the therapeutic process

History	Relevance
General health and development ▪ Has growth been normal? Was there any nausea or weight loss? ▪ Any excessive thirst with polyphagia? ▪ Are there any developmental delays, particularly gross and fine motor?	 ▪ Renal disease ▪ Diabetes mellitus ▪ Underlying neurological condition
Enuresis history and fluid intake ▪ How frequent is NE per week? ▪ Are there changes in the frequency of NE over time? ▪ Has there been a prolonged dry period beyond 6 months? ▪ What is the overall and type of fluid intake and the relation of fluid intake to the time of day?	 ▪ Nightly NE is associated with poor prognosis ▪ Natural history of NE is spontaneous resolution ▪ Secondary NE is more often associated with psychological comorbidities ▪ Timing of fluid intake (increased afternoon or evening fluid intake) may suggest an aetiology of nocturnal polyuria (e.g. diabetes mellitus, diabetes insipidus)
Daytime symptoms ▪ How often does the child void (normal voiding: four to seven times per day)? ▪ Does the child experience daytime wetting or urgency? ▪ Any holding manoeuvres (legs crossing, pressing the heel into the perineum) or voiding difficulties (interrupted or weak stream or straining)? ▪ Any previous urinary tract infection?	Dysfunctional voiding or anatomical abnormality

History	Relevance
Bowel habits ▪ Are the bowel frequency and habits suggestive of constipation?	Constipation may reduce the bladder capacity
Review of systems ▪ Does the child snore at night? ▪ Any gait abnormalities? ▪ Any staring spells? ▪ Any perianal itching or vulvovaginitis?	 ▪ Obstructive sleep apnoea ▪ Spinal dysraphism ▪ Seizure disorder ▪ Pinworms
Family history ▪ Is there a family history of NE?	Genetic factors may contribute to NE
Behavioural problems ▪ How has bedwetting affected the child (at home or in school)? ▪ How are caregivers coping or supporting the child?	Severe behavioural problems may need to be addressed concomitantly with NE therapy

Ong LM, Leow EHM, Ng YH et al. Approach to nocturnal enuresis in children. Singapore Med J 2024;65:242-8.

Evaluation of a Child with NE: Examination

- General physical examination with focus on
  - General health
  - Signs of occult spinal dysraphism (lower back findings, leg and anal cleft asymmetries, abnormal neurology of the lower limb)

Physical examination	Examination findings	Possible significance
General appearance	Poor growth	Renal disease
Blood pressure	Hypertension	Renal disease
Ear, nose, throat	Large tonsils Swollen nasal turbinates	Tonsillar hypertrophy which may contribute to OSA Allergic rhinitis which may contribute to OSA
Developmental assessment	Delayed development	Possible neurological conditions
Abdomen	Palpable faecal masses Palpable bladder	Constipation
Perineum	Wetness in undergarments Perianal excoriation or vulvovaginitis Observation of slow urinary stream, straining, dribbling, intermittent stream	Daytime incontinence Natural history is spontaneous resolution Urological abnormality
Neurological exam	Abnormal neurological examination of the perineum and lower extremities	Spinal lesions which may result in neurogenic bladder/bowel
Spine	Cutaneous stigmata of spinal dysraphism (sacral dimple, naevus, lipoma, tufts of hair over the midline, abnormal or asymmetric gluteal cleft)	Underlying spinal cord abnormalities (spina bifida, tethered cord, cord lipoma, persistent dural sinus)

Ong LM, Leow EHM, Ng YH et al. Approach to nocturnal enuresis in children. Singapore Med J 2024;65:242-8.

Red Flags in Nocturnal Enuresis

Daytime Symptoms	Daytime incontinence Voiding>7 or <4 times per day Sudden and urgent need to urinate Straining to void Holding manoeuvres (leg crossing, pressing the heel into the perineum) Interrupted or weak stream of urine
Significant History	Secondary nocturnal enuresis Encopresis Marked behavioural symptoms Loss of weight, failure to thrive Previous febrile or recurrent urinary tract infections Previous pelvic/urological surgery/interventions Abnormal antenatal scans of kidneys or urinary tract
Significant findings on physical examination	

Ong LM, Leow EHM, Ng YH et al. Approach to nocturnal enuresis in children. Singapore Med J 2024;65:242-8.

Evaluation of a Child with NE: Investigations

- Urine tests
  - Urine dipstick / UFEME will suffice (for glucosuria and leukocytes)
    - Urine culture (only if indicated) to exclude UTI
    - Urine specific gravity or urine osmolarity if there is significant polyuria
- Blood tests only indicated if there is glucosuria or warning signs of kidney failure
- Voiding chart / diary
  - Recommended in initial evaluation of all enuretic children
  - Must be done in non-monosymptomatic NE
  - Standard voiding chart should include assessment of incontinence (night or day) for at least 1 week, daytime voided volumes and fluid intake for at least 2 days

Evaluation of a Child with NE: Investigations

- Imaging studies are generally not indicated unless
  - Diurnal voiding symptoms, evidence of UTI, neurological signs or other concerns
  - Type and extent of imaging studies will depend on patient profile
    - Ultrasound kidneys and bladder
    - US rectum
      - Confirm a suspicion of constipation unrecognized by the family
      - Transversal rectal diameter behind the bladder >30 mm is suggestive of rectal impaction
    - Uroflow and bladder scan with post void residual volume
    - Micturating cystourethrogram (MCU)
    - Urodynamics study
    - MRI Spine

Uroflow: Prerequisites

- Child must be toilet trained
- Adequate amount of voided volume
  - Curves change when voided volume is <50% of expected bladder capacity for age
- Obtain more than one curve to improve accuracy, reliability and interpretation of the test
- Uroflowmetry may be done with or without electromyography (EMG) testing of the perineal muscles
  - Ability to appreciate synergy or dyssynergy between the bladder and the pelvic floor if EMG is combined with uroflowmetry

Uroflow: Normal Values (PVR)

- Post void residual (PVR) urine
  - Redefined as single PVR ≥30 ml or ≥21% of Bladder Capacity (BC) in children aged ≤ 6 years OR ≥20 ml or ≥15% of BC for age ≥7 years
- Elevated PVR: lower value of 2 consecutive PVRs ≥20 ml or ≥10% BC in children aged ≤6 years OR ≥10 ml or ≥ 6% BC for age ≥7 years
- Prerequisites
  - Bladder should not be underdistended (<50%) or overdistended (>115%) in relation to EBC
  - PVR should be obtained immediately after voiding (<5min)

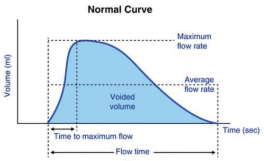
Age- and gender-specific nomograms for single and dual post-void residual urine in healthy children. Shang-Jen Chang et al. Neurourol. Urodynam. 32: 1014–1018, 2013

Uroflow: Normal Values (Bladder Capacity)

- Estimated bladder capacity (EBC)
  - EBC = (age in years x 30) + 30ml for age >5years (Butler/ Hjalmas formula)
- Bladder capacity: voided volume + PVRU

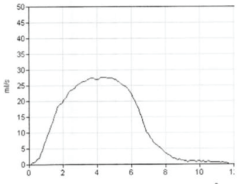
Uroflow: Normal Values (Qmax, Qave)

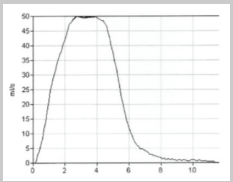
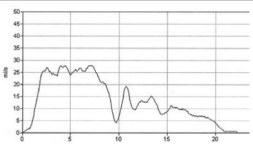
- Maximum flow rate (Qmax) is the most relevant quantitative variable when assessing bladder outflow
  - Sharp peaks in the curve are usually artefacts
  - Maximum flow rate should be registered only when a peak level has a duration of >2sec
  - If the square of the maximum flow rate[$(ml/s)^2$] ≥ voided volume (ml), the recorded maximum flow is most probably normal
- Qave: average flow rate
  - 85% < Qave > 50% Qmax



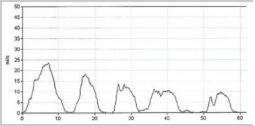
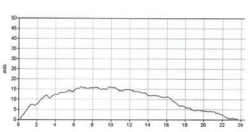
Uroflow Curves

- Precise shape is determined by detrusor contractility and influenced by abdominal straining, coordination with the bladder outlet musculature and any distal anatomic obstruction
- Bell Shaped: Normal

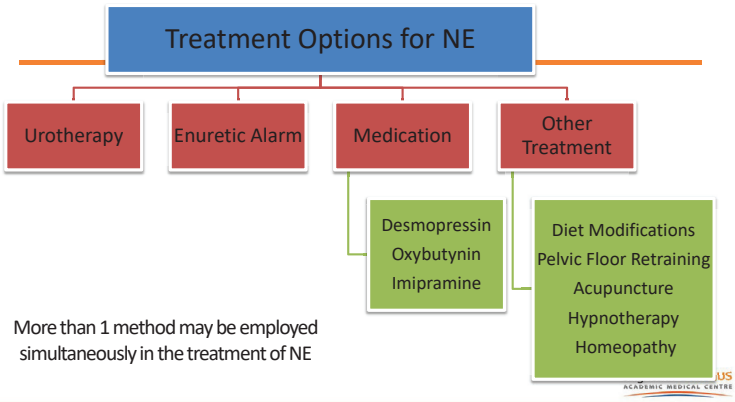


Uroflow Curve Shape	Description	Notes	
Tower Shaped	Sudden, high-amplitude curve of short duration that Qmax >25ml/s	May suggests an **overactive bladder** produced by an explosive voiding contraction	
Staccato-shaped	Irregular flow pattern and fluctuating throughout voiding but the flow is continuous, never reaching zero during voiding and with sharp peaks and troughs in the flow curve	Suggests **incoordination of the bladder and the sphincter** with intermittent sphincter overactivity during voiding (i.e. dysfunctional voiding)	

Age- and gender-specific nomograms for single and dual post-void residual urine in healthy children. Shang-Jen Chang et al. Neurourol. Urodynam. 32: 1014–1018, 2013

Uroflow Curve Shape	Description	Notes	
Interrupted-shaped curve	Flow will display discrete peaks with spikes similar to a staccato-shaped curve but with segments where zero flow with complete cessation between these peaks exists Each peak represents abdominal muscle straining creating the main force for urine evacuation. In between each strain, the flow ceases	Suggests an **underactive bladder** Flow pattern can be seen with incoordination between the bladder and external urethral sphincter	
Plateau-shaped curve	Fattened, low-amplitude prolonged flow curve that is Flow electromyography (EMG) may differentiate between BOO subtypes Abdominal pressure monitoring during the uroflow can help delineate an underactive bladder condition	Suggests **bladder outlet obstruction** (BOO). BOO can be anatomical (e.g. PUV or urethral stricture) or dynamic. (e.g., continuous, tonic sphincter contraction) May also be seen with an **underactive bladder** during a long continuous abdominal strain	

Age- and gender-specific nomograms for single and dual post-void residual urine in healthy children. Shang-Jen Chang et al. Neurourol. Urodynam. 32: 1014–1018, 2013



More than 1 method may be employed simultaneously in the treatment of NE

Treatment of Nocturnal Enuresis: Goals

- Goals of NE treatment
  - Reducing total number of enuretic nights
  - Avoiding enuresis on specific nights in specific locations
  - Stress reduction for the child and family
  - Avoidance of NE recurrence

Treatment of Nocturnal Enuresis: Education

- First line treatment for NE
  - Invest in time to educate, reassure, engage and should include goal setting and prognosis
  - Address myths and dispel practices that may not work
    - Regular waking by parents, lifting
    - Excessive restriction of the child's fluid intake

Urotherapy in NE

- Establish regular voiding habits with micturition ~5-6 times/day
- Advice on good hydration and fluid intake habits
  - Shift fluid intake by drinking 2/3 of total daily fluids during the morning to early afternoon and rest of 1/3 in the remainder of the day
- Reduce consumption of diuretic fluids
- Avoid excessive fluid intake 1-2 hours before bedtime
- Empty bladder immediately before bedtime
- Treat constipation if present
- Keep both a bladder and bowel diary for indicated cases

Urotherapy in NE

- Especially beneficial in NMNE to normalize function of the bladder during daytime which will improve function at night
- Further education (urotherapy) may need to include
  - Normal bladder function and voiding habits
  - How the child differs from normal
  - How to change voiding behaviour (posture, timing, holding maneuvers)

Motivational Therapy (Positive Reinforcement)

- Motivational therapy following urotherapy is helpful for motivated children
  - Shown to be 25% effective with a relapse rate of ~5% and reported symptom improvement in 80% of patients between 5-7 years with mild symptoms
  - Star Charts
- Punishment is NOT an acceptable treatment option
- Allow 6 weeks to evaluate effectiveness of behavioural therapy before implementing other treatment strategies

Monosymptomatic NE: 1st Line Treatment

- Enuretic Alarm (evidence level Ia)
- Desmopressin (evidence level Ia)

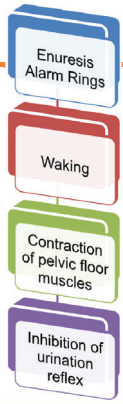
Enuresis Alarm

- Device which gives a strong arousal stimulus, usually acoustic, to the child and family when urine activates a detector located in the child's bed or clothing

Different Types of Enuresis Alarms

Enuresis Alarm

- Serves as a conditioning device using a noise to link the stimulus of a full bladder beginning to void with the desired behaviour of inhibiting micturition and waking



Enuresis Alarm

- Usually combined with motivational therapy
- Effectiveness
  - Effective in up to 70% of patients with NE
  - At least 2/3 of these will remain dry after treatment
  - Non inferior to desmopressin in children who are motivated and able to understand the alarm system
- Favorable prognostic indicators for alarm therapy
  - Frequent enuresis
  - A motivated child and family

Enuresis Alarm

- Considerations as choice of therapy
  - Suboptimal compliance if parents have sleep problems or if the child shares a room with siblings
  - Concomitant ADHD (↓ success rate)
  - NOT recommended for infrequent or periodic enuresis
  - May not be 1st choice as monotherapy if child wets more than once per night

Enuresis Alarm: Practical Tips

1. The alarm should only be used by well-motivated, well informed families
2. The device should be demonstrated for both child and parents
3. The alarm needs to be used continuously, every night without interruption
4. The parents need to be prepared to wake the child immediately when the signal is heard
5. The healthcare provider should contact the family after 1-3 weeks to give encouragement and solve technical problems during this crucial period
6. If there is no sign of progress after 6 weeks, therapy should be stopped
7. If there is progress (smaller wet spot, occasional dry nights) then therapy should be continued until 14 consecutive dry nights have been achieved

Medication: Desmopressin

- Synthetic analog of anti diuretic hormone (ADH)
- Mechanism of action
  - Reduce nocturnal urine production to a level which can be accommodated within the bladder
- Effectiveness
  - ~1/3 of children with NE will be dry as long as they take the drug, 1/3 will have no benefit and 1/3 will have an intermediate response
  - Recurrence rate of up to 70% following discontinuation
- Favorable prognostic indicator for desmopressin
  - MNE who have nocturnal polyuria and normal daytime voided volumes
- Also suitable for use in children with poor arousability where enuresis alarms tend to fail

Medication: Desmopressin

- Formulations approved for use in NE
  - Tablet
  - Sublingual preparation (preferred)
  - **Nasal preparation not for treatment for NE**
- Dosing
  - 0.2-0.4mg (tablet preparation), 120-240mcg (sublingual preparation)
  - Medication given 60 min before bedtime
  - May either start with the full dose and titrate down after a week or so in case of good treatment effect or adopt the opposite strategy
- Efficacy will be immediately evident
  - Avoid prolonged medication more than 1-2 weeks in a child who has no beneficial effects of the therapy

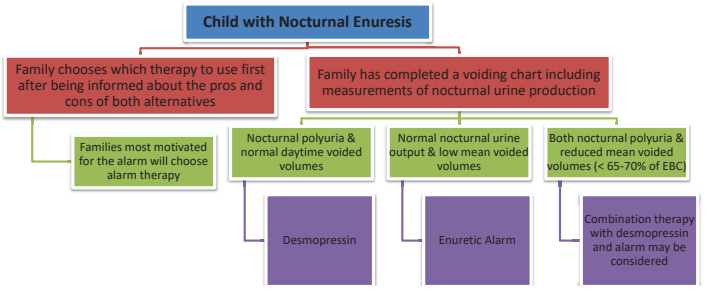
Medication: Desmopressin

- Can be used long-term without substantial risks and side-effects are rare
- Key contraindication for habitual polydipsia
- Risk of water intoxication with hyponatremia if medication is combined with excessive fluid intake
- Caution on excessive fluid intake while on desmopressin especially in the hour before bedtime and during the night

Medication: Desmopressin

- If the child is dry on therapy
  - Family and child can decide whether to use the drug every evening or just on "important nights"
  - Drug holidays needed to assess if treatment is still needed for former strategy
    - Some evidence to suggest that probability of continued dryness after therapy is slightly higher if medication is discontinued gradually by reducing dosage over a couple of weeks or months before stopping

1st Choice of Therapy: Which One?



Emphasis on the prognostic indicators for desmopressin or the alarm may be used as a guide

Evaluation of NE Treatment

- Definition of treatment success in NE

Success type	Definition	Term
Initial	0%-49% decrease in symptom frequency	Non response
	50%-99% decrease in symptom frequency	Partial response
	100% decrease in symptom frequency	Full response
Long Term	>1 symptom recurrence in 1 month	Relapse
	≥6 months without relapse off treatment	Continued success
	≥2 years without relapse off treatment	Complete success

- If 1st first choice therapy has no response, the other alternative should be offered
- If both fails as monotherapy, combination of the two can be considered

Austin PF et al. The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Update Report From the Standardization Committee of the International Children's Continence Society. Neurourology and Urodynamics 35:471–481 (2016)

Therapy-Resistant Enuresis

- Review with the following focus
  - History
    - Extra focus on comorbidities (constipation, sleep disordered breathing and behavioural issues) and reasons for failure of first-line therapy
      - Common pitfalls: Improper alarm used or improper technique
      - Diet (high evening salt and/or protein intake) may be suspected to influence negatively desmopressin response
      - Constipation must be treated
      - Role of other specialty review: psychologist, sleep / ENT
  - Examination: Focus on signs of spinal dysraphism

Therapy-Resistant Enuresis

- Review with the following focus
  - Investigations
    - Voiding chart including nocturnal urine production assessment
      - Presence of nocturnal polyuria → desmopressin can be considered as part of a combination treatment
    - Uroflow and residual urine measurement
      - Finding of pathological curves or post-void residual urine on repeated measurements implies
        - Anatomic obstruction or neurogenic bladder should be excluded
        - Anticholinergic treatment is contraindicated

Medication: Anticholinergics

- 2nd line therapy for NE
- Often in combination with desmopressin (evidence level Ib)
- Rationale
  - Role of detrusor overactivity especially in NMNE or NE nonresponsive to desmopressin therapy
- Child should not have significant residual urine and constipation is excluded or successfully treated
  - Treatment for constipation should continue while on anticholinergics
- Side-effects
  - Constipation, postvoid residual urine and dry mouth
  - Psychiatric side-effects such as mood swings (sometimes with oxybutynin)
- Effective (57-66%) in children refractory to initial therapies

Medication: Anticholinergics

- Only oxybutynin is available for label use in children

Table 2 Proposed dosage of anticholinergics in nocturnal enuresis.

Drug	Proposed dosage[a]
Oxybutynin	2.5–5 mg
Tolterodine[b]	2–4 mg
Fesoterodine[b]	4–8 mg
Solifenacin[b]	5–10 mg

[a] All doses are oral tablets given 1 h before bedtime.
[b] Not yet approved for label use in children.

- Effect should be evaluated after 1-2 months
  - Insufficient reduction of wet nights but no side-effects → desmopressin may be added (in standard dosage) and anticholinergic dose increased OR
  - Start with combination therapy and then try to discontinue desmopressin
- If there is good effect, gradually discontinue medication every 3rd month

Nevéus T et al. Management and treatment of nocturnal enuresis-an updated standardization document from the International Children's Continence Society. J Pediatr Urol. 2020 Feb;16(1):10-19. doi: 10.1016/j.jpurol.2019.12.020. Epub 2020 Jan 30. PMID: 32278657.

Anticholinergics: What to be aware of

- Residual urine should be measured once after 3-6 months
  - New measurements should be made if
    - If the drug is used twice daily due to concomitant daytime incontinence
    - Development of UTI symptoms
- If initial therapeutic response is good but the wet nights start to recur → assess for constipation
  - Temporary discontinuation of anticholinergic medication while constipation is treated often leads to dryness when the drug is reintroduced
- Mirabegron (noradrenergic) proven to be an efficient and safe addition or alternative to anticholinergics in adults with detrusor overactivity
  - Role in children with enuresis to be determined

Medications: Imipramine (TCA)

- Can be used by specialists as a 3rd line therapy if desmopressin, alarm and anticholinergics have all been unsuccessfully tried &/or are contraindicated (evidence level Ia)
- Mode of action unclear
  - May be due to a combination of noradrenergic, serotoninergic and anticholinergic action on the bladder, urine production and arousal mechanisms
- 30-50% of therapy resistant children with NE may benefit from imipramine
  - Proportion increases if desmopressin is added
- No known clear prognostic indicators for imipramine therapy

Medications: Imipramine (TCA)

- Dosage 25-50 mg, administered ~1 Hour before bedtime
- Assess for therapeutic response after 1 month. Desmopressin may be added if the effect is incomplete
  - Alternative strategy: start with desmopressin combination therapy
- If treatment is successful, regular drug-free periods should be interspersed to reduce the risk for tolerance
  - Potential strategy: drug holiday of 2 weeks is given every 3rd month
- Drug discontinuation should be done gradually, with dosage halved for 1-2 weeks, to reduce risk for side-effects on discontinuation

Imipramine (TCA): What to be aware of

- Key factor limiting use in enuresis: cardiotoxicity
  - ECG should be done before initiation of drug if child has any history of unclear syncope, palpitations or a positive family history of sudden cardiac death
- Drug should be securely locked
- Recommended dosage should never be exceeded
- Most common and limiting side-effects in clinical practice
  - Mood swings and nausea
- Tendency for tolerance
  - An initially good effect may fade over time

New Attempts with the Enuresis Alarm?

- Applicability
  - Children who have not responded to 2nd &/or 3rd line therapy, should be encouraged to try the enuresis alarm again
  - Children who are dry on medication may desire for a therapy that allows for a chance to stay dry without taking drugs
- Encourage children to make fresh attempts with alarm therapy every 2 years for those with treatment resistant NE

New Attempts with the Enuresis Alarm?

- Prior to new attempts, the family should complete a voiding chart including measurements of nocturnal urine production
  - If nocturnal polyuria is present, consider adding desmopressin
- In children with previous response to alarm therapy but then have relapsed, "overlearning" methods may improve the chance of cure during the next alarm attempt
  - Instruct the child, after 14 consecutive dry nights have been achieved, to drink 1-2 extra glasses of water every evening (desmopressin is contraindicated in such instances)
  - When 14 consecutive dry nights have been achieved in spite of the extra fluid then the chance for long term remission or cure can be assumed to have increased

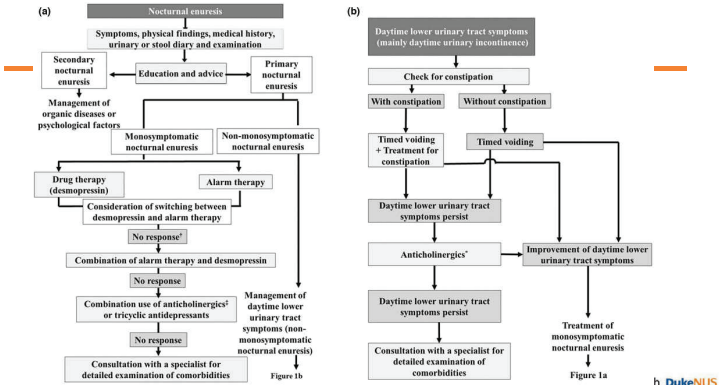


FIGURE 1 (a) Algorithm for monosymptomatic nocturnal enuresis by the guidelines for the treatment of nocturnal enuresis, published by the Japanese Society on Enuresis and Incontinence in 2021.
Tsuji S et al. Treatment of treatment-resistant nocturnal enuresis. Pediatr Int. 2023;65:e15573. https://doi. org/10.1111 /ped.15573

Summary

1. NE is a common problem with ~15% of children at the age of 5 years being affected
2. Most children with NE do not have underlying health problems
3. Offer active treatment when child is above age of 6 years
4. If prolonged and left untreated, NE can have adverse outcomes on psychological development
5. There is no one good cure available. Various treatment options are available and more than 1 form of therapy may be used at the same time
   - Urotherapy should be advocated for all patients
   - Enuresis alarm and desmopressin are the recommended 1st line therapies in MNE
   - Children with therapy resistant NE remains a challenging group
   - Management should be individualized to the patient


End.
KK Women's and
Children's Hospital
SingHealth

National University Hospital

The Hostile Bladder
for the nephrologist

Nyo Yoke Lin
Paediatric Surgery and Paediatric Urology

WORLD'S BEST HOSPITALS 2024 Newsweek statista NATIONAL UNIVERSITY HOSPITAL

Overview

Terminology
Context
Function of the bladder
Basic Science
Classifications
Recommendations
Case studies

What is a Hostile Bladder?

Bladder "hostility"

Terminology

Predates: EAU/ESPU guidelines 2019, UMPIRE protocol paper 2021

Other similar terms – end stage bladder, bladder failure, high risk bladder

End stage bladder – usually used in context of intractable LUTS symptoms, treatment refractory interstitital cystitis and end stage bladder cancers

Bladder failure – suggested terminology in International Neurourology Journal (INJ) in 2012, similar group that we are defining in terms of the functions of storage and voiding.

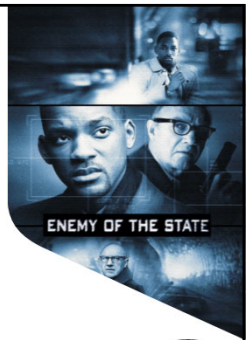
High Risk bladder – UMPIRE 2021

Bladder "hostility"

My preference

Enemy of the state (the kidneys)
Justification of a lot of "resources and energy", attention
"Crisis-mode" mentality
Helps parents understand

Yet…
Not an enemy till it becomes an enemy



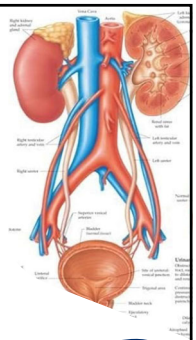
What is the context?

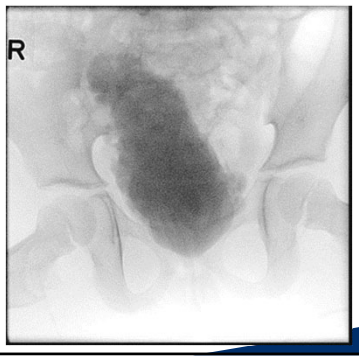
Primarily a bladder issue then later a renal issue

Majority would be neurogenic
Causes of neurogenic bladder:
- myelodysplasia eg myelomeningocoele
- spinal cord injury/trauma
- transverse myelitis
- cerebral palsy

Others:
Posterior urethral valves

Not: CAKUT



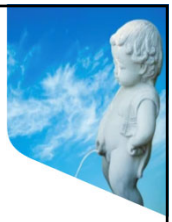


Function and basic science

What is the function and how this is achieved by the anatomy and physiology (and the cellular anatomy and physiology)?

Function of the bladder

Function of the bladder



At low pressures

Storage | Voiding

To completion

Function of the bladder

Seamless transition

Storage | Voiding

Seamless transition

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DOI: 10.1016/S0002-9440(10)63303-9

Matrix Pathobiology

Mechanotransduction of Extracellular Signal-Regulated Kinases 1 and 2 Mitogen-Activated Protein Kinase Activity in Smooth Muscle Is Dependent on the Extracellular Matrix and Regulated by Matrix Metalloproteinases

Karen J. Aitken, Gregory Block, Armando Lorenzo, Daniel Herz, Nesrin Sabha, Omar Dessouki, France Fung, Marta Szybowska, Laura Craig, and Darius J. Bägli

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Review

Molecular regulation of mechanotransduction

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REGIONAL ALTERATIONS IN THE EXPRESSION OF SMOOTH MUSCLE MYOSIN ISOFORMS IN RESPONSE TO PARTIAL BLADDER OUTLET OBSTRUCTION

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Inhibition of DNA methylation during chronic obstructive bladder disease (COBD) improves function, pathology and expression

Martin Sidler[1], K. J. Aitken[1,2], Jia-Xin Jiang[3], Priyank Yadav[1], Erin Lloyd[1], Malak Ibrahim[1], Sanaa Choufani[4], Rosanna Weksberg[4] & Darius Bägli[1,2]

[Insert data classification]

REVIEWS

The bladder extracellular matrix. Part I: architecture, development and disease

Karen J. Aitken and Darius J. Bägli

REVIEWS

The bladder extracellular matrix. Part II: regenerative applications

Karen J. Aitken and Darius J. Bägli

Abstract | Bladder regeneration is a long-sought goal that could provide alternatives to cystoplasty using non-urological tissues. Regeneration might be achieved in different ways, such as seeding matrices with stem cells or conventional cells, or repopulation of the matrix by the body's own reservoir of cells. Consideration of how the extracellular matrix directs cell behavior will be crucial to the success of regenerative therapies.

Aitken, K. J. & Bägli, D. J. Nat. Rev. Urol. 6, 612–623 (2009); doi:10.1038/nrurol.2009.202

[Insert data classification]

Function of the bladder

What we know now

Importance of cycling of the bladder – mechanotransduction –

Extracellular matrix (ECM) and its remodelling

Role of the urothelium as a sensory organ

Neurotransmitters and neurotrophic factors

Triple innervation of the bladder – sympathetic, parasympathetic, somatic

Etc

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[Insert data classification]

Summary

It (the bladder's situation) is not "cast in stone".

And our understanding is still quickly evolving.

"watch this space"

[Insert data classification]

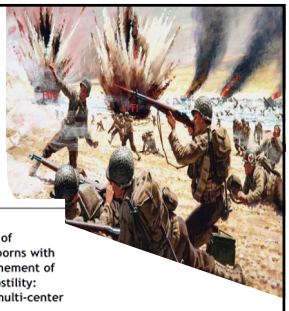
Can we predict hostility?

Which of these bladders will become hostile?

How long before the hostility begins?

UMPIRE protocol

- "safe" & "normal" – out of the equation
- Is low risk always low risk?



Journal of Pediatric Urology (2021) 17, 726–732

Urodynamic characteristics of neurogenic bladder in newborns with myelomeningocele and refinement of the definition of bladder hostility: Findings from the UMPIRE multi-center study

Stacy T. Tanaka[a,*], Elizabeth B. Yerkes[b], Jonathan C. Routh[c], Duong D. Tu[d], J. Christopher Austin[e], John S. Wiener[f], Evalynn Vasquez[g], David B. Joseph[a], Jennifer J. Ahn[h], M. Chad Wallis[i], Tonya Williams[j], Charles Rose[k], Michelle A. Baum[l], Earl Y. Cheng[b]

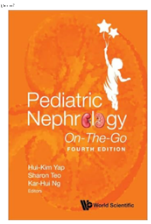
[Insert data classification]

UDS classification

	Detrusor Overactivity (DO)	Detrusor Underactivity (DU)
Sphincter Overactivity (SO)	SO/DO Detrusor/sphincter dyscoordination (deleterious for kidney renal function)	SO/DU Incomplete bladder emptying (may be deleterious to kidney function)
Sphincter Underactivity (SU)	SU/DO Urinary inconmtinence (not deleterious to kidney function)	SU/DU Urinary incontinence with incomplete bladder emptying (risk of kidney impairment induced by UTI)

EAU/ESPU guideline

Proactive vs reactive strategy



REVIEW ARTICLE

EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part I diagnostics and conservative treatment

Raimund Stein[1] | Guy Bogaert[2] | Hasan S. Dogan[3] | Lisette Hoen[4] | Radim Kocvara[5] | Rien J. M. Nijman[6] | Josine S. L. T. Quadackers[6] | Yazan F. Rawashdeh[7] | Mesrur S. Silay[8] | Serdar Tekgul[3] | Christian Radmayr[9]

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Logic of the proactive approach

If there are enemy boots on our shore, the war is lost

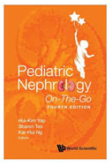
Early initiation of CIC

Early use of antimuscarinics

Prevention of UTI

Managing constipation

Regular follow up with imaging and UDS as necessary



[Insert data classification]

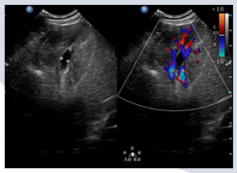
Case reviews

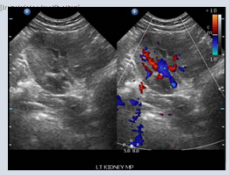
[Insert data classification]

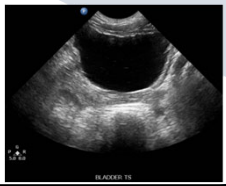
Case 1: Princess Elsa

5 year old girl
Lipomyelomeningocele and tethered cord
Underwent cord de-tethering 7mths old. Complicated by CSF leak and wound infection.
Neurogenic bladder followed up with Paeds Uro and Paeds Nephro
On clean intermittent catherisation (CIC) since 8 months old
Noted constipation since 9 months old

Social:
Both parents working, father has long shifts
Difficulty in adherence to frequent CIC. Only coping with 3x a day.
Not adherent / willing to take anticholinergics







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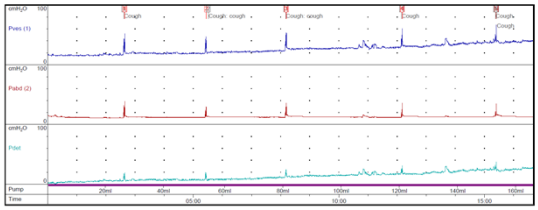
UDS 2023

4 years old, no sedation, cooperative

Graph



No Leak

No overactivity

25 cmH2O

166ml

Polling will open on the next slide

[Insert data classification]

Q: Is this a hostile bladder?

A. Yes
B. No

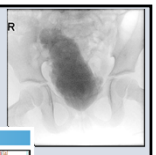
[Insert data classification]

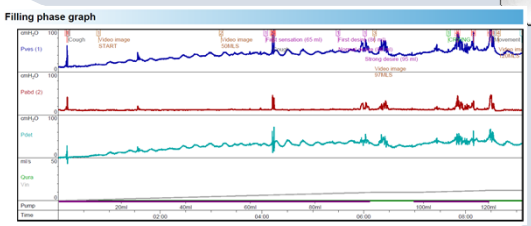
Q: Is this a hostile bladder?

A. Yes
B. No

[Insert data classification]

VUDS 2024





Detrusor overactivity
No leak

120ml
43cmH2O

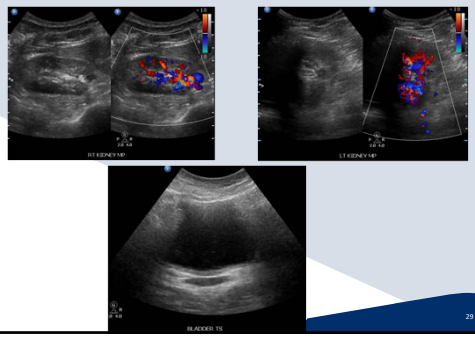
[Insert data classification]

Case 2: Robin Hood

17 year old male
Fell from height 4 years ago.
Spinal injury, paraplegic since
Followed up for neurogenic bladder
Permanent colostomy

[Insert data classification]

US 2021



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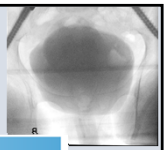
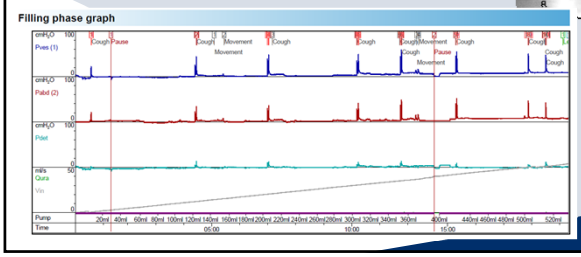
VUDS 2021





No overactivity
Leaked at the end

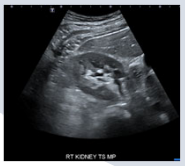
dLPP 1cmH2O

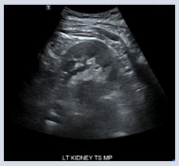
1 cmH2O

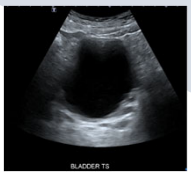
541 ml

Case 2: Robin Hood

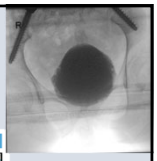
3 years later
He is well, confident
Motivational speaker
Competitive sportsman



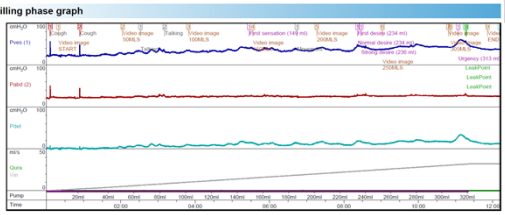




VUDS 2024



Filling phase graph



Detrusor overactivity.
Leaked at the end,
dLPP 34cmH2O

320ml,
22cmH2O

Q: Is this a hostile bladder?

A. Yes
B. No

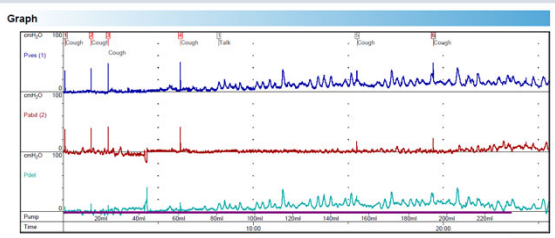
Q: Is this a hostile bladder?

A. Yes
B. **No**

Case 3: The Negotiator

17 year-old male
Bright, studious
Understands his problem and negotiates
Spinal cord lipoma excised 1 year old
Paraparesis
Neurogenic bladder and neurogenic bowel
CIC from 3 hourly to 2 hourly

UDS



Detrusor overactivity
No leak

235ml
10cmH2O

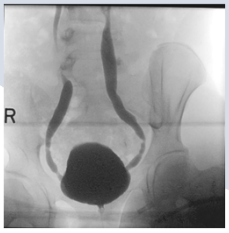
Q: Is this a hostile bladder?

A. Yes
B. No

Q: Is this a hostile bladder?

A. Yes
B. **No**

VUDS



Summary

Hostile bladder demands attention
Many times it is not a matter of "if it is hostile" but "when it becomes hostile"
Vigilance is key
There are many things of the bladder we are yet to discover

Thank you.

National University Hospital | NUHS National University Health System | National University Centre for Women & Children | NUS National University of Singapore | Yong Loo Lin School of Medicine

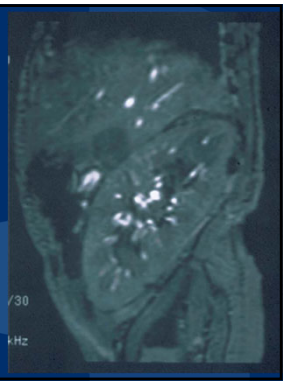
Challenges in transplanting the young child: Post-op Medical Management

Dr Perry Lau
Senior Consultant
Division of Paediatric Nephrology, Dialysis and Kidney Transplantation
KTP-NUCMI

1

Outline

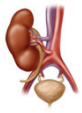
- ✓ Fluid Management
- ✓ Immunosuppression
- ✓ Infectious risks



Transplanting adult-sized kidney (ASK) into a small recipient

Large blood flow demand from an ASK in a small child with a small blood volume

- Acute tubular necrosis
  - Especially around time of reperfusion of ASK when clamp released



Relative state of intravascular hypervolemia desirable during transplantation surgery and early post-op period

Pre-op: do not UF excessively

Op:

- Raise CVP to between 13-15 mmHg just before reperfusion
- Volume expansion with whole blood (especially if Hb <10 g/dL), 5% albumin or 0.9% N/S before release of vascular clamp
- Consider dopamine infusion if SBP cannot be maintained despite adequate volume infusion (CVP not low). Keep SBP >100 mm Hg even in small children

3

Transplanting adult-sized kidney (ASK) into a small recipient

Post-op:
Meticulous fluid management by replacing

- Insensible losses
- Naso-gastric losses and
- Urine losses ml for ml for first 3-5 days especially in patients <30 kg

Why prevent ATN?

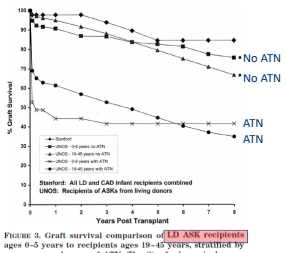


FIGURE 3. Graft survival comparison of LD ASK recipients ages 0–5 years to recipients ages 19–45 years, stratified by presence or absence of ATN. The Stanford survival curve combines all infant recipients of both ASK grafts (LD and CAD) and pediatric CAD kidneys *$P<0.001$.

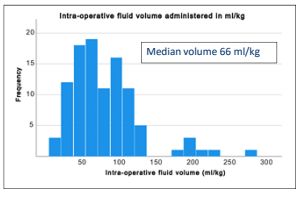
- Superb long-term graft survival potential of ASKs without ATN transplanted into infants and small children
- Presence of ATN following transplantation results in a 20-35% inferior graft survival rate in comparison to recipients without ATN at all time points following transplantation

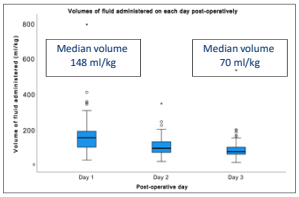
Sarwal et al. Adult-size kidneys without ATN provide exceedingly superior long-term graft outcomes for infants and children. Transplantation 2000;70:1728-1736.

5

Perioperative fluid management and associated complications in children receiving kidney transplants

Natalie Wyatt et al collected data from 5 UK paediatric kidney transplant centres on perioperative fluid volumes administered and explored associations between fluid volume administered, graft function and fluid-related adverse events.





Median total volume of fluid administered in 72 h was 377 ml/kg (IQR 149 ml/kg) with a high degree of variability.

Pediatr Nephrol 2023; 38:1299

Perioperative fluid management and associated complications in children receiving kidney transplants

Table 2 Incidence of adverse events during the postoperative period

Adverse event	Number of patients (%)	Median total amount of fluid received ml/kg in those with the adverse outcome	Median total amount received in the group who did not develop the adverse outcome	Difference in fluid administered and development of an adverse outcome?
Pulmonary oedema	14 (14)	353	386	No ($p = 0.27$)
Hypertension	53 (52)	367	395	No ($p = 0.28$)
Oxygen requirement	31 (30)	361	393	No ($p = 0.15$)
Unexpected PICU admission	9 (9)	355	388	No ($p = 0.40$)

No significant difference between fluid volumes received in children who did or did not experience these adverse events was found.

Pediatr Nephrol 2023; 38:1299

Perioperative fluid management and associated complications in children receiving kidney transplants

Characteristic		<20 kg group N = 28	≥20 kg group N = 74	Overall N = 102
Age at transplant, years Median (IQR)		4 (2)	14 (4)	12.5 (9)
Weight, kg Median (IQR)		14.5 (4.5)	45.4 (23)	39.8 (30.9)
Total fluid administered ml/kg Median (IQR)		507 (225.5)	356 (139)	374.5 (148)
Occurrence of adverse events N (%)	Pulmonary edema	3 (10.7)	11 (14.8)	14 (13.7)
	Hypertension	13 (4.6)	40 (54)	53 (52)
	Oxygen requirement	6 (21.4)	25 (33.7)	31 (30.4)
	Unplanned PICU admission	3 (10.7)	6 (8.1)	9 (8.8)
	Delayed graft function	1 (3.5)	2 (2.7)	3 (2.9)
Day 7 eGFR, ml/min/1.73m² Median (IQR)		135 (60.3)	69.9 (42.7)	84.1 (57.6)
Length of stay Median (IQR)		10 (4)	10 (6)	10 (5)

Incidence of adverse events similar in children < 20 kg and those ≥ 20 kg.

A significant difference in day 7 graft function was noted between these groups with smaller recipients having higher eGFR.

- Due to a greater relative size mismatch of adult donor kidneys in smaller recipients

Pediatr Nephrol 2023; 38:1299

Choosing type of IV fluid to reduce risk of delayed graft function

Saline solution (0.9% sodium chloride)

- Supraphysiological chloride concentration (154 mmol/L)
- → Hyperchloraemic metabolic acidosis
- → Reduced kidney perfusion and acute kidney injury

Balanced crystalloid solution

- Chloride concentrations that approximate human plasma
- Potassium 4-5 mmol/L
- → Can exacerbate hyperkalaemia in the setting of poor kidney allograft function
- → Cardiac arrhythmia, haemodynamic instability, need for acute dialysis

Systematic reviews and meta-analyses of balanced low chloride solutions versus normal saline in kidney transplantation (published in 2016 and updated in 2021) found uncertain effects on the risks of DGF and effects on graft function

9

Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial

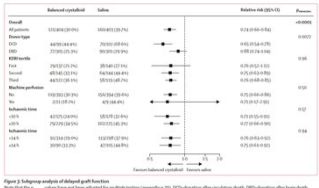
Michael G Collins, Magid A Fahim*, Elaine M Pascoe, Carmel M Hawley, David W Johnson, Julia Varghese, Laura E Hickey, Philip A Clayton, Kathryn B Darvie, Rachael C McConnachie, Lisa A Vergara, Charani Kiriwandeniya, Donna Reidlinger, Peter F Mount, Laurence Weinberg, Colin J McArthur, P Toby Coates, Zoltan H Endre, David Goodman, Kirsten Howard, Martin Howell, Jagadish S Jamboti, John Kanellis, Jerome M Laurence, Wai H Lim, Steven J McTaggart, Phillip J O'Connell, Helen L Pilmore, Germaine Wong, Steven J Chadban†, on behalf of the BEST-Fluids Investigators‡ and the Australasian Kidney Trials Network*

Balanced crystalloid solution should be the standard-of-care IV fluid used in deceased donor kidney transplantation.

- Adults and children of any age receiving a deceased donor kidney transplant
- Multi-organ transplant or <20 kg weight excluded
- Participants randomized to balanced crystalloid solution (Plasma-Lyte 148) or saline during surgery and up until 48 hour after transplantation
- Primary outcome : DGF (need for dialysis within 7 days)

Findings:

- DGF occurred in 121 (**30%**) of 404 participants in the balanced crystalloid group versus 160 (**40%**) of 403 in the saline group (adjusted relative risk 0·74 [95% CI 0·66 to 0·84; p<0·0001]; adjusted risk difference 10·1% [95% CI 3·5 to 16·6]).
- Secondary outcomes (kidney functional recovery based on serum creatinine, hyperkalaemia, graft function from 12 to 52 weeks, graft failure, mortality, length of hospital stay) did not differ between the groups



Lancet 2023; 402:105

10

11

Immunosuppression

Immunosuppressive protocols for paediatric kidney transplant:

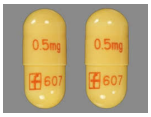
- **Induction:**
  - Interleukin 2 receptor antagonists (eg basiliximab) for low immunological risk children
  - Lymphocyte-depleting agent (eg ATG) for high immunological risk children
- **Maintenance:**
  - Combination of 3 drugs:
    - Steroid
    - Calcineurin inhibitor eg cyclosporine, tacrolimus
    - Antiproliferative agent eg azathioprine, mycophenolate mofetil

Variation between children and adults in immunosuppressive metabolism can vary significantly, especially in those <2 years old.

12

Tacrolimus

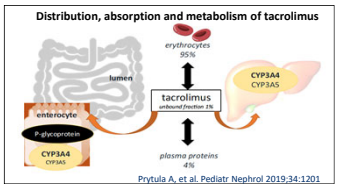
- In paediatric renal transplant recipients TAC has been shown to be more effective than CsA-based regimens in preventing acute rejection and improving long-term graft survival.
- TAC has narrow therapeutic index in which toxicity can appear with slightly higher concentration than therapeutic ones.
- Therapeutic Drug Monitoring ensures efficacy of tacrolimus while minimizing its toxicity.



Period post-transplant	Tac trough level (mg/L)
1st 2 weeks	10-12
2 weeks to 3 months	8-10
4-6 month	7-9
>6 month	5-7 (minimum 4)

13

Challenges in achieving desired TAC levels



Prytula A, et al. Pediatr Nephrol 2019;34:1201

Oral absorption of TAC in children is incomplete and highly variable, with a reported bioavailability of immediate release formulations ranging from 5% to 70%

- TAC best administered on an empty stomach as the absorption decreases in the presence of food, particularly high-fat meals

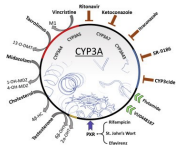
Studies demonstrate that **younger children require significantly higher mg per kg TAC doses compared to adolescents and adults**.

- Explanation not entirely clear
- Variability in pharmacokinetics between children and adults eg intestinal uptake, hepatic blood flow, proportion of liver to body weight, immature CYP3A4/5 enzymatic pathways etc
- Suggested initial dose for immediate-release TAC in pediatric kidney transplant recipients 0.2-0.3 mg/kg per day divided every 12 hours (recommended initial dose 0.1 mg/kg per day in adults)

Challenges in achieving desired TAC levels

If difficulty in achieving desired TAC levels, consider:

- Add diltiazem or fluconazole
- ? 8-hourly dosing instead of 12-hourly dosing



W, C. Wright.; *et al.* 2019

Efficacy and safety of three times daily dosing of tacrolimus in pediatric kidney transplantation patients: A single-center comparative study

Pediatr Transplant 2020;24(6):e13733

Zinah Alabdulkarim[1] | Ahmed Al-Jedai[1,2,3] | Delal Alkortas[1] | Khalid Alhasan[4,5] | Edward Devol[6]

Methods and Materials: Retrospective, single-center, and comparative cohort study. All pediatric kidney transplant recipients received either tacrolimus BID (group 1) or tacrolimus TID (group 2).

Results: A total of 87 patients were included in this study; 48 patients received BID tacrolimus (group 1), and 39 patients received TID tacrolimus (group 2). The percentage of patients who achieved therapeutic trough concentrations in group 2 did not significantly differ from those in group 1 at day 7 (84.62% TID vs 83.33% BID; $P = .42$). The median time to reach therapeutic trough concentrations was three days in group 1 compared to four days in group 2.

Conclusion: No significant difference was observed between tacrolimus BID and TID dosing in the time to reach therapeutic trough concentration or in the proportion of patients achieving therapeutic trough concentrations at day 7.

Tacrolimus: Pharmacogenomics

Rationale for routine CYP3A5*1*3 testing to guide TAC dose in transplant recipients:

- Tacrolimus is metabolised in the liver and intestine by the CYP3A isoforms CYP3A4 and CYP3A5
- Polymorphisms of the CYP iso-enzymes 3A4 and 3A5 have been extensively studied in adults with regard to TAC pharmacokinetics
  - **CYP3A5 expressers (genotype CYP3A5*1/*1 or CYP3A5*1/*3) require higher TAC doses to achieve a given TAC concentration.**
    - Recommendation for adult SOT recipients is to increase the standard TAC dose by 1.5- to 2-fold in CYP3A5 expressers, but not to exceed the daily dose of 0.3 mg/kg, followed by strict TDM.
  - CYP3A5 non-expressers (genotype CYP3A5*3 homozygotes)
- Children with the CYP3A5*1 allele have higher TAC dose requirements than CYP3A5 non-expressers.
  - For children and adolescents with at least one CYP3A5*1 allele, a 1.5- to 2-fold increase in dose followed by TDM is recommended.

To date: there is no evidence that routine CYP3A5 genotyping can positively impact patient outcomes

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Tacrolimus: Intra-patient variability

Consequences of high intra-patient variability in TAC exposure:

- Increased risk of late acute rejection and allograft loss
- Increased risk of pathologic changes: fibrosis and tubular atrophy
- Development of HLA-antibodies

Factors:

- Poor therapy adherence
- Concomitant medications eg antibiotics, CYP3A4/A5 inducers and inhibitors
- Concomitant food ingestion
- Diarrhoea

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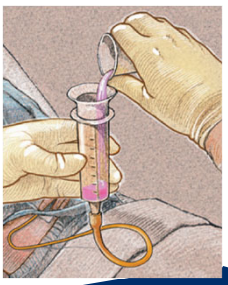
Challenges in achieving desired TAC levels

Giving medications via gastrostomy tube (G-tube)

Many children with chronic kidney disease are reliant on enteral tube feeds to achieve adequate nutritional intake. Following a successful kidney transplant, G-tube feeding continues for ensuring fluid and medication intake.

Method of administering the Tacrolimus must be **consistent**:

- If medication in tablet formulation, tablet has to be crushed. Use a pill crusher to grind it to a fine powder and mix it with 30 to 50 ml of water.



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Avoiding steroid side effects in children

Steroid therapy has been a cornerstone of immunosuppressive therapy in kidney transplantation for >40 years

Marked growth retardation in children

Efforts to withdraw (early or late) or avoid steroid therapy in paediatric kidney transplantation

- Initial studies of SW/avoidance conducted in the setting of CSA and AZA:
  - Increased incidence of AR but no increase in graft loss or mortality
- Studies performed under modern immunosuppression (induction therapy, Tac, and MMF):
  - **No significant increase in AR or graft loss with SW/avoidance immunosuppression**
- SW/avoidance immunosuppression associated with significant improvement in growth, BMI, BP control, and lipid profile in paediatric kidney transplant recipients

Infectious Disease Risks

Younger age at transplantation may increase the risk of viral infections

- Incomplete immunization schedule
- Seronegative for CMV, EBV and BKPyV when they undergo transplantation.

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Infectious Disease Risks

- Appropriate preventive measures:
- Vaccinations
  - Immunization responses pre-transplant are more robust than primary vaccinations initiated post-transplant
    - Pre-transplant immunization is associated with increased memory responses with post-transplant booster dosing
    - Should we delay transplantation till appropriate vaccinations completed?
    - For children who completed national immunization schedule, serologic assessment for vaccine responses to measles, hepatitis B, varicella can guide pre-transplant immunization recommendations
  - Vaccination post-transplant:
    - Ideal time around 3-6 months when immunosuppression tapered to maintenance levels
    - Although small studies in paediatric liver transplant recipients have suggested the safety of using live vaccines such as measles, mumps, rubella, and varicella, the consensus remains to avoid live vaccines post-transplant due to the potential risk of disseminated disease
  - Vaccination of recipients AND their close contacts

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Infectious Disease Risks

Appropriate preventive measures:

- **Regular monitoring of CMV, EBV and BKV by PCR**

Monitoring post-transplant		
CMV PCR	Seronegative recipients: weekly for Month 1 Then 2 weekly for Month 2 Then monthly till 1 year	After 1 year post-transplant: yearly
	Seropositive recipients: monthly	
EBV PCR	Seronegative recipients: monthly	After 1 year post-transplant: 3-monthly for first 2 years Then 6-monthly till seroconversion Then yearly
	Seropositive recipients: 3-monthly	
BKPyV PCR	Monthly for first 9 months	After 9 months: 3-monthly for first 2 years Then yearly

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Infectious Disease Risks

Appropriate preventive measures:

- **Use of preventive medications eg valganciclovir prophylaxis, IVIG**

CMV status	ATG	IVIG	IV Ganciclovir	Valganciclovir
Negative donor to negative recipient + blood transfusion	Y/N	N		3 months
Positive donor to positive recipient	Y	N		3 months
Positive donor to positive recipient	N	N		3 months
Negative donor to positive recipient	Y	N		3 months
Negative donor to positive recipient	N	N		3 months
Positive donor to negative recipient	Y	Y	10 days	6 months (Prolong to 1 year if lymphopenic)
Positive donor to negative recipient	N	Y		6 months
Negative donor to negative recipient on mTORi	Y	N		3 months

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Infectious Disease Risks

Appropriate preventive measures:

- **Use of preventive medications eg valganciclovir prophylaxis, IVIG**

EBV status	ATG	CMV Hyperimmune globulin	IV Ganciclovir	Valganciclovir
Negative donor to negative recipient + blood transfusion	Y	Y (single dose)		
Positive donor to positive recipient	Y	Y (single dose)		3 months
Negative donor to positive recipient	Y	Y (single dose)		3 months
Positive donor to negative recipient	Y/N	Y 2-weekly for total of 6 doses followed by 1 dose at Week 16	10 days	6 months (Prolong to 1 year if lymphopenic)

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Summary

- Transplanting an adult-sized kidney into a small child has unique challenges: vessel anastomosis, placement, risk of acute tubular necrosis
- Improved kidney graft survival and patient survival in a young kidney transplant recipient with time due to advances in surgical techniques, anaesthetic care and immunosuppression management
- Post-transplant care in children challenging in terms of pharmacokinetic differences, drug dosing and administration
- Viral infections are problematic for children relative to adult kidney transplant recipients, needing routine monitoring and prophylaxis

25

Thank you.

26

National University Hospital | NUHS National University Health System | National University Centre for Women & Children | NUS National University of Singapore | Yong Loo Lin School of Medicine

Tubulopathies

Dr Perry Lau
Senior Consultant
Division of Paediatric Nephrology, Dialysis and Kidney Transplantation
KTP-NUCMI

1

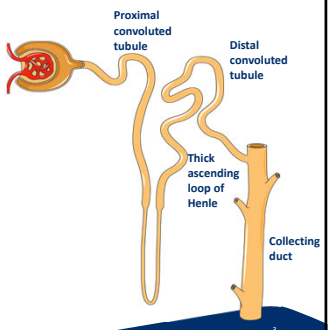
Outline

- ✓ Function of kidney tubules
- ✓ When do we suspect tubulopathy?
- ✓ Diagnostic kit
- ✓ Cases : diagnostic and management challenges

2

Kidney tubules

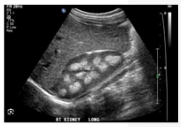
- Preservation of fluid, electrolyte and acid-base homeostasis
- Complex transport function mostly performed by specialized proteins distributed along kidney tubules
  - Active and passive mechanisms
- Divided into 4 broad segments based on anatomical and functional characteristics
- Dysfunction of any of these tubular mechanisms → **Tubulopathy**
- Inherited or acquired etiologies

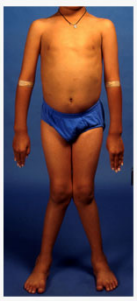


3

Clinical Presentation of Tubulopathies

- Polyuria and polydipsia
- Irritability
- Recurrent dehydration
- Growth failure
- Developmental delay
- Rickets
- Nephrocalcinosis
- Muscle weakness or cramps
- Abnormalities in BP
  - Hypertension
  - Hypotension





4

Initial Investigations

Blood	Urine
Electrolytes: sodium, potassium, chloride, bicarbonate Calcium, phosphate, magnesium Uric acid Urea, creatinine Venous blood gas	Urine dipstick for glucose, protein Urine microscopy Urine protein/creatinine ratio

Distinctive biochemical abnormalities may localize which tubular segment are implicated
- Hypernatraemia with low urine specific gravity
- Hypokalaemic metabolic acidosis
- Hypokalaemic metabolic alkalosis
- Hyperkalaemic metabolic acidosis
- Glycosuria and proteinuria

5

Further Investigations

Blood	Urine
Electrolytes: sodium, potassium, chloride, bicarbonate Calcium, phosphate, magnesium Uric acid Urea, creatinine Venous blood gas	Urine dipstick for glucose, protein Urine microscopy Urine protein/creatinine ratio
Osmolality Renin, aldosterone	Urine osmolality Urine pH Urine sodium, potassium, chloride Urine calcium/creatinine ratio Urine phosphate, magnesium Urine creatinine Urine β2 microglobulin

Paired urine and serum samples are obtained to enable calculation of fractional excretion of solute/ tubular handling of solute

6

Assessment of tubular handling of acid and solutes

	Formula	Normal value	Interpretation
Urine pH		Urine pH <5.5 in the setting of severe metabolic acidosis	Urine pH >5.5 in the setting of severe metabolic acidosis → Defect in distal acidification mechanism (type 1 RTA)
Urine anion gap	Urine Na + K -Cl	Negative urine AG in presence of acidosis	Normal acidification of urine. Rules out type 1 and type 4 RTA.
FeNa	$\frac{Na(urine) \times Cr(serum)}{Na(serum) \times Cr(urine)} \times 100$	FeNa <1% (with normal salt load & normal GFR)	If >1% → - Kidney salt wasting - Appropriate natriuresis in the context of salt loading
FeMg	$\frac{Mg(urine) \times Cr(serum)}{Mg(serum) \times Cr(urine) \times 0.7} \times 100$	FeMg <4%	If >4% → - Kidney magnesium wasting in setting of hypomagnesaemia
TTKG	$\frac{K(urine) \times Osmolality(serum)}{K(serum) \times Osmolality(urine)} \times 100$	TTKG 4-6% (interpretation dependent on kalaemic state)	In hypokalaemic states: <2% → appropriate kidney handling >4% → kidney losses
TmP/GFR	$PO_4(Serum) \times [1 - \frac{PO_4(urine) \times Cr(serum)}{PO_4(serum) \times Cr(urine)}]$	Range varies with age Birth: 1.43-3.43 mmol/L 3 mths: 1.48-3.30 mmol/L 6 mths: 1.15-2.60 mmol/L 2-25yrs: 1.15-2.44 mmol/L	Less than lower limit of range for age → Kidney phosphate wasting

Assessment of tubular handling of acid and solutes

Always analyze urinary data with serum levels!

- **Urine osmolality = 100 mmol/kg**
  - Serum Na 135 mmol/L → Psychogenic polydipsia
  - Serum Na 145 mmol/L → Diabetes insipidus
- **Urine pH 7**
  - Serum HCO3 14 mmol/L → Distal RTA
  - Serum HCO3 20 mmol/L → Distal or proximal RTA
- **Hypokalaemic alkalosis**
  - FeCl > 0.5% → Bartter syndrome
  - FeCl < 0.1% → Cystic fibrosis

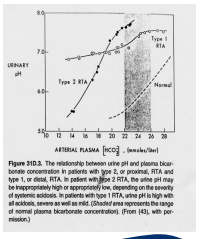
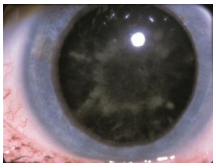


Figure 31D.3. The relationship between urine pH and plasma bicarbonate concentration in patients with type 2, or proximal, RTA and type 1, or distal, RTA. In patient with type 2 RTA, the urine pH may be inappropriately high or appropriately low, depending on the severity of systemic acidosis. In patients with type 1 RTA, urine pH is high with all acidosis, severe as well as mild. (Shaded area represents the range of normal plasma bicarbonate concentration). (From (43), with permission.)

Evaluation

- Any previous normal biochemical profile
- Drug history
- Family history
- Extra-kidney manifestations:
  - Eye eg cataracts
  - Sensorineural hearing loss
- Kidney ultrasound
- Genetic test



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

Rajiv Sinha[1,2] · Subal Pradhan[3] · Sushmita Banerjee[1,4] · Afsana Jahan[5] · Shakil Akhtar[1] · Amitava Pahari[2] · Sumantra Raut[6] · Prince Parakh[7] · Surupa Basu[1] · Priyanka Srivastava[8] · Snehamayee Nayak[3] · S. G. Thenral[9] · V. Ramprasad[6] · Emma Ashton[10] · Detlef Bockenhauer[11] · Kausik Mandal[12]

Total number of children: 77
Total number of variants: 68
Total number of pathogenic or likely pathogenic variants: 55
Novel pathogenic/likely pathogenic variants: 24
Positive yield of WES: 70% (n=54)

Children with clinically suspected tubulopathy underwent WES.

Suspected phenotype (Total 77)	Clinical implications of genetic testing	
	Revision of diagnosis: 14 (18%)	Impact on clinical Management: 24 (31%)
Distal RTA n= 25	None	Identification of co-morbidities: SNHL 4, Hemolytic anemia 2, dental problems 1 (Total 7)
Bartter Syndrome n=18	Non tubulopathy: 5 Another type of tubulopathy: 1	Identification of congenital chloride diarrhoea and cystic fibrosis facilitated specific treatment: 5
Hypophosphataemic rickets n=6	None	None
Proximal Tubular Dysfunction n=12	Total: 3	Facilitated specific treatment: cystinosis 4 and tyrosinemia 2
Nephrogenic DI n=6	Non tubulopathy: 1 Another type of tubulopathy:1	Identification of dRTA allowed treatment with alkali: 1 Dx of nephronophthisis changed Mx plan : 1
Isolated kidney stone or nephrocalcinosis n=6	Diagnosed as Bartter syndrome: 1	Dx of Bartter syndrome helped in appropriate Mx planning: 1 Identification of HOGA variant helped in prognostication: 1
Others n=4	Non tubulopathy: 1 Another type of tubulopathy:1	Identifying HNF1B phenotype helped in prognostication: 1 Audiological assessment conducted post availability of genetic result diagnosed SNHL: 1

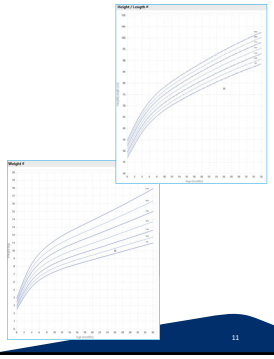
WES had a definite impact on clinical management in nearly one third (31%) of children with clinically suspected tubulopathy from Eastern India

Pediatr Nephrol 2022; 37(8): 1811

Case 1

A 2-year old Chinese boy was referred for assessment of **isolated gross motor delay and failure to thrive**.

Height: 77.5 cm (<<3 %tile)
Weight: 10 kg (3-10 %tile)
Genu valgum
Eyes normal
Heart and lungs examination unremarkable
Abdomen : **hepatomegaly** (5cm felt, firm), no splenomegaly
Neurological examination normal



Case 1: 2-year old boy with gross motor delay and FTT

Blood investigations	Reference range	Results
Urea	3.2-7.9 mmol/L	4.6
Creatinine	15-35 umol/L	10 (eGFR 283) (0.11 mg/dL)
Sodium	132-147 mmol/L	137
Potassium	3.5-5.5 mmol/L	3.8
Chloride	95-110 mmol/L	108
Bicarbonate	22-31 mmol/L	12
Anion gap	10-14 mmol/L	17
Total calcium	2.20-2.70 mmol/L	2.37
Phosphate	1.40-2.33 mmol/L	0.92
ALP	160-380 U/L	707
Magnesium	0.75-1.07 mmol/L	0.9
Uric acid	100-290 umol/L	<89
Glucose	4.0-7.8 mmol/L	3.4
25OH vitamin D	30-100 ug/L	19.8
PTH	1.3-9.3 pmol/L	12.4

Urine dipstick:

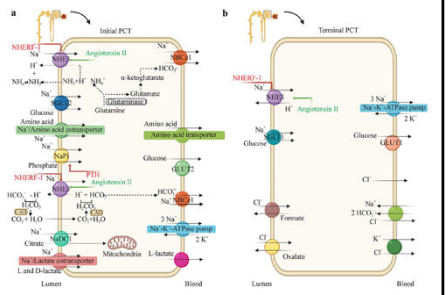
Specific gravity	1.003
pH	5
Leukocyte esterase	Negative
Nitrite	Negative
Glucose	3+
Ketone	2+
Protein	3+
Hb	Trace

Question 1:
What is the possible diagnosis in this boy?

Proximal Tubular Cell

Reabsorption of majority of water and solutes:

- Sodium
- Glucose
- Amino acids
- Low-molecular-weight proteins (LMWPs)
- Bicarbonate
- Phosphate



Albuquerque et al. World J Pediatr. 2023;19(7):619

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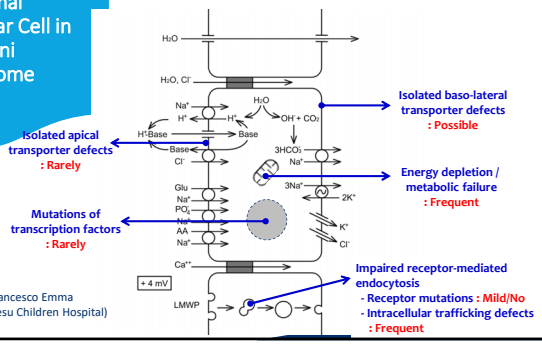
Proximal Tubular Cell in Fanconi syndrome



Thanks to Francesco Emma
(Bambino Gesu Children Hospital)

Causes of Fanconi syndrome

PRIMARY FANCONI SYNDROME

FRTS1 (GATM mutations, AD)
FRTS2 (SLC34A1 mutations, AR)
FRTS3 (EHHADH mutations, AD)
FRTS4 (HNF4α mutations, AD)
FRTS5 (NDUFAF6 mutations, AR)
Mitochondrial DNA deletion
Idiopathic Fanconi syndrome (unknown genetic mechanism)

FRTS: Fanconi renal tubular syndrome

SECONDARY TO HEREDITARY DISORDERS

Cystinosis (CTNS)
Lowe syndrome (OCRL1)
Dent disease (CLCN5, OCRL1)
ARC syndrome (VPS33B, VIPAR)
Fanconi-Bickel (GLUT2)
Lysinuric protein intolerance (SLC7A7)
Mitochondrial myopathies

Metabolic diseases
Galactosemia (GALT)
Hereditary fructose intolerance (ALDOB)
Tyrosinemia type 1 (FAH)
Wilson's disease (ATP7B)

ACQUIRED

Antiretroviral drugs (tenofovir, lamivudine, didanosine, stavudine)
Anticancer drugs (ifosfamide, cisplatin, immune checkpoint inhibitors, tyrosine kinase inhibitors)
Antibiotics (aminoglycosides, expired tetracyclines)
Anticonvulsants (topiramate, valproate)
Bisphosphonate (zolendronate)
Iron-chelating agents (defarosirox)
Heavy metals (lead, mercury, copper, cadmium)
Aristolochic acid (Chinese herb nephropathy)
TIN with uveitis

Albuquerque et al. World J Pediatr. 2023;19(7):619

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Treatment of Fanconi syndrome

1. **Management of underlying cause**
   - Cystinosis: oral cysteamine to reduce intralysosomal cystine stores
   - Medication-induced Fanconi syndrome: stop medication
2. **Correction of electrolyte disorders and acidosis**
   - Bicarbonate requirements 10-20 mmol/kg/day in divided doses (6-8 hourly): sodium bicarbonate, sodium citrate, potassium citrate
   - Phosphate solution
   - Calcium lactogluconate
   - Calcitriol
   - Potassium phosphate
   - Magnesium sulphate 0.1 to 0.2 mmol/kg/d
3. **Carnitine supplementation**

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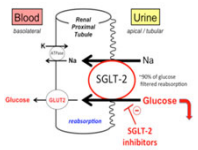
Treatment of Fanconi syndrome

> J Inherit Metab Dis. 2024 May 27. doi: 10.1002/jimd.12752. Online ahead of print.

Repurposing SGLT2 inhibitors: Treatment of renal proximal tubulopathy in Fanconi–Bickel syndrome with empagliflozin

Ruben J Overduin [1], Sarah C Grünert [2], Martine T P Besouw [3], Mathieu S Bolhuis [4], Joost Groen [5], Andrea B Schreuder [1], Mathias Woidy [6], Simona Murko [6], René Santer [6], Terry G J Derks [1]

- Case series of 7 persons from 5 families (5 males, 2 females; 3 children, who were 14y5m, 2y9m, and 1y6m old) with genetically confirmed Fanconi-Bickel syndrome, off-label treated with empagliflozin.
- Biochemical parameters of tubular cell integrity (urinary N-acetyl-glucosaminidase) and/or tubular functions (including urinary α1-microglobulin) improved in all.
- Clinically, supplementations (i.e., phosphate, alkali, carnitine, and alfacalcidol) could be completely discontinued in the 3 children whereas results in the 4 adult patients were more variable and not as significant.
- Well tolerated. No significant hypoglycaemia.



TUSOM/PharmWiki

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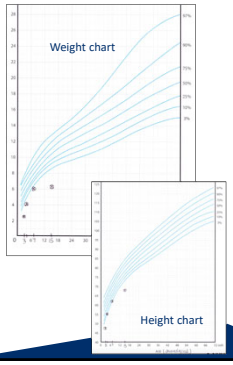
Case 2

A Indian boy was referred at 1-year-3-month old (chronological age) for evaluation of failure to thrive.
He was born at 28 weeks gestation. Antenatally there was severe polyhydramnios. There was AKI secondary to hypotension at birth. This was managed conservatively and kidney function recovered to almost normal with no electrolyte or acid-base abnormalities at discharge from neonatal unit at 3 months (chronological age) old and weight of 2kg.
He was on total breastfeeding and weaned to semi-solids and formula milk at 7 months old. **He had a preference for plain water to formula milk. Parents also noted more wet diapers since after weaning.**
Height: 68 cm (<3 %tile)
Weight: 6.3 kg (<3 %tile)
BP 90/50 mmHg
No pallor or rickets
Cardiac, respiratory, abdomen and neurological examination normal



Case 2: 1-year old boy with FTT

Blood investigations	Reference range	Results At 3 mo	Results At 15 mo
Urea	1.5-5.5 mmol/L	7.2	6.2
Creatinine	23-46 umol/L	35	42 0.48 mg/dL
Sodium	132-147 mmol/L	141	153
Potassium	3.5-5.5 mmol/L	3.6	2.9
Chloride	98-107 mmol/L	101	109
Bicarbonate	18-29 mmol/L	28	28
Anion gap	10-14 mmol/L	12	16
Total calcium	2.05-2.85 mmol/L	2.67	2.71
Phosphate	1.64-2.47 mmol/L	2.11	1.84
ALP	70-350 U/L	430	373
Magnesium	0.75-1.07 mmol/L		1.10
Uric acid	80-310 umol/L	258	125

Question 2:
What do you suspect this boy has?

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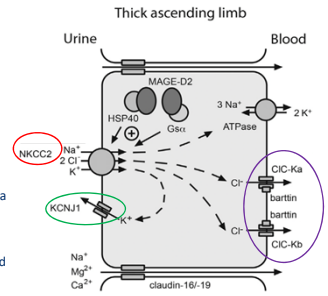
Thick ascending Loop of Henle



Reabsorb about 25% filtrate
- Active sodium reabsorption via **NKCC2**
- Potassium recycled to tubular lumen via **KCNJ1 channel**
- Chloride exits to interstitial space via chloride channels **ClC-Ka and ClC-Kb,** both of which require a ß-subunit called barttin
- Contributes to Ca and Mg homeostasis via paracellular mechanisms

Konrad et al. KI 2021;99:324

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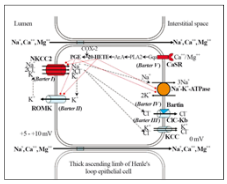
Bartter syndrome



- Urinary NaCl losses
- Hypercalciuria & Hypermagnesuria (due to ↓ voltage-driven paracellular reabsorption of Ca^{2+} and Mg^{2+})
- Polyuria
→ Volume contraction
→ ↑ Renin, ATII, aldosterone, PGE2

Koulouridis E et al. World J Pediatr 2015;11(2):113

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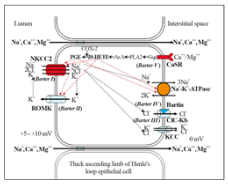
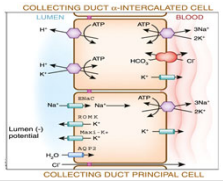
Bartter syndrome





- Urinary NaCl losses
- Hypercalciuria & Hypermagnesuria (due to ↓ voltage-driven paracellular reabsorption of Ca^{2+} and Mg^{2+})
- Polyuria
→ Volume contraction
→ ↑ Renin, ATII, aldosterone, PGE2

NaCl delivery to distal nephron + aldosterone
→ H^+ and K^+ secretion

- Metabolic alkalosis
- Hypokalaemia
→ Impaired vasopressin-stimulated urinary concentration

Koulouridis E et al. World J Pediatr 2015;11(2):113

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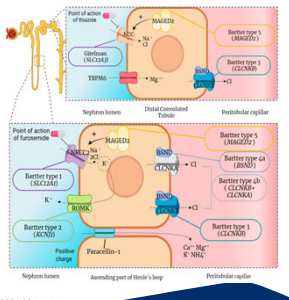
Bartter syndrome

Type	Channel /Protein	Genes	Inheritance	Site in kidney tubule
Bartter I (antenatal Bartter)	NKCC2	SLC12A1	AR	TAL
Bartter II (antenatal Bartter)	KCNJ1 (ROMK or Kir1.1)	KCNJ1	AR	TAL
Bartter III (classic Bartter)	ClC-Kb	CLCNKB	AR	TAL/DCT
Bartter IV (antenatal Bartter with sensorineural deafness)	IVa: Barttin IVb: ClC-Ka +ClC-Kb	IVa: BSND IVb: CLCNKA +CLCNKB	AR	TAL/DCT /ear
Bartter V (transient antenatal Bartter)	MAGE-D2	MAGED2	XLR	TAL/DCT



Nunez-Gonzalez et al. Int J Mol Sci 2021;22:11414

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Bartter syndrome

Type	Channel /Protein	Genes	Inheritance	Site in kidney tubule	Clinical features	Hypercalciuria and nephrocalcinosis
Bartter I (antenatal Bartter)	NKCC2	SLC12A1	AR	TAL	Polyhydramnios, preterm	Very frequent
Bartter II (antenatal Bartter)	KCNJ1 (ROMK or Kir1.1)	KCNJ1	AR	TAL	Polyhydramnios, preterm **Transient neonatal hyperkalemia**	Very frequent
Bartter III (classic Bartter)	ClC-Kb	CLCNKB	AR	TAL/DCT	**Term** Present in childhood with FTT **Mild hypomagnesemia in 20%**	+/-
Bartter IV (antenatal Bartter with sensorineural deafness)	IVa: Barttin IVb: ClC-Ka +ClC-Kb	IVa: BSND IVb: CLCNKA +CLCNKB	AR	TAL/DCT /ear	Polyhydramnios, preterm **Deafness** **Risk for CKD, ESKD**	+/-
Bartter V (transient antenatal Bartter)	MAGE-D2	MAGED2	XLR	TAL/DCT	Polyhydramnios (very severe), preterm, large for gestational age **Transient disease**	Hypercalciuria but nephrocalcinosis rare or mild

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Bartter syndrome Type I presenting as nephrogenic DI

- Bockenhauer et al. described the occurrence of NDI in four patients with inherited tubulopathy, including one case in a child with Bartter syndrome [Nephron Physiology 2010, 116(4):23-29]
  - Molecular analysis of the AVPR2 and AQP2 genes was unremarkable in all patients, suggesting that NDI was a secondary complication rather than an incidentally second inherited disease
- **Postulated mechanisms:**
  - Hypokalaemia associated with decreased AQP2 expression,
  - Hypercalciuria affects renal concentrating ability via activation of the calcium-sensing receptor
  - Nephrocalcinosis may impair water reabsorption

EARLY recognition of underlying BS and appropriate management is important

- Bartter syndrome is a salt wasting disorder and requires supplementation with large amount of salt, whereas in NDI, salt restriction is crucial to minimize renal solute load and thus urine output.
- NDI requires treatment with thiazide diuretics that can be very dangerous in patients with BS.

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Recommendations for therapy of Bartter syndrome

Postnatal period

- Consider pharmacologic doses (5-10 mmol/kg/d) of NaCl supplementation in patients with BS.
- Do not recommend salt supplementation in patients with BS and secondary nephrogenic diabetes insipidus (weak recommendation)
- Use KCl for potassium supplementation
- Do not recommend aiming for complete normalization of plasma potassium levels. (weak recommendation)
- Whenever needed, use oral magnesium supplements, at best organic magnesium salts owing to their better bioavailability
- Recommend spreading out salt and electrolyte supplements throughout the day as much as possible
- Recommend considering treatment with NSAIDs in symptomatic patients with BS, especially in early childhood
- Recommend using gastric acid inhibitors together with nonselective cyclooxygenase inhibitors
- Do not recommend routine use of potassium-sparing diuretics, ACE inhibitors, or angiotensin receptor blockers in BS (weak recommendation)
- Do not recommend the use of thiazides to reduce hypercalciuria in BS (weak recommendation)

Executive summary of the consensus and recommendations from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders. KI (2021) 99:324

Case 3

A 13-year old Chinese girl was diagnosed with DM 3 years ago when she presented with diabetic ketoacidosis. She was non-adherent to the insulin injections.

She is currently admitted for **weakness, dizziness, polyuria, polydipsia and severe dehydration**.

Blood investigations	Reference range	Results
Urea	2.0-6.5 mmol/L	17.6
Creatinine	50-90 umol/L	192 (eGFR 30) 2.17 mg/dL
Sodium	135-150 mmol/L	111
Potassium	3.5-5.5 mmol/L	2.9
Chloride	98-107 mmol/L	60
Bicarbonate	22-31 mmol/L	24
Anion gap	10-14 mmol/L	27
Total calcium	2.15-2.55 mmol/L	2.43
Phosphate	0.85-1.45 mmol/L	1.87
Magnesium	0.75-1.07 mmol/L	0.53
Uric acid	150-370 umol/L	962
Glucose	4.0-7.8 mmol/L	85.8

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Case 3: Diabetic girl with electrolyte abnormalities

Blood investigations	Reference range	Results
Urea	2.0-6.5 mmol/L	17.6
Creatinine	50-90 umol/L	192 (eGFR 30) 2.17 mg/dL
Sodium	135-150 mmol/L	111
Potassium	3.5-5.5 mmol/L	2.9
Chloride	98-107 mmol/L	60
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Anion gap	10-14 mmol/L	27
Total calcium	2.15-2.55 mmol/L	2.43
Phosphate	0.85-1.45 mmol/L	1.87
Magnesium	0.75-1.07 mmol/L	0.53
Uric acid	150-370 umol/L	962
Glucose	4.0-7.8 mmol/L	85.8

Serum ketones elevated BUT apparently normal serum bicarbonate
High anion gap of 27
Delta Ratio $\Delta AG / \Delta HCO_3^-$ = 15 (1-1.6)
→ Presence of concurrent metabolic alkalosis

Question 3:
What is the explanation of the hypokalaemia, hypochloraemia and metabolic alkalosis?

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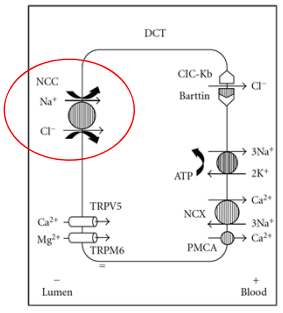
Distal Convoluted Tubule

Thiazide-sensitive NaCl cotransporter reabsorbs 5-10% filtered Na

Ca and Mg homeostasis via transcellular mechanisms



Bhat et al. Int J Pediatr 2012; doi:10/1155/2012/857136

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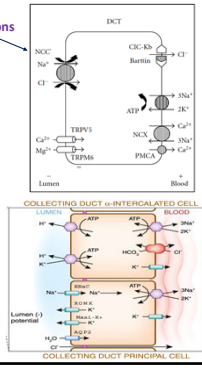
Gitelman syndrome

SLC12A3 mutations



- Urinary NaCl losses
- **Hypocalciuria (chronic)**
- Hypermagnesuria (chronic) → Hypomagnesemia
- ± preserved urine concentration ability

NaCl delivery to distal nephron + aldosterone → H^+ and K^+ secretion

- Metabolic alkalosis
- Hypokalaemia

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Diagnostic criteria for Gitelman syndrome (GS)

Criteria for suspecting a diagnosis of GS
- Chronic hypokalaemia (<3.5 mmol/L) with inappropriate renal potassium wasting (spot K/Cr ratio > 2.0 mmol/mmol [> 18 mmol/g])
- Metabolic alkalosis
- Hypomagnesemia (<0.7 mmol/l [<1.70 mg/dl]) with inappropriate renal magnesium wasting (fractional excretion of magnesium >4%)
- Hypocalciuria (spot calcium-creatinine ratio <0.2 mmol/mmol [<0.07 mg/mg])
- High plasma renin activity or levels
- Fractional excretion of chloride > 0.5%
- Low or normal-low blood pressure
- **Normal renal ultrasound**

Features against a diagnosis of GS
- Use of thiazide diuretics or laxatives
- Family history of kidney disease transmitted in an autosomal dominant mode
- Absence of hypokalaemia (unless renal failure)
- Absence of metabolic alkalosis (unless coexisting bicarbonate loss or acid gain)
- Low renin values
- Urine: low urinary potassium excretion (spot K/Cr ratio <2.0 mmol/mmol [<18 mmol/g])
- Hypercalciuria
- Hypertension
- Renal ultrasound: nephrocalcinosis, nephrolithiasis, unilateral kidneys, cystic kidneys
- Prenatal history of polyhydramnios, hyperechogenic kidneys
- Presentation before age 3 years

Consensus from KDIGO. KI 2017; 91:24

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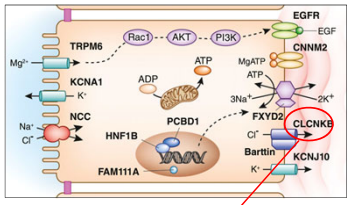
Differential Diagnoses of Gitelman syndrome (GS)

Features against a diagnosis of GS
- Use of thiazide diuretics or laxatives
- Family history of kidney disease transmitted in an autosomal dominant mode
- Absence of hypokalaemia (unless renal failure)
- Absence of metabolic alkalosis (unless coexisting bicarbonate loss or acid gain)
- Low renin values
- Urine: low urinary potassium excretion (spot K/Cr ratio <2.0 mmol/mmol [<18 mmol/g])
- Hypercalciuria
- Hypertension
- Renal ultrasound: nephrocalcinosis, nephrolithiasis, unilateral kidneys, cystic kidneys
- Prenatal history of polyhydramnios, hyperechogenic kidneys
- Presentation before age 3 years

Consensus from KDIGO. KI 2017; 91:24

Distal Convoluted Tubule



Classic BS

32

Differential Diagnoses of Gitelman syndrome (GS)

Features against a diagnosis of GS
- Use of thiazide diuretics or laxatives
- Family history of kidney disease transmitted in an autosomal dominant mode
- Absence of hypokalaemia (unless renal failure)
- Absence of metabolic alkalosis (unless coexisting bicarbonate loss or acid gain)
- Low renin values
- Urine: low urinary potassium excretion (spot K/Cr ratio <2.0 mmol/mmol [<18 mmol/g])
- Hypercalciuria
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- Presentation before age 3 years

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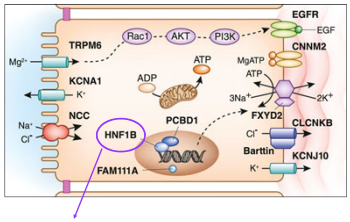
Distal Convoluted Tubule



HNF1β gene mutations

Some inactivating mutations can inhibit the Na-K-ATPase and Kir5.1, thereby causing hypomagnesemia/Gitelman-like syndrome

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Management of Gitelman syndrome

1. ***Ad libitum* NaCl intake**
2. **Potassium supplements (KCl)**
   - Starting dose of ≥ 40 mmol (1-2 mmol/kg in children) in divided doses throughout the day
   - K supplements should not be taken on an empty stomach to minimize GI irritation or damage
   - Reasonable target for K may be 3.0 mmol/L
3. **Magnesium supplements**
   - Starting dose of 300 mg/day (12.24 mmol) of elemental Mg; 5 mg/kg (0.2 mmol/kg) in children. Supplementation divided into 2 to 4 doses, preferably with meals
   - Reasonable target for Mg may be 0.6 mmol/L (1.46 mg/dl)
   - Persistent diarrhoea may mandate a drop in dosage, which paradoxically may improve serum levels due to increased bioavailability or decreased intestinal transit time
4. **Potassium sparing diuretics eg amiloride, spironolactone, eplerenone**
5. **Renin angiotensin system inhibitors eg ACE inhibitors, angiotensin receptor blockers**
   - Both K sparing diuretics and RAS inhibitors aggravate renal salt wasting and increase risk of symptomatic hypovolaemia
   - To stop when there is concurrent acute salt-losing conditions such as vomiting, diarrhoea
6. **NSAIDs eg indomethacin**
   - Rarely used in GS, because urinary prostaglandin E2 levels in GS are usually normal

Case 4

A 6-month old boy was admitted for elective MCUG. He had 2 febrile UTIs previously.

On admission, he had **fever and dehydration**. Mother gave a history of polydipsia in her family.

Length: 63 cm (3 %tile)
Weight: 5 kg (<3 %tile)
OFC: 41cm (3 %tile)
Irritable
Evidence of dehydration: eyes sunken, dry oral mucosa dry, delayed capillary refill

Blood investigations	Reference range	Results
Urea	1.3-6.0 mmol/L	4.3
Creatinine	25-46 umol/L	24
Sodium	132-147 mmol/L	158
Potassium	3.6-5.8 mmol/L	4.4
Chloride	95-110 mmol/L	123
Bicarbonate	17-29 mmol/L	22
Anion gap	10-14 mmol/L	13
Total calcium	2.00-2.80 mmol/L	2.73
Phosphate	1.52-2.92 mmol/L	1.74
Magnesium	0.75-1.07 mmol/L	1.07
Uric acid	90-380 umol/L	373

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Case 4: Boy with hypernatraemic dehydration

Blood investigations	Reference range	Results
Urea	1.3-6.0 mmol/L	4.3
Creatinine	25-46 umol/L	24
Sodium	132-147 mmol/L	158
Potassium	3.6-5.8 mmol/L	4.4
Chloride	95-110 mmol/L	123
Bicarbonate	17-29 mmol/L	22
Anion gap	10-14 mmol/L	13
Total calcium	2.00-2.80 mmol/L	2.73
Phosphate	1.52-2.92 mmol/L	1.74
Magnesium	0.75-1.07 mmol/L	1.07
Uric acid	90-380 umol/L	373

Further investigations:

Serum osmolality 339 mmol/kg (275-300)
Urine osmolality 117 mmol/kg (100-1200)
Urine sodium <10 mmol/L

Vasopressin test showed no response to ADH (rise in urine osmolality <10%)

Blood for genetic test sent.
He was started on
- Hydrochlorothiazide 1mg/kg/dose BD
- Amiloride 0.1 mg/kg/dose BD

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Case 4: Boy with hypernatraemic dehydration

Blood investigations	Reference range	Results Admission	Results Discharge	Results 2 weeks
Urea	1.3-6.0 mmol/L	4.3	0.9	4.3
Creatinine	25-46 umol/L	24	20	18
Sodium	132-147 mmol/L	158	141	133
Potassium	3.6-5.8 mmol/L	4.4	3.9	5.1
Chloride	95-110 mmol/L	123	106	99
Bicarbonate	17-29 mmol/L	22	24	18
Anion gap	10-14 mmol/L	13		16
Total calcium	2.00-2.80 mmol/L	2.73		3.06
Phosphate	1.52-2.92 mmol/L	1.74		1.84
Magnesium	0.75-1.07 mmol/L	1.07		
Uric acid	90-380 umol/L	373		363

Weight decreased by 170 grams over 2 weeks

Question 4: What is the cause of the hypercalcaemia?

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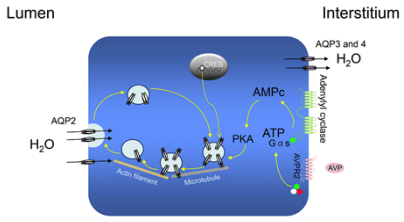
Collecting Duct

Principal cells facilitate water reabsorption (10-12% of glomerular-filtered volume) via water channel **aquaporin-2 (AQP2)** which is stimulated by the binding of antidiuretic hormone arginine vasopressin (AVP) to the **receptor AVPR2**



Marguerite Hureaux et al. Mol Cell Endocrinol. 2023;560:111825

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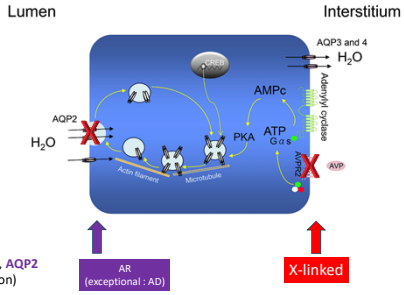
Nephrogenic DI (resistance to AVP)



Polyuria
Hypernatraemic dehydration

Causes:
Hereditary
- Mutations in AVPR2 (90% cases), AQP2

Acquired (decreased AQP2 expression)
- Drug exposure eg lithium
- Electrolyte disorders eg hypoK, hyperCa
- Medullary damage eg obstructive uropathy, infiltrative disease (amyloidosis, sarcoidosis), sickle cell disease

AR (exceptional : AD)

X-linked

Marguerite Hureaux et al. Mol Cell Endocrinol. 2023;560:111825

Management of congenital nephrogenic DI

Early recognition in infants is crucial since treatment can enable normal growth and appropriate development.

1. **Decreased dietary solute**
   - Reduced osmotic load, hence amount of water to excrete this osmotic load
   - Low protein (but meets RDA requirements), low salt diet
     - Stimulate isotonic proximal tubular reabsorption, thereby reducing solute delivery to distal nephron
2. **Diuretics**
   - Thiazide with potassium-sparing diuretic
   - Hydrochlorothiazide 2mg/kg/day in 2 divided doses
   - + Amiloride 0.1-0.3 mg/kg/day
3. **NSAIDs**
   - Indomethacin 1-3 mg/kg/day in 3 or 4 divided doses

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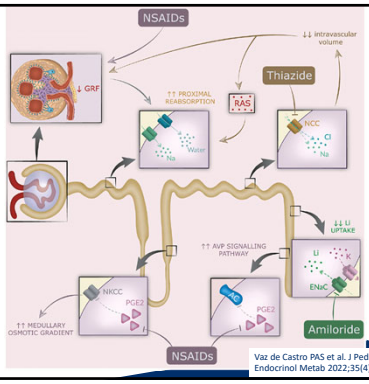
Management of congenital nephrogenic DI

Thiazides
- Inhibit the NCC in the distal convoluted tubule

→ Decreasing the intravascular volume
→ Upregulating the renin-angiotensin system (RAS)
→ Diminishing GFR
→ Increasing proximal reabsorption of sodium (Na) and water



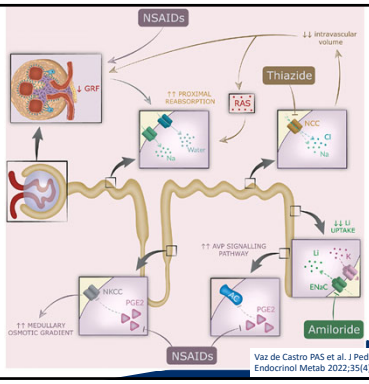
Vaz de Castro PAS et al. J Pediatr Endocrinol Metab 2022;35(4):421

Management of congenital nephrogenic DI

NSAIDs
- Inhibit cyclooxygenase, decreasing prostaglandin synthesis, including prostaglandin E2 (PGE2)

→ PGE2 not available to inhibit adenylate cyclase (AC) and to reduce NKCC expression
→ Enhance the AVP signaling pathway and the medullary osmotic gradient.

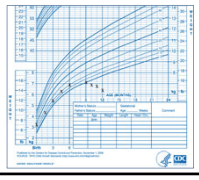
- Decreases GFR by preventing afferent arteriole vasodilation



Vaz de Castro PAS et al. J Pediatr Endocrinol Metab 2022;35(4):421

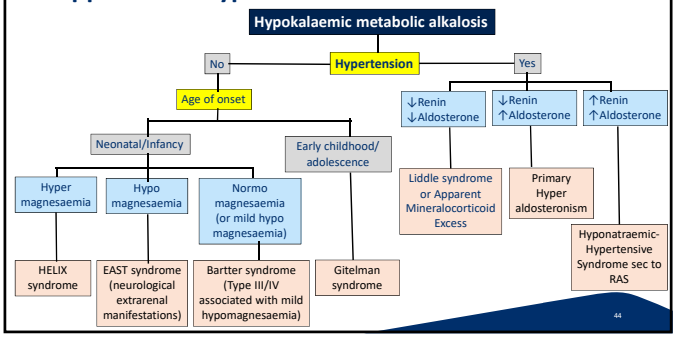
Case 5

A 1-year old boy was investigated for **poor feeding and poor weight gain.**
He was on total breast-feeding and growing well along 10th percentile till 6 months old when he was weaned to rice porridge. **Since 6 months old, he was noted to have marked preference for drinking plain water and wet heavy diapers every 30 minutes.**
In the ward, he was dehydrated and irritable. **BP was 180/100 mmHg.**



Blood investigations	Reference range	Results
Urea	1.5-5.5 mmol/L	1.8
Creatinine	23-46 umol/L	35 0.4 mg/dL
Sodium	132-147 mmol/L	122
Potassium	3.5-5.5 mmol/L	2.9
Chloride	98-107 mmol/L	86
Bicarbonate	18-28 mmol/L	28
Anion gap	10-14 mmol/L	8
Total calcium	2.05-2.85 mmol/L	2.65
Phosphate	1.64-2.47 mmol/L	1.84
Magnesium	0.75-1.07 mmol/L	
Urine dipstick		Hb1+, protein 2+
UFEME		7 RBC/hpf 12 WBC/hpf
UPCr	<0.06 g/mmol	1.06

Approach to hypokalaemic metabolic alkalosis



Summary

- Tubulopathies can present with a variety of non-specific clinical features and can be diagnostically challenging.
- The biochemical presentation of tubulopathies is an important diagnostic tool which can guide further investigations and management.
- Early recognition of tubulopathy in infants and children is crucial since treatment can enable normal growth and appropriate development.

[Input data classification]

Thank you.

CKD – MBD – an update

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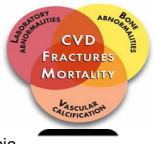
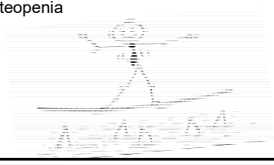
Disclosures and declarations

- Pharmaceutical Industries:
  - Research grants from Fresenius Medical Care
  - Scientific advisor to Amgen, Astra Zeneca and Fresenius Medical Care.
  - Lecture fees from Amgen, Vifor and Fresenius Medical Care.
- Membership:
  - KDIGO Executive Committee
  - KDIGO committee for the CKD-MBD guideline
  - NICE committee for the CKD-MBD guideline
  - ESPN working group on CKD-MBD (chair) and Dialysis (board)
  - Paediatric Renal Nutrition Taskforce (chair)

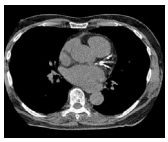
CKD-MBD in children – managing Ca and P



Too little Ca
- Bone pain
- Rickets / osteopenia
- Fractures

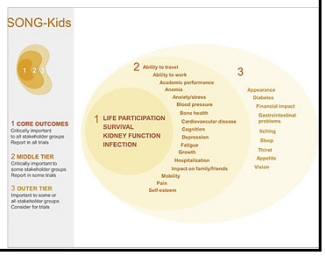


Too much Ca
- Vascular calcification
- Cardiovascular mortality



CKD-MBD – aims of management

- ✓ Prevent skeletal deformities, bone pain, fractures
- ✓ Maintain normal growth
- ✓ Prevent secondary hyperparathyroidism
- ✓ Prevent vascular calcifications
- ✓ Decrease cardiovascular mortality



Outline

CKD-MBD management

- Case based study
  - Monitoring – biomarkers vs DXA
  - Dietary requirements for Ca and P
  - Vitamin D – native vit D and vit D analogues
  - Phosphate binders – types, pros and cons
  - Calcimimetics
- Practical tips

Q 1 – the neonate with CKD

John is a 2-week old term baby diagnosed with posterior urethral valves. His creatinine is 210µMol/L. Ca and P levels are normal.
He has persistent vomiting and requires nasogastric tube feeds.

What Ca, phosphate and PTH levels should we aim for in a neonate. Which ONE is correct?

A. Same levels as for all healthy children
B. Same as for healthy adults
C. Lower than requirements for healthy infants
D. Higher than requirements for healthy infants
E. You should not measure PTH levels in newborns

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B. Same as for healthy adults
C. Lower than requirements for healthy infants
D. Higher than requirements for healthy infants
E. You should not measure PTH levels in newborns ✓

Q 2 – the neonate with CKD

John requires nasogastric tube feeds.

The dietitian asks you how much Ca and P to provide in baby John's feeds.

A. Same requirement for all healthy children
B. Same as for healthy infants
C. Same as for healthy adults
D. Lower than requirements for healthy infants
E. Higher than requirements for healthy infants

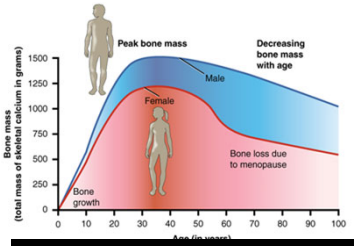
Q 2 – the neonate with CKD

John requires nasogastric tube feeds.

The dietitian asks you how much Ca and P to provide in baby John's feeds.

A. Same requirement for all healthy children
B. Same as for healthy infants ✓
C. Same as for healthy adults
D. Lower than requirements for healthy infants
E. Higher than requirements for healthy infants

Calcium requirements at different ages



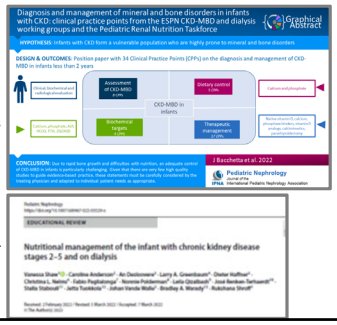
Age	Balance	Ca/day
Infancy and Childhood	+ + (200-300 mg/d)	250-1000 mg
Adolescent and Young adults	+ (10-50 mg/d)	1000-1300 mg

Growing children need calcium!

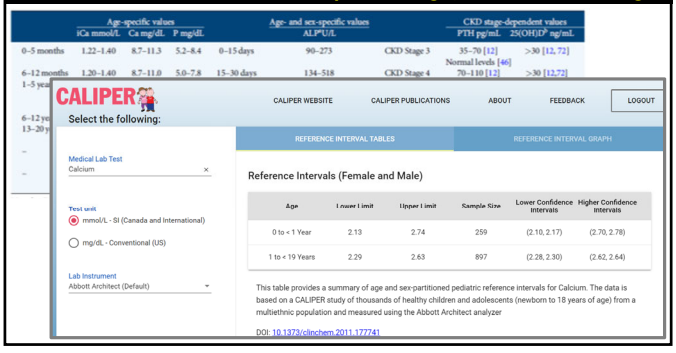
CKD-MBD in infants: a highly vulnerable population

- Infants with CKD are especially prone to MBD
- Period of the most rapid growth
  - High demands of Ca and phosphate
  - To obtain a positive mineral balance and adequate endochondral ossification
  - But this is a fine balance to avoid vascular calcifications
- Infants are particularly vulnerable for complications such as rickets, skeletal deformaties, bone pain, and growth retardation
- Secondary hyperparathyroidism
  - May really be tricky…
  - Calcium deficiency may worsen SHPT
  - Feeding difficulties
- Beware of CAKUT, TCF2/HNF1B and severe SHPT…

Ferré JCEM 2013



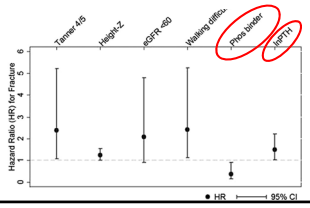
Reference values must be adapted to age, sex and CKD stage



Fractures in children with CKD

537 children
Mild - moderate CKD (83% in CKD stages 2-3)
~4 year follow-up

2-3 fold higher fracture risk in boys and girls with CKD compared to their healthy peers

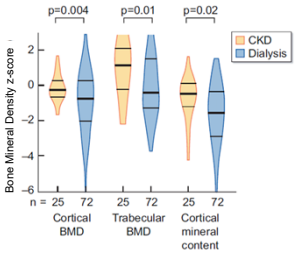


Denburg, et al. JASN 2016

Bone pain and fractures in children with CKD

58% reported bone pain and 10% had fractures

Bone pain:
- Lower limbs & back
- Mild exercise, walking
- Required use of analgesics



Lalayiannis A et al; NDT 2021

Q 3 – evaluation of CKD-MBD

John is now 4 years old and is in CKD stage 3.

How do you evaluate for mineral bone disease in children?
Select TWO correct answers

A. Follow trends in serial measures of Ca, P, PTH, ALP and 25-hydroxyvitamin D
B. Follow trends in serial measures of Ca, P, PTH, ALP and 1,25-dihydroxyvitamin D
C. Check serum bicarbonate levels with every blood test
D. Annual x-ray of the wrist
E. Annual DXA (dual energy x-ray absorptiometry) scans

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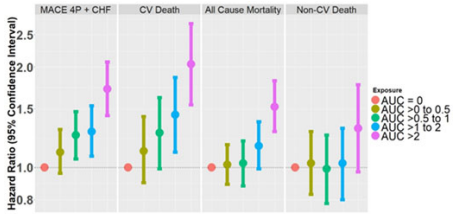
How to evaluate MBD in daily practice?

The treatment(s) of CKD-MBD should be based on serial assessments of calcium, phosphate, PTH, alkaline phosphatase and vit D considered together, following trends in levels.

There is no benefit from performing routine DXA scans in children with CKD
- 2D image, cannot distinguish between cortical and trabecular bone
- No evaluation of geometry, microarchitecture and mineralization
- Systematic underestimation of BMD in children with poor growth

ESPN guidelines; Bakkaloglu et al, NDT 2020

Follow trends in levels – AUC approach

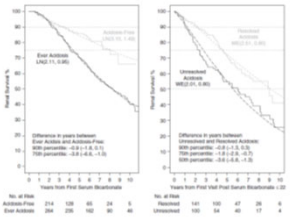


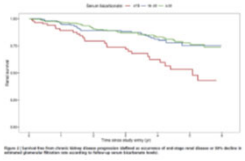
Note: Acronyms used: CV death: death, due to cardiovascular causes (17414 observations, number of events=1102). MACE 4P + CHF: Major adverse cardiovascular events (cv death + non-fatal myocardial infarction + non-fatal angina + non-fatal stroke + congestive heart failure; 15099 observations, number of events= 2396). Non-CV Death: death to non-cardiovascular causes (17414 observations, number of events=1179).

DOPPS data; NDT 2020

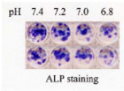
Acidosis and the risk of CKD progression in children

European 4C study; n = 704
Threshold 18 mmol/L
No association with longitudinal growth.





North-American CKID study
Threshold here 22 mmol/L
Only 36% of patients with acidosis were supplemented



Acidosis can promote bone demineralisation

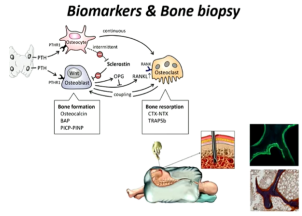
Kraut, Kidney International 1986
Kato, BioScience Trends 2013c

Harambat Kidney Int 2017; Brown cJASN 2020

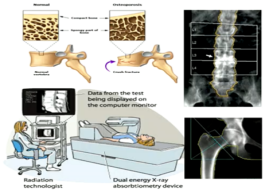
Role of biomarkers, radiology and histology

Shifts of Ca from the skeletal store can be assessed by considering skeletal remodeling rates and bone demineralization.

Biomarkers & Bone biopsy



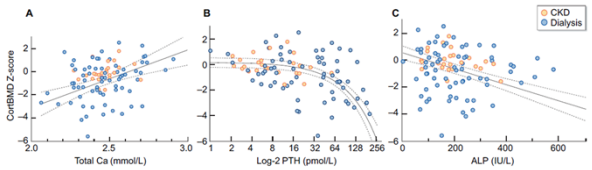
Radiology



Real-time (short-term)
Ca efflux from bone

Long-term
Ca efflux from bone

Routine biomarkers more useful than DXA



β 0.21, p=0.005 β -0.43, p<0.0001 β -0.36, p<0.0001

Do not perform routine DXA scans in children with CKD stages 4-5 and 5D

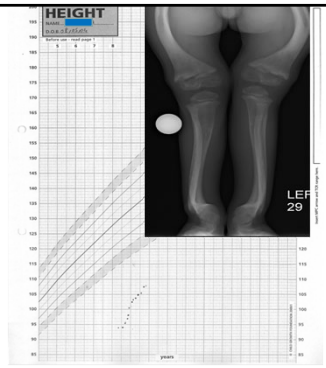
Lalayiannis et al, NDT 2020

Q 4 – bone disease

John is now 10 years old. The family stopped all medical care and tried herbal remedies for several years. His weight and height are at -4 SDS.
His blood results show:

- serum Ca (total) 1.8 mMol/L
- serum phosphate 1.6 mMol/L
- PTH 125 pMol/L (normal <6 pMol/L)
- 25-hydroxyvitamin D 25 nMol/L (= 10 ng/ml)

Growth chart, images and x-ray -



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Which one of the following medications will you start first?

A. Cholecalciferol
B. Alfacalcidol
C. Paricalcitol
D. Cinacalcet
E. Pamidronate

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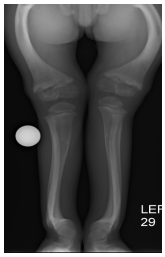
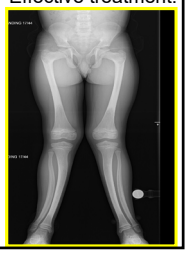
The metabolic mayhem of untreated CKD-MDB



Effective treatment!



↓ Calcium, ↑↑↑PTH, ↓vitamin D

Vitamin D guidelines

We suggest that serum 25(OH)D levels are maintained above 75nMol/L (>30ng/ml) in children with CKD stages 2 – 5D.

We classify vitamin D status as follows:

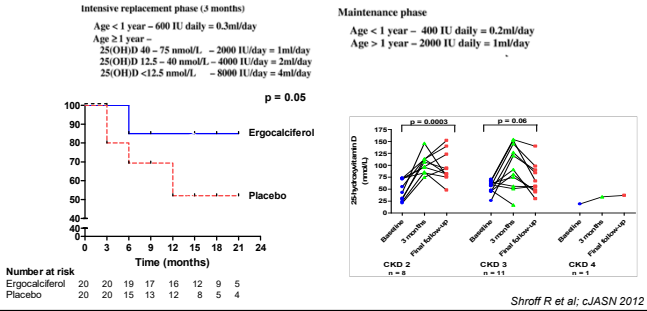
- sufficiency > 75 nMol/L (>30 ng/ml)
- insufficiency 50 – 75 nMol/L (20 – 30
- deficiency 12- 50 nMol/L (5 – 20 ng
- Severe deficiency <12 nMol/L (<5 ng/

Frequency of monitoring: no more than 3

Aim for levels: 75 – 120nMol/L

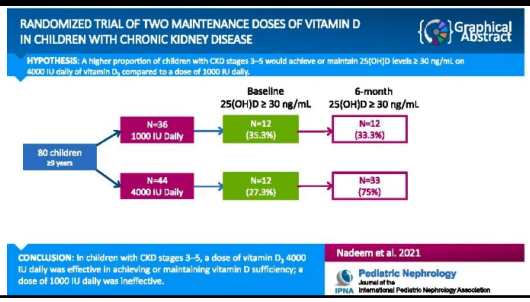
	25(OH)D (nmol/L*)
Rickets or osteomalacia, severe hyperparathyroidism, Ca malabsorption	< 10
PTH stimulation, reduced calcium absorption	10 - 30
Sometimes mildly raised PTH	30 - 50
No increase in 1,25(OH)$_2$D production or increased calcium absorption	> 75
Abolition of seasonal variations in PTH level	>100
Hypercalcaemia	>>> 250

Vitamin D delays the onset of secondary hyperparathyroidism

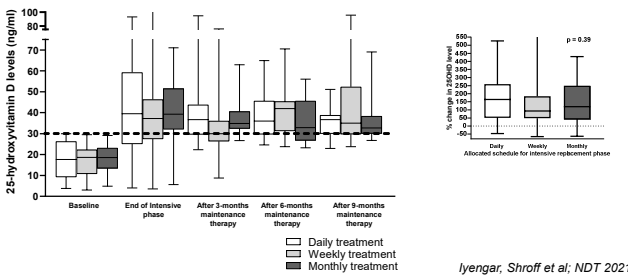


Shroff R et al; cJASN 2012

Children with CKD require higher doses of colecalciferol to achieve adequate 25(OH)D levels

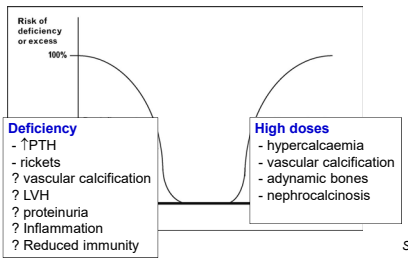


Daily vs weekly vs monthly treatment regimens –RCT



Iyengar, Shroff et al; NDT 2021

Active vit D
Risk of toxicity? A biphasic dose –response curve



Shroff; JASN 2008

Shroff; Ped Nephrol 2010

Active vit D analogues

	CATEGORY	RECOMMENDATION	GRADE
1	***Target population***	We suggest using vitamin D analogues in children with CKD 2-5D who have persistent secondary hyperparathyroidism	2B
2	***Type of vitamin D analogue supplementation***	We suggest that any vitamin D analogue can be used to reduce PTH levels in children with CKD 2-5D.	2C
3	***Route of vitamin D analogue administration***	We suggest that daily oral calcitriol is safe, effective and well tolerated in children with CKD 2-5D.	2B
4	***Dose of active vitamin D analogues: therapeutic targets and safety***	We suggest starting vitamin D analogues in the lowest dose to achieve target PTH concentrations and maintain normocalcemia. Subsequent titration of vitamin D therapy may be performed based on trends in serum calcium, phosphate and PTH levels.	2D

european society for paediatric nephrology

To D or not to D? Personal practice

- Monitor 25(OH)D levels at baseline, 3-months, then annually
- If deficient OR high PTH /low serum calci… give cholecalciferol supplementation fo… with CKD 2-3 and transplants in CK…
- Aim for levels:
'Adequate levels' > 75… …ng/ml)
Stop treatment at … …
Risk of toxi… …nmol/L
- In CK… 4, 5 and dialysis –
Combine cholecalciferol with active vit D analogue

Not evidence based

Q 5 – medications

John is 10 years old and has been started on PD. His blood results show:
- serum Ca 2.3 mMol/L
- serum phosphate 2.9 mMol/L
- PTH 37 pMol/L (normal <6pMol/L)
- 25-hydroxyvitamin D 82 nMol/L

Which of the following medications will be most appropriate for him?

A. Cholecalciferol
B. Alfacalcidol
C. Calcium carbonate
D. Sevelamer carbonate
E. Cinacalcet

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Guideline recommendations: phosphate binders

In children with CKD Stages 3a–5D, **base the choice of phosphate-lowering treatment on serum calcium levels.**

Use a **calcium-based phosphate binder** as the first-line phosphate binder to control serum phosphate in addition to dietary management.

Maintain serum calcium in the age-appropriate normal range.

Types of P-binders

Compound	Formulation(s) available	Calcium content (%)	Calcium absorbed (%)	Phosphate bound per mg Ca^{++} absorbed	Comments
Calcium Carbonate	250mg, 500mg, 1.25g, 2.5g tablets or as 250mg/5ml liquid	40	20-30	= 1 mg / 8 mg	High Ca load, cheap, few GI side effects
Calcium Acetate	475mg or 950mg tablets	25	22	= 1 mg / 3 mg	Less Ca load than $CaCO_3$, inexpensive, GI side effects more common particularly in infants
Sevelamer hydrochloride or Sevelamer carbonate	800mg tablets for both or 2400mg sachet (for sevelamer carbonate only)	0	0	NA	Ca^{++} and Al^{+++} free, acts as cholesterol binding resin and lowers serum cholesterol, binds fat soluble vitamins, expensive, difficult to administer to younger children, metabolic acidosis (with hydrochloride preparation)
Aluminium containing binders	100mg capsules	0	0	NA	Very effective P binding but risk of aluminium toxicity; can be used short-term under close monitoring of aluminium levels; recommended for 'rescue therapy' from severe hyperphosphatemia only
Mg + Ca carbonate	variable strength tablets	variable	20-30 % of Ca	= 1 mg / 2.3 mg	Less Ca^{++} load, GI side effects, long term effects?
Lanthanum carbonate	chewable tablets or sachets with 500mg, 750mg or 1000mg	0	0	NA	Gastrointestinal side-effects are very common; accumulates in bone and long-term effects in the growing bone are unknown; expensive.
Sucro-ferric oxyhydrixyde	**500mg chewable tablets**	**0**	**0**	**NA**	Gastrointestinal side-effects – diarrhea, nausea.

RCTs in children comparing P binders

Table 20 | RCTs of phosphate binders in children with CKD

Author (year)	*N*	Population	F/U	Study design	Arm 1	Arm 2	Outcomes
Salusky (2005)[17]	29	PD	8 months	RCT	Sevelamer	Ca carbonate	Bone Bx, P, Ca, Ca × P, PTH, hypercalcemic episodes
Pieper (2006)[354]	18	HD, PD, CKD stages 3-4	8 weeks	RCT, cross-over	Sevelamer	Ca acetate	P, Ca, iPTH, lipids

Bx, biopsy; Ca × P, calcium-phosphorus product; CKD, chronic kidney disease; HD, hemodialysis, iPTH, intact parathyroid hormone; PD, peritoneal dialysis; PTH, parathyroi hormone; RCT, randomized controlled trial.

Sevelamer hydrochloride was as effective as calcium acetate in lowering phosphate levels but was associated with a higher rate of metabolic acidosis (34.4% vs. 3.3%)

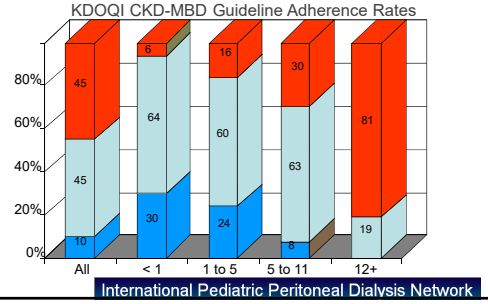
Sevelamer carbonate now available.

Ca-based P-binders – practical points

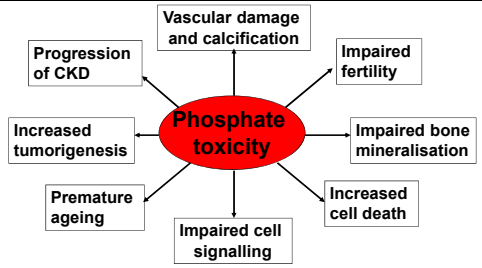
	CaCO3	Ca acetate
Elemental calcium content	40%	25%
Solubility	Low pH	Wider range
mg P bound/mg Ca absorbed	1:8	1:3
% Ca absorbed	20-30%	20%
mg P bound b		
Cost		

- Should be **given with meals and high P snacks**, never on an empty stomach (else more Ca is absorbed)
- Requires an acidic pH to dissociate **– don't give with ranitidine, omeprazole**
- Ca can precipitate in the duodenum as CaCO3 **– don't give with bicarb supplements**
- May forms insoluble compounds in the gut **– don't give with iron preparations, phytates or oxalate**

High P levels in 45% of PD patients



Phosphate toxicity



Increased P is associated with a higher mortality risk even in the healthy population *Melamad; cJASN 2010*

Q 6 – dietary management

John is now 13 years old and remains on dialysis.
His blood results show:

- serum Ca 2.1 mMol/L
- serum phosphate 3.2mMol/L
- PTH 125 pMol/L (normal <6 pMol/L)
- 25-hydroxyvitamin D 55nMol/L

Which one of the following is the most appropriate advise for him?

A. Stop eating chocolates
B. Stop all dairy products, meat, fish, eggs and pulses
C. Stop drinking coffee
D. Stop drinking coca cola
E. Stop eating potatoes

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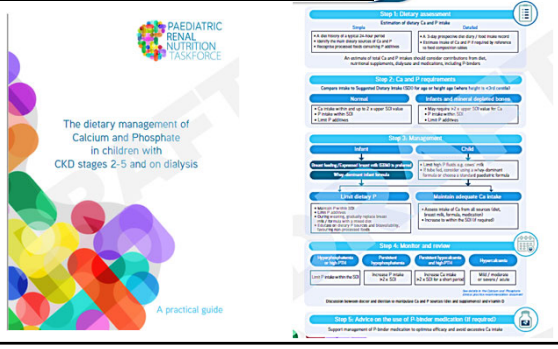
Dietary phosphate

- **Organic** – bioavailability 30- 70%
- **Inorganic** – bioavailability ~100%

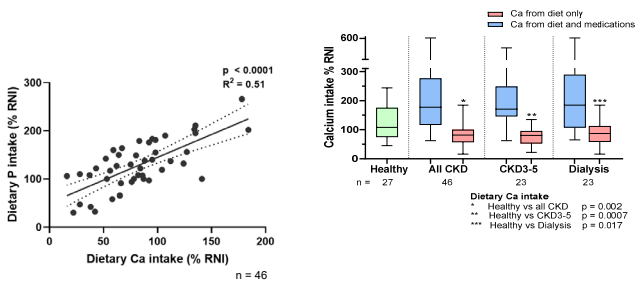
Phosphate additives
- raising agents, extend shelf-life, improve colour / flavour / moisture
- Can increase P content by > 50%
- Manufacturers are not legally required to list th
- Not included in nutrient databases/dietary asse
- **Avoid processed foods**

E338	Phosphoric acid	E452	Polyphosphate
E339	Sodium phosphate	E541	Sodium aluminium phosphate
E340	Potassium phosphate	E1410	Monostarch phosphate
E341	Calcium phosphate	E1412	Distarch phosphate
E343	Magnesium phosphate	E1413	Phosphated distarch phosphate
E450	Diphosphate	E1414	Acetylated distarch phosphate
E451	Triphosphate	E1442	Hydroxyl propyl distarch phosphate

Practical tips for dietary management

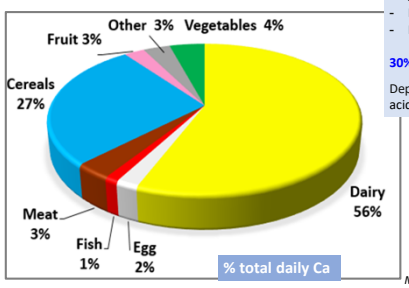


Reduced dietary Ca intake with a PO4 restricted diet



McAlister et al; Ped Nephrol 2020

Foods contributing to calcium intake in healthy people



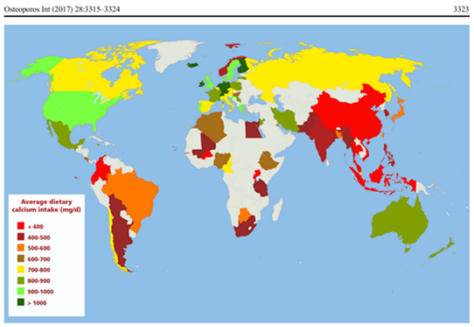
Depends on:
- Age
- Food preferences
- Food fortification (national guidelines)

30% of dietary Ca is absorbed (5 - 82%)

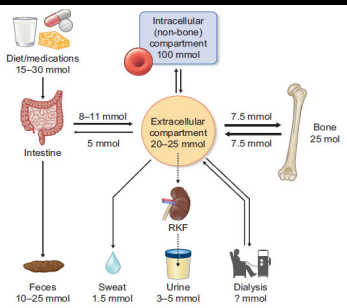
Depends on source (e.g. oxalate and phytic acid content), intake, vitamin D status, age

McAlister et al (2020) Pediatric Nephrology

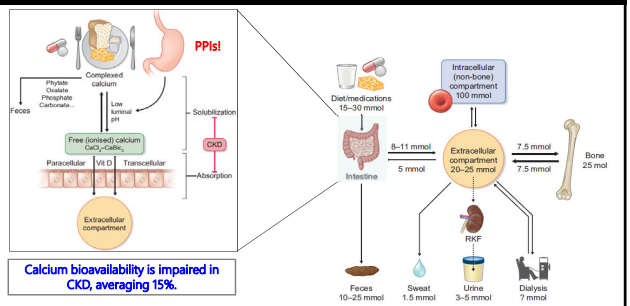
Dietary intake of calcium shows regional variability



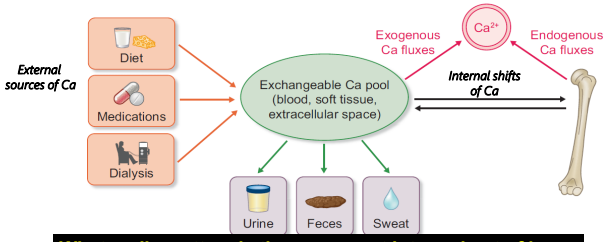
Ca balance and its determinants



Reduced bioavailability of Ca balance in CKD



What are the determinants of Ca balance in CKD?



What really matters is the movement into and out of bone, where > 99% of calcium is stored

Growing bones need calcium – radiology studies

Cross-sectional
- 171 patients, age 5-21 yrs
- CKD 2-5D

	β (95% CI)	p-value
Calcium (per 1 mg/dl)	0.31 (0.08, 0.54)	0.01
25(OH)D (per 10 ng/ml)	0.18 (0.01, 0.34)	0.04
$1,25(OH)_2D$ (per 10%)	-0.07 (-0.10, -0.04)	< 0.001
PTH (per 10%)	-0.02 (-0.04, -0.01)	0.002
FGF23, underlying renal disease and acidosis were not significant.		

Longitudinal
- After 12 months
- 89 patients

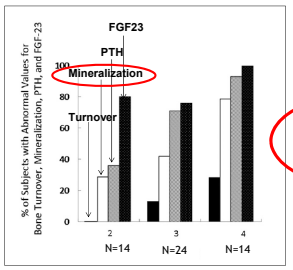
Decline in cortical BMD Z-scores:
- Higher baseline $1,25(OH)_2D$
- ↑ΔPTH

↑Δ Calcium - ↑ cortical BMD (especially in growing children)

1 SD decrease in BMD → 2-fold increase in fracture risk

Denburg, et al. JCEM 2013

Growing bones need calcium – bone biopsy studies



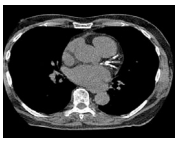
Defective mineralization present in:
- 29% of patients with stage 2
- 42% with stage 3
- 79% with stage 4/5 CKD

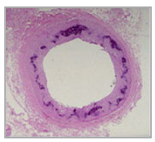
Abnormal mineralization
↓ serum calcium
↑ PTH

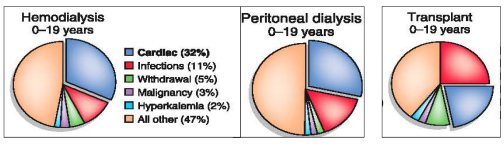
Bone biopsies in 52 children with CKD 2-4
Age - 2 to 21 years

Wesseling-Perry et al; cJASN 2012

BUT – too much Ca can cause vascular calcification!







USRDS 2011 report

Q 7 – medications

John is now 16 years old and sadly returns to dialysis after a failed kidney transplant.
His blood results show:

- serum Ca 2.8 mMol/L
- serum phosphate 3.2mMol/L
- PTH 125 pMol/L (normal <6pMol/L)
- 25-hydroxyvitamin D 25nMol/L (=10ng/ml)

Which of the following medications will be most appropriate for him?

A. Cholecalciferol
B. Alfacalcidol
C. Calcium carbonate
D. Calcium acetate
E. Cinacalcet

Q 7 – medications

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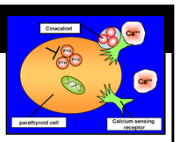
Which of the following medications will be most appropriate for him?

A. Cholecalciferol
B. Alfacalcidol
C. Calcium carbonate
D. Calcium acetate
E. Cinacalcet √

Use of calcimimetics (cinacalcet)



- Increases Ca sensing receptor sensitivity to ionized calcium
- Dose dependent suppression of PTH up-to 80%
- Increase therapeutic window for vitamin D / Ca based P binder therapy
- Cinacalcet is licensed in children > 3 yrs on dialysis;
- BEWARE OF HYPOCALCAEMIA - Corrected serum calcium should be in the upper normal range prior to administration
- Keep corrected calcium and ionized calcium within the normal range by reducing cinacalcet dosage or additional vitamin D/ calcium medication

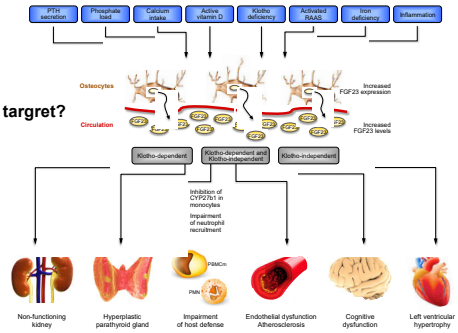
ESPN guideline; NDT 2020

european society for paediatric nephrology

Don't forget other factors affecting renal bone disease!

- Metabolic acidosis
- Malnutrition – obesity, sarcopenia, obese sarcopenia
- Disturbances of the growth hormone axis
- Corticosteroid therapy (osteoporosis)
- Hypophosphatemia (diet, intensive dialysis, P-binders)
- Hypocalcaemia (infants, at periods of rapid growth, "crash landers")
- Reduced physical activity, poor muscle strength

FGF23:
The future targret?



Leifheit-Nestler, Pediatr Nephrol 2017

KEY MESSAGES

- Interdependency of serum calcium, phosphate, PTH and vit D for clinical therapeutic decision-making.
- There is a fine balance between enough calcium for bone mineralisation vs too much calcium causing vascular calcification.

What the guidelines say

NHS National Institute for Health and Clinical Excellence

KDIGO Kidney Disease: Improving Global Outcomes

european society for paediatric nephrology

PAEDIATRIC RENAL NUTRITION TASKFORCE

Control hyperphosphataemia

….and avoid hypo or hypercalcaemia!

Thank you!

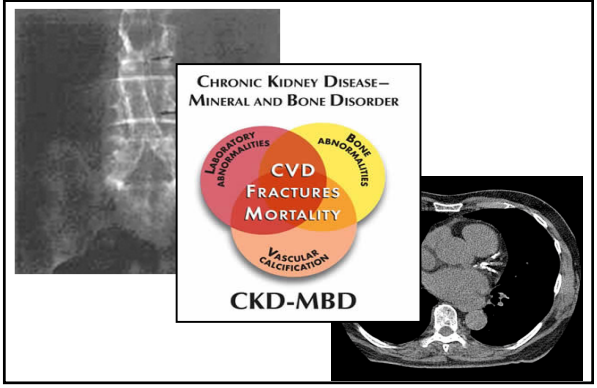
Cardiovascular sequaele in CKD

Rukshana Shroff

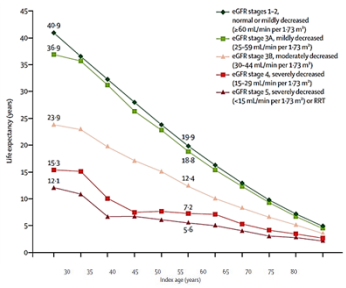
Great Ormond Street Hospital for Children and Institute of Child Health, London, UK.

Artificial Intelligence is not yet a solution

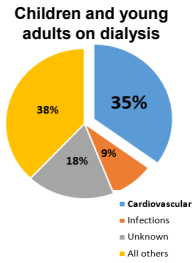
Bones demineralise & vessels calcify



Life expectancy and causes of death in patients with CKD



Gansevoort et al. Lancet 2013



USRDS 2018 Annual Report

Q 1 – CVD in children with CKD

Is CVD in a child with end-stage kidney disease preventable?

A. No
B. Yes, but only by kidney transplantation
C. Yes, but only with expensive medications
D. Yes, it is preventable in ALL children

Q 1 – CVD in children with CKD

Is CVD in a child with end-stage kidney disease preventable?

A. No
B. Yes, but only by kidney transplantation
C. Yes, but only with expensive medications
D. Yes, it is preventable in ALL children! ✓

Outline

- Pathophysiology of CVD and bone disease in CKD
  - modifiable risk factors
- Bone – vascular cross-talk
- The role of 'inflammaging'
- Can we do better - improving CVD and bone outcomes

Prevention vs damage limitation

- Can we **prevent the development** of CVD?
- Can we **halt the progression** of CVD?
- Can we **reverse** cardiovascular damage?

Q 2 – Which one of these is not a risk factors for CVD in children with CKD are:

A. Hypotension

B. Hypertension

C. Calcium

D. 25-hydroxyvitamin D

E. 1,25-dihydroxyvitamin D

Q 2 – Which one of these is not a risk factors for CVD in children with CKD are:

A. Hypotension ✓

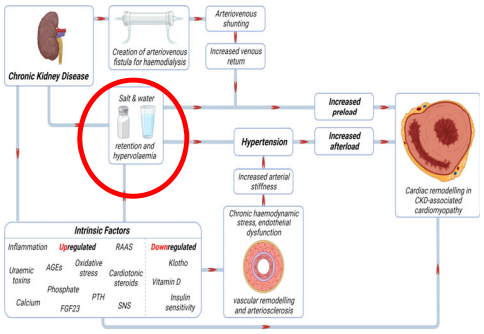
B. Hypertension

C. Calcium

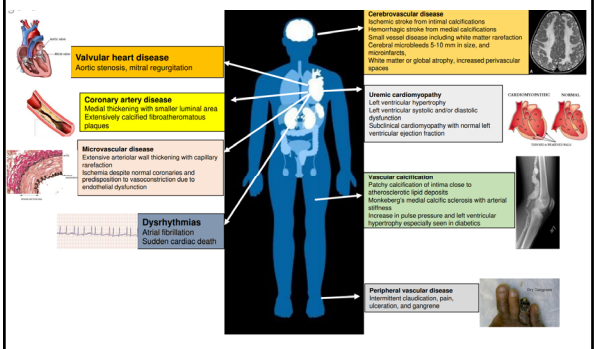
D. 25-hydroxyvitamin D

E. 1,25-dihydroxyvitamin D

Hypertension and CVD damage

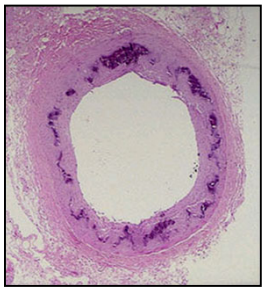


Law JP et al. Hypertension and cardiomyopathy associated with CKD:. J Hum Hypertens. 2023



Nature Rev Neph; 2021

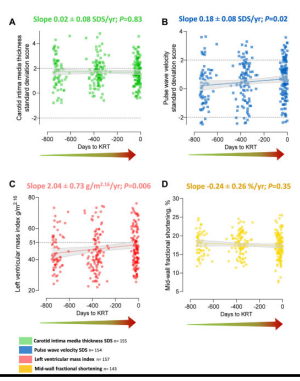
Medial vascular calcification in CKD



'Traditional' Framingham risk factors and CKD – related risk factors

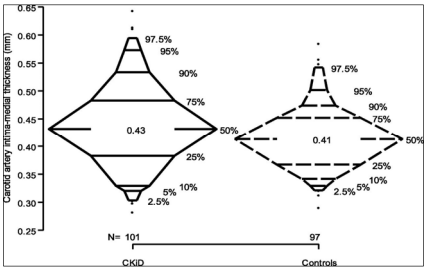
- Abnormal Ca & Phosphate
- Hyperparathyroidism
- Vitamin D
- Oxidative stress
- Hyperhomocysteinemia
- Albuminuria
- Malnutrition
- Dialysis

CVD begins early in CKD



Khandelwal, Shroff et al. Lancet eClin Health 2024

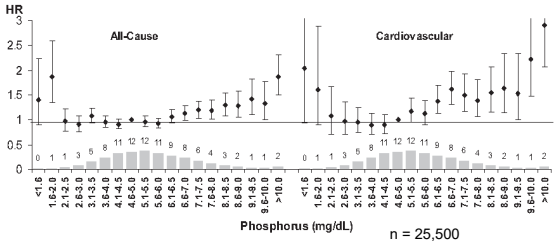
Increased cIMT in early CKD



- 100 children with a median GFR 43 ml/min/1.73 m^2
- Increased cIMT was associated with HT and dyslipidemia

Brady et al; CJASN 2012

Phosphate and mortality risk

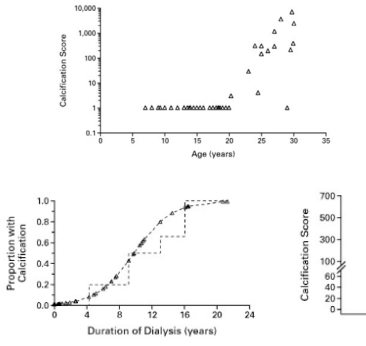


n = 25,500
All-cause deaths – 5857
CV deaths - 1930

'Safe' P levels 3.6 - 5.0 mg/dL (0.84 - 1.62 mmol/L)

Tentori et al; AJKD 2008

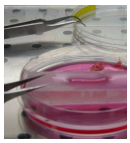
Coronary calcification in children and young adults

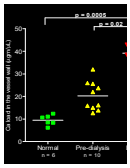


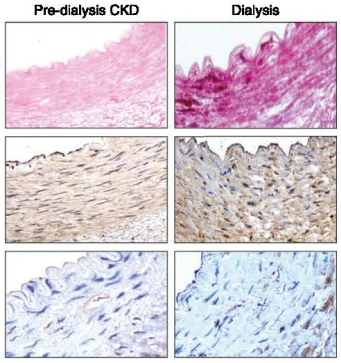
Serum P and the Ca x P positively correlated with change in calcification scores at follow-up

Authors / Journal	Number of dialysis pts	Vascular measures	Clinical / biochemical associations with cIMT
Oh / Circulation 2002	39	cIMT CAC	- dialysis duration - mean serum P - PTH levels
Litwin / JASN 2005	37	cIMT	- dialysis duration - mean serum P - Mean calcitriol dose
Mitsnefes / JASN 2005	16	cIMT distensibility	- dialysis duration - mean serum Ca x P - Mean calcitriol dose - mean PTH levels
Shroff / JASN 2007	85	cIMT PWV CAC	- dialysis duration - mean serum P and Ca x P - Mean calcitriol dose - mean PTH levels
Civilibal / Ped Neph 2007	37	cIMT FMD ECHO	- mean serum P - total & LDL cholesterol - mean calcitriol dose
Reusz / Ped Neph 2009	11	PWV	- mean serum Ca x P - mean calcitriol dose

Vascular calcification – arterial biopsy model

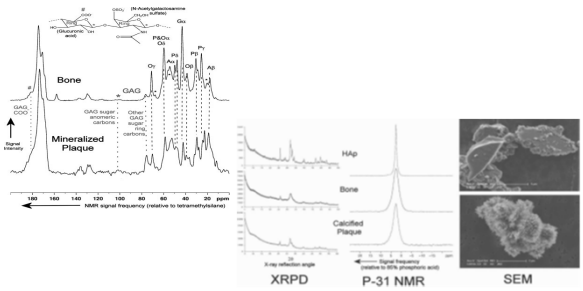






Shroff R, et al: Circulation 2008; J
2013; Circ Res 2013; PLoS One 2

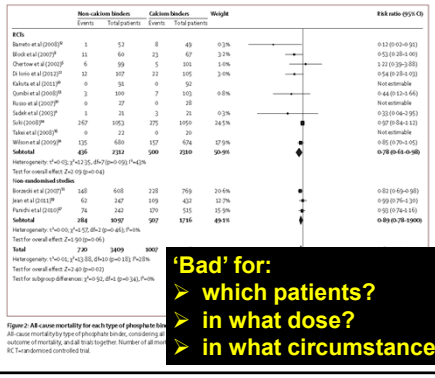
Calcification in bones and vessels is a similar process



GAG, glycosaminoglycan; NMR, nuclear magnetic resonance; SEM, scanning electron microscopy; XRPD, X-ray powder diffraction.

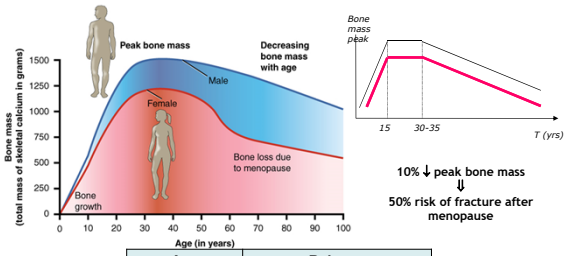
Duer MJ, et al.; ATVB 2008

Calcium is 'bad'



'Bad' for:
- which patients?
- in what dose?
- in what circumstances?

Skeletal mineralization

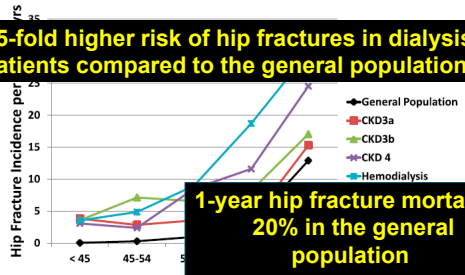


10% ↓ peak bone mass
⇓
50% risk of fracture after menopause

Age	Balance
Infancy and Adolescence	+ + (200-300 mg/d)
Young adults	+ (10-50 mg/d)
Mature adults	0
Elderly	negative

Incidence of hip fractures increases as GFR declines

4.5-fold higher risk of hip fractures in dialysis patients compared to the general population



1-year hip fracture mortality: 20% in the general population
50% in dialysis patients

Moe and Nickolas, cJASN 2016
Alem, et al. Kidney Int 2000

CKD patients fracture at a greater BMD

N = 2750; CKD stage 3 – 5 (non-dialysis)
Hip BMD measured by DEXA
11-year follow-up
Only incident fractures recorded

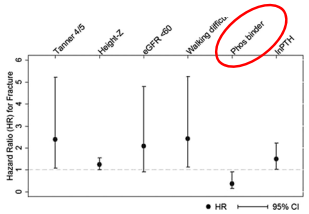
	HR (95% CI) per SD lower Femoral Neck BMD T-score		Interaction p-value
	No CKD	CKD	
Unadjusted	2.45 (2.13, 2.82)	2.32 (1.79, 3.01)	0.72
Adjusted	2.14 (1.80, 2.55)	2.69 (1.96, 3.69)	0.70
PTH & Vit D	2.15 (1.80, 2.57)	2.74 (1.99, 3.77)	0.68

Yenchek, et al. CJASN 2012

Fractures in CKD children

537 children
Mild - moderate CKD (83% in CKD stages 2-3)
~4 year follow-up

2-3 fold higher fracture risk in boys and girls with CKD compared to their healthy peers



58% reported bone pain and 10% had fractures

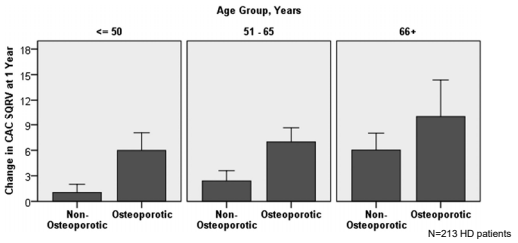
Bone pain:
- Lower limbs & back
- Mild exercise, walking
- Required use of analgesics

Lalayiannis A et al; NDT 2021

Denburg, et al. JASN 2016

Bone–vascular link?

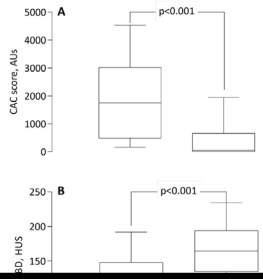
In adults with CKD: the worse the bone, the worse the vessel



Osteoporosis was a significant predictor of CAC progression

Malluche HH, et al. JASN 2015

CAC, vertebral BMD and death

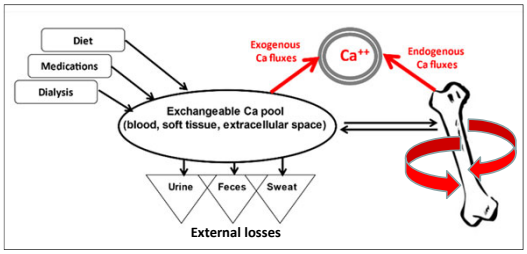


n= 231
CKD5/5D/Tx patients

Low vertebral body BMD strongly associated with CAC

Predictive of mortality even after adjusting for age, diabetes, gender, inflammation

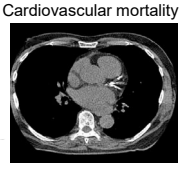
Calcium fluxes – internal vs external



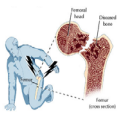
What really matters is the movement into and out of bone, where > 99% of calcium is stored

CKD-MBD management

Too much Ca
- Vascular calcification
- Cardiovascular mortality



Too little Ca
- Bone pain
- Rickets / osteopenia
- Fractures



Recommended calcium intake in adults and children with chronic kidney disease – a European consensus statement

Nephrol Dial Transplant. Sept 2023

Nephrol Dial Transplant, 2023, 0, 1–26
https://doi.org/10.1093/ndt/gfad185
Advance access publication date: 11 September 2023

SPECIAL REPORT

Recommended calcium intake in adults and children with chronic kidney disease—a European consensus statement

Pieter Evenepoel[1,2], Hanne Skou Jørgensen[3,4,5], Jordi Bover[6,7], Andrew Davenport[8], Justine Bacchetta[9,10], Mathias Haarhaus[11,12,13], Ditte Hansen[14,15], Carolina Gracia-Iguacel[16], Markus Ketteler[17], Louise McAlister[18], Emily White[19], Sandro Mazzaferro[20], Marc Vervloet[21,22] and Rukshana Shroff[23,24], on behalf of European Renal Osteodystrophy (EUROD), an initiative of the Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) and the European Renal Nutrition (ERN) Working Groups of the European Renal Association (ERA) and the European Society of Pediatric Nephrology (ESPN)

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CKD-MBD Chronic Kidney Disease Mineral and Bone Disorder

ERN European Renal Nutrition

EUROD European Renal Osteodystrophy

european society for paediatric nephrology

Recommended calcium intake in adults and children with chronic kidney disease – a European consensus statement

Focus of study was to establish optimal calcium intake in chronic kidney disease (in adults and children) which is not addressed in current clinical practice guidelines

Methods

Literature review by expert panel

Delphi survey

Revision based on survey response

Results

Too little — Too much

Calcium

Key recommendations:

Adults

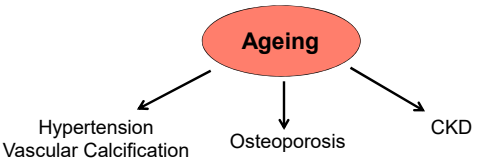
Total calcium intake (diet and medications): 800–1000 mg/day

We suggest not to exceed a total Ca intake of 1500 mg/d to avoid hypercalcemia and risk of vascular calcification.

Evenepoel, P. et al. NDT (2023) @NDTSocial

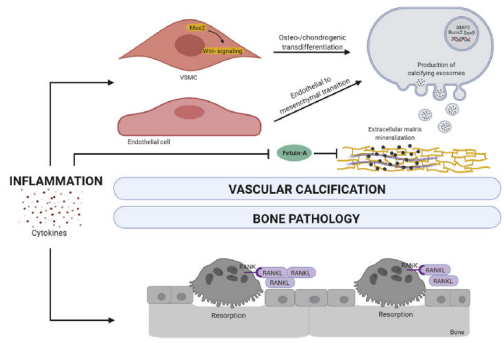
This consensus statement provides key evidence and clinical practice points on calcium management that may assist in clinical decision-making in children and adults with CKD.

The concept of 'inflammaging'



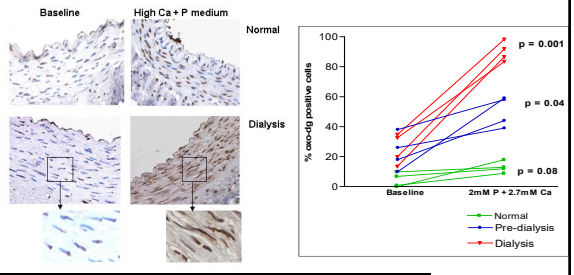
- Elevated Phosphate/FGF23/Klotho
- Low Vitamin D
- DNA damage
- Oxidative Stress
- Systemic Inflammation

Inflammation drives bone resorption and vascular calcification

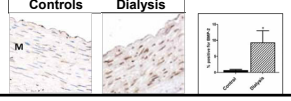


Evenepoel et al; ACKD 2019

Oxidative DNA damage & vascular senescence

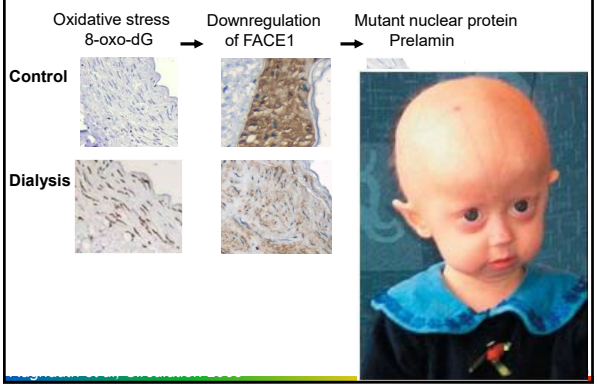


Senescence drives osteogenic differentiation

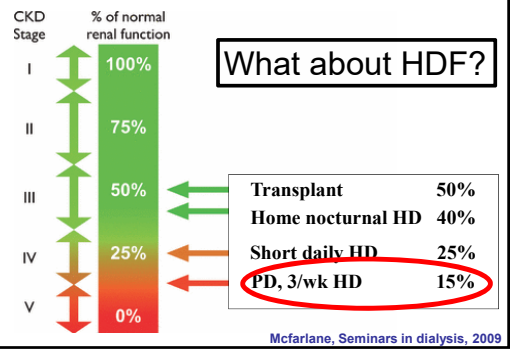


Shroff et al. Circulation 2010

Premature ageing of dialysis vessels

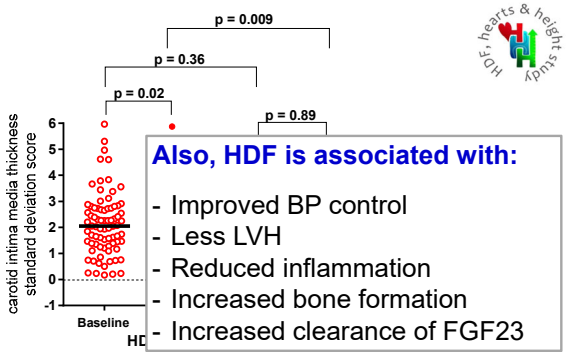


Dialysis - can we do better?



Mcfarlane, Seminars in dialysis, 2009

HDF attenuates the progression of cIMT



Shroff et al; JASN 2019

The importance of bone calcium balance

- Serum calcium levels are <0.1% of total body calcium
- No non-invasive tools to assess changes in bone calcium

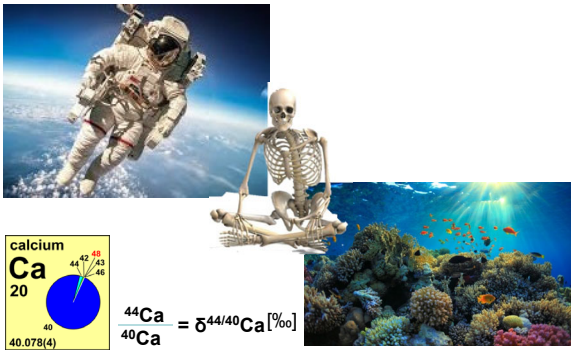
- bone biopsies – invasive
- radiological changes – single site, slow to change
- biomarkers – reflect bone turnover, not mineralisation

Ca balance studies

- Radioactive calcium; given IV
- 'Metabolic cage' setting
- Only 2 studies with 14 adult CKD patients, mean age 65 years

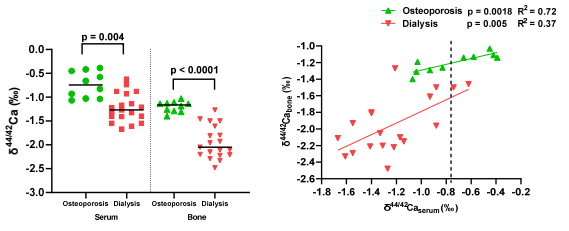
Hill KM, et al. Kidney Int 2013
Spiegel DM, et al. Kidney Int 2012

Calcium isotope studies



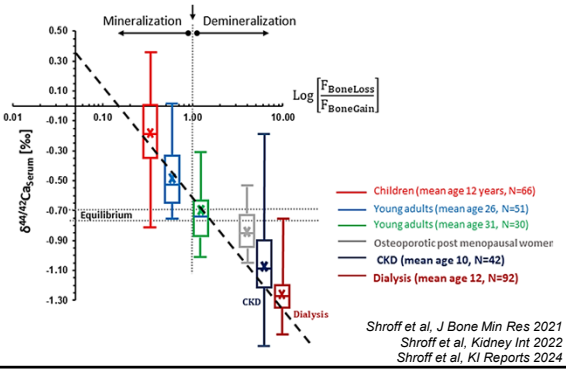
Ca isotope fractions in serum and bone

N = 19 dialysis patients; median age = 59.8 yrs; median dialysis vintage 3.4 yrs
Compared with 10 adults with hip fractures (median age = 84 yrs)



Shroff, Evenepoel et al; In press

Assessing bone mineral balance



Shroff et al, J Bone Min Res 2021
Shroff et al, Kidney Int 2022
Shroff et al, KI Reports 2024

Q 3 – In a child on dialysis which factor will not affect the progression of CVD:

A. Lipid levels

B. Bone health

C. Dialysate Calcium

D. Serum Calcium

E. Serum Magnesium

Q 3 – In a child on dialysis which factor will not affect the progression of CVD:

A. Lipid levels

B. Bone health

C. Dialysate Calcium

D. Serum Calcium

E. Serum Magnesium √

Conclusions

- **Athero- and arteriosclerosis begin early in CKD**
- **Mineral dysregulation and hypertension are the most important modifiable risk factors for CVD**
- **Intensified dialysis regimens and renal transplant reduce cardiovascular risk**

Prevention vs damage limitation

1. Can we prevent development of CVD? ?√

At least for uraemia-related CVD

2. Can we halt the progression of CVD? ?√

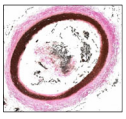
Yes, intensified dialysis and transplantation

3. Can we reverse cardiovascular damage ?X

Conclusions: Bone ↔ vessel cross-talk

Is bone talking to vessels?

Phosphate / FGF23 /SOST?



Are vessels talking to bone?

?

Are vessels becoming a bone-derived tissue?
Osteogenic conversion of vascular smooth muscle cells

Do other tissues play a role in this cross-talk?
Inflammation; Hepatocytes and fetuin; renal tubular cells and Klotho

Do our treatments influence this cross-talk?
Calcium intake, phosphate binders, optimize dialysis

Acknowledgements

NHS National Institute for Health Research

Kidney Research UK

Kids Kidney Research

British Heart Foundation

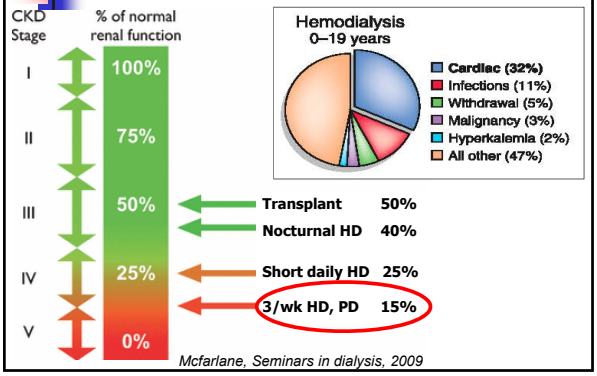
BMA

Haemodialysis vs Haemodiafiltration – which one is better for children?

Rukshana Shroff

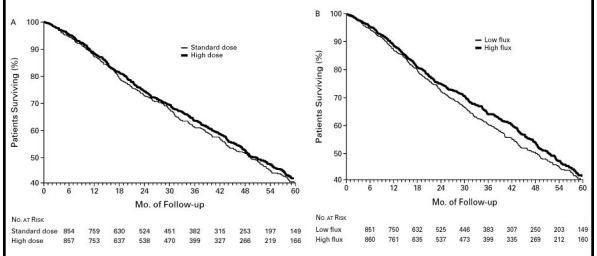
Great Ormond Street Hospital for Children
and Institute of Child Health
London, UK

Effectiveness of treatment types



Mcfarlane, Seminars in dialysis, 2009

A 'urea-centric' approach does not improve survival



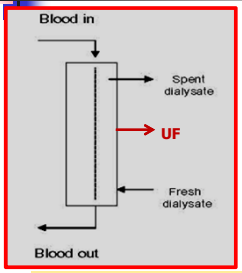
HEMO study, NEJM, 2002

Outline

- Principles of HD and HDF
- Technical requirements of HD and HDF
- Learning from adult studies
- Studies in children - effects of HDF on:
  - cardiovascular outcomes & BP
  - bone disease and growth
  - health related quality of life measures

Technical differences

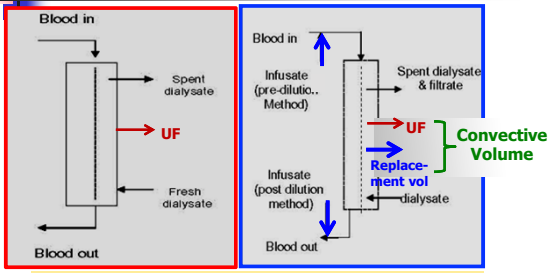
HD



Diffusion (Low molecular weight toxins)

Technical differences

HD **HDF**



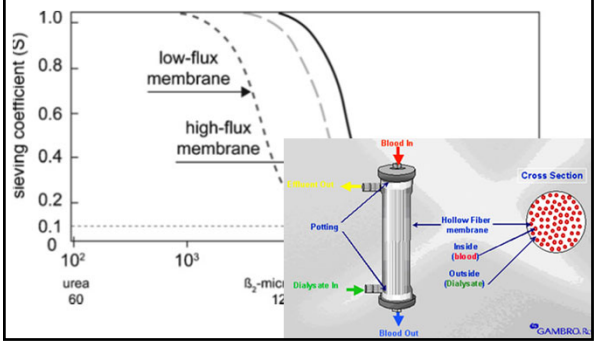
Diffusion (Low molecular weight toxins)

Convection (low + middle MW toxins)

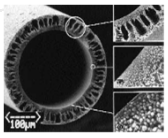
Requirements for HDF

1. High-flux membrane
2. Large quantities of IV quality fluid ('ultrapure' dialysate) as replacement fluid
3. Machines with accurate UF control systems

1. High flux membrane



Characteristics of high-flux membranes



1. Flux - Measure of ultrafiltration capacity

Low flux: Kuf <10 mL/hr/mm Hg
High flux: Kuf >20 mL/hr/mm Hg

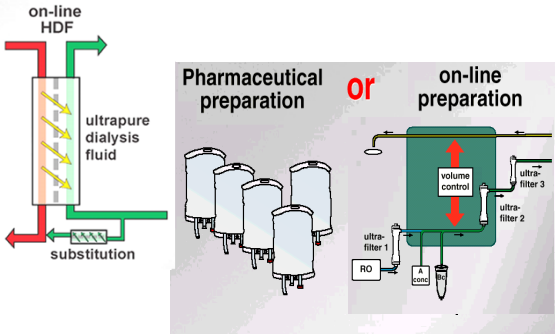
2. Permeability - Measure of the clearance of β2-microglobulin (= middle mol wt solutes)

Low permeability: β 2-microglobulin clearance <10 mL/min
High permeability: β 2-microglobulin clearance >20 mL/min

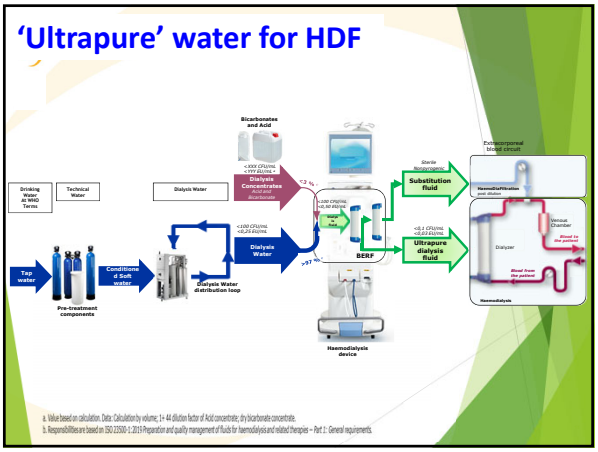
3. Efficiency - Measure of urea (= low mol wt solute) clearance

Low efficiency: KoA <500 mL/min
High efficiency: KoA >600 mL/min

2. Substitution fluid to drive UF



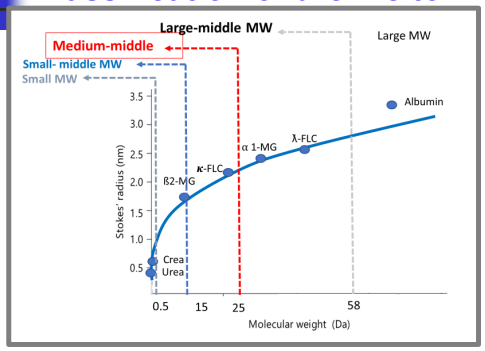
'Ultrapure' water for HDF



Mechanisms for improved outcomes on HDF

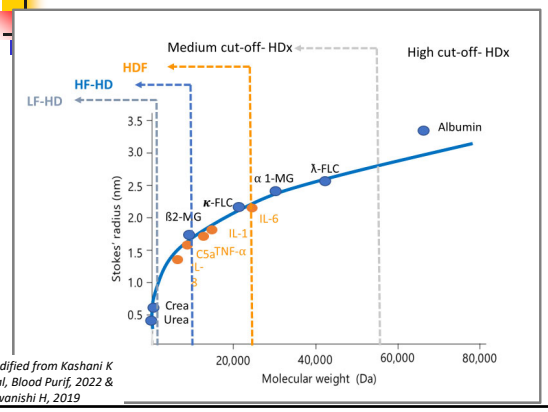
1. Clearance of uraemic solutes across a wide molecular weight range
   - 70 – 78% reduction in β_2 microglobulin on HDF (vs <20% with high-flux HD)
   - Removal of inflammatory cytokines
2. Improved biocompatibility
   - Reduced oxidative stress
   - Removal of AGEs
3. Hemodynamic stability
   - Cooling during HDF
   - Reduced intra-dialytic hypotension

Classification of uremic toxins



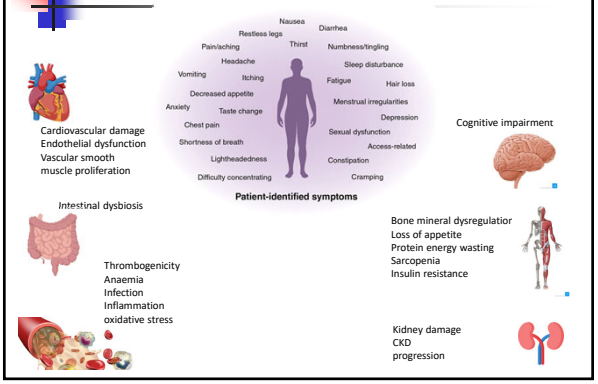
Modified from Kashani K et al, Blood Purif, 2022 and Kawanishi H, 2019

Clearance of uremic toxins



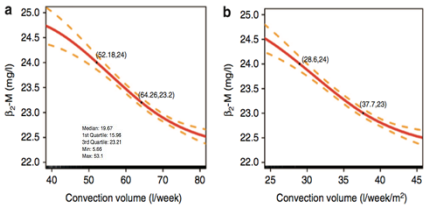
Modified from Kashani K et al, Blood Purif, 2022 & Kawanishi H, 2019

Uraemic toxins are toxic!



Convective Dose and Predialysis ß2-M Concentration Inverse Dose-Effect Relationship*

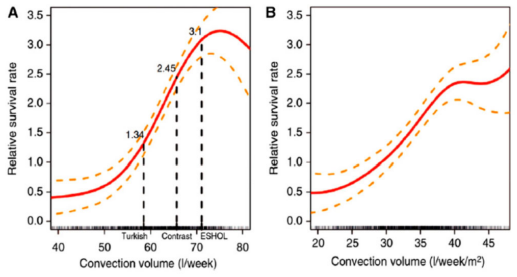
ß2-M concentrations is reduced by 0.6 mg/l for every 10 l of additional convection volume per week



*Fully adjusted for age, gender, Charlson Comorbidity Index, vascular access, albumin, log C-reactive protein and Kt/V.

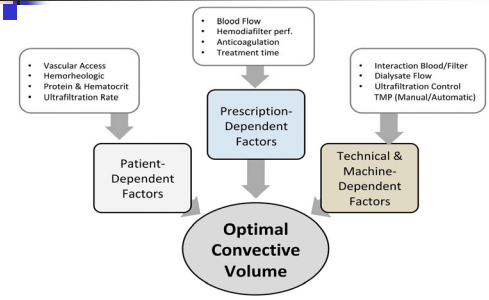
Canaud B et al, *Kidney Int.* 2015;88(5):1108-16

Convection volume – the holy grail of HDF treatment



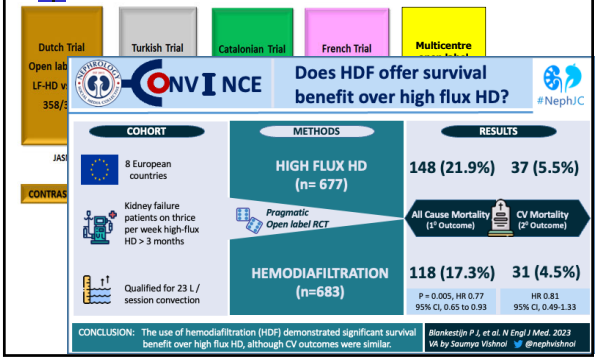
Canaud et al; KI 2015

How to achieve optimal convection vol



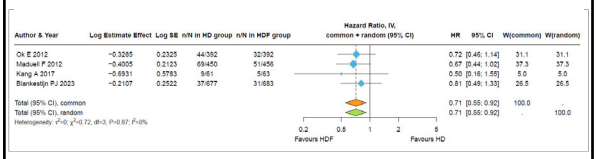
Convection volume target in post-dilution HDF ≥23 L/session, 3x /week

HDF – RCTs in adults



Meta-analysis of RCTs in adults

All-cause mortality



3H (HDF, Hearts and Height) study

Hypothesis

Children on HDF compared with HD have improved:

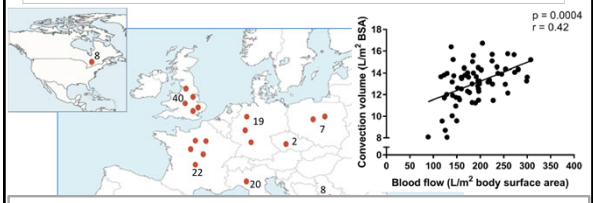
- Cardiovascular risk profile
- Growth and nutritional status
- Quality of life

Shroff et al; BMC Neph 2018
Shroff et al; JASN 2019
Snauwaert et al; NDT 2020
De Zan et al; Ped Nephrol 2021
Fischer et al; Kidney Int Reports 2021
De Zan et al; Semin Daily 2022
Paglialonga et al; J Ren Nutr 2023

Recruitment

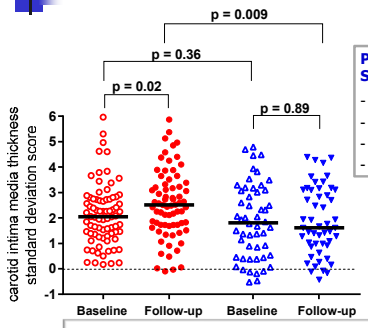
29 centres in 10 countries

190 children recruited
78 on HD and 55 on HDF completed 1-year follow-up



Median convective volume 13.2 (12.1 - 14.3) L/m²/session
corresponds to 23L/m² BSA in adults

cIMT SDS at baseline and 1-year

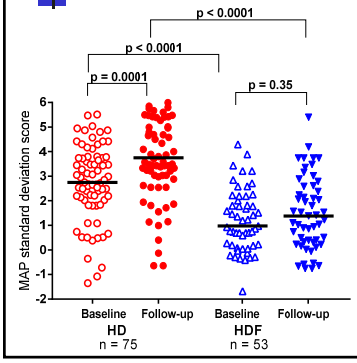


Predictors of higher cIMT-SDS at 12-months

- HD group
- Higher IDWG% and UF rate
- Higher systolic BP
- higher β2-microglobulin

HDF halts the progression of cIMT

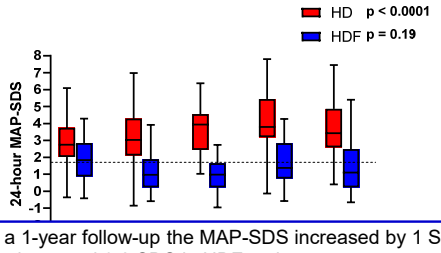
MAP-SDS at baseline and 1-year



At 12-months MAP > 2SD in

HD 81%
HDF 37%

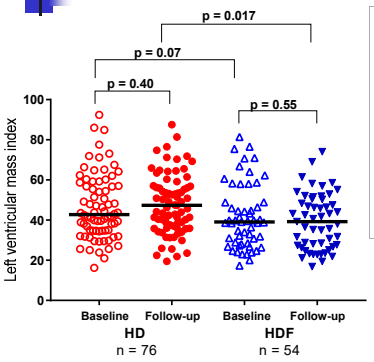
Sustained improvement in BP on HDF compared to HD



Over a 1-year follow-up the MAP-SDS increased by 1 SDS in HD patients and 0.2 SDS in HDF patients.

HD modality and higher IDWG% are risk factors for a higher MAP-SDS over the one year follow up.

LVMI at baseline and 1-year



Predictors of higher LVMI at 12-months

- higher IDWG%
- higher MAP-SDS
- Low Hb
- higher PTH
- Higher BMI SDS

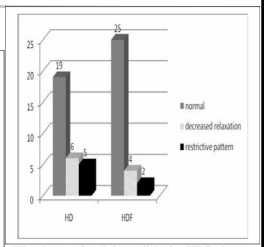
Improvement in cardiac function

N = 30 children

Converted from HD to HDF

At 6-months:

- ✓ decrease in frequency of diastolic dysfunction
- ✓ *improvement in systolic function (FS and EF)*
- ✓ LVMI did not change



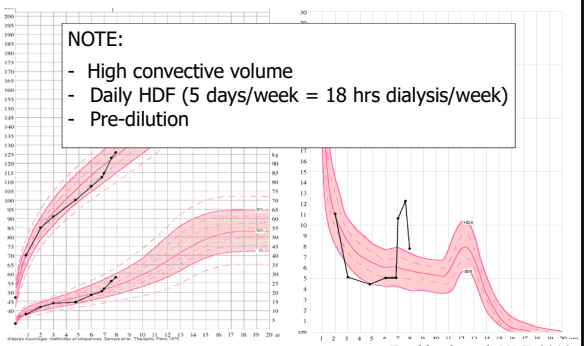
HD: Conventional hemodialysis, HDF: hemo-diafiltration.

Fadel et al., Saudi J Kidney Dis Transplant 2015

Improved growth on HDF

NOTE:

- High convective volume
- Daily HDF (5 days/week = 18 hrs dialysis/week)
- Pre-dilution



Fischbach et al; NDT, 2010

Dialysis dose and growth

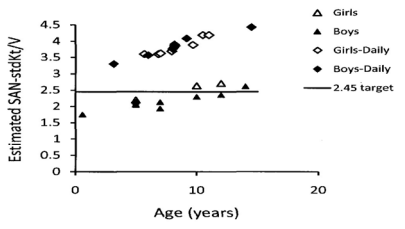


Figure 6. Estimated SAN-stdKt/V *versus* age in two studies in which increased growth rates were linked to intensified dialysis regimens, one with hemodialysis treatments given 3 times/wk by Tom *et al.* (10) and one using 6-times/wk hemodiafiltration by Fischbach *et al.* (11).

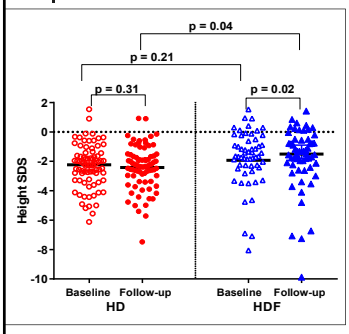
Daugirdas et al; Clin JASN 2010

Anabolic effect of daily HDF

- Stimulates appetite - removal of circulating satiety factors (leptin, cholecystokinin, tryptophan)
- Correction of metabolic acidosis. Acidosis can:
  - activate the ubiquitin-proteosome pathway & increase protein degradation
  - suppresses endogenous GH secretion
- Minimises inflammatory cytokine release
- ? Removal of somatomedin and gonadotropin inhibitors by HDF
- ? reverses rhGH resistance

Schaefer et al. NDT 2010

Change in Height SDS



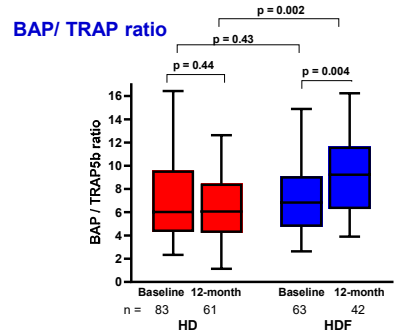
15% on HD and 25% on HDF on growth hormone treatment

No difference in height-SDS in GH-Rx HDF vs HD patients (p = 0.08).

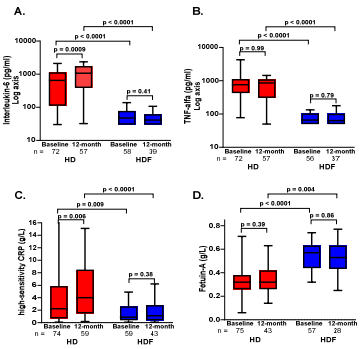
There was an inverse association between final height-SDS and β2-MG

(beta = -0.07 per 10 mg/L higher level; 95%CI = -0.14 to 0; p = 0.05).

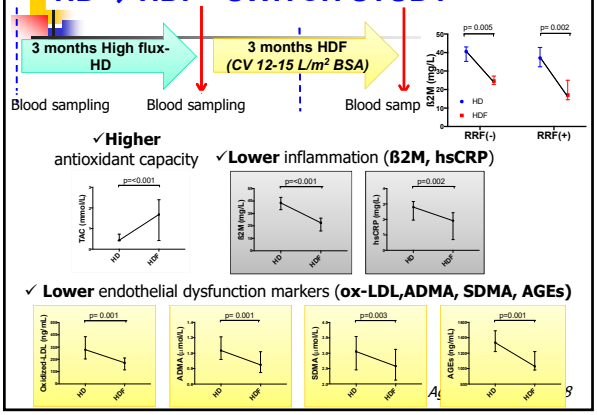
Bone formation vs resorption ratios



Reduced systemic inflammation in HDF

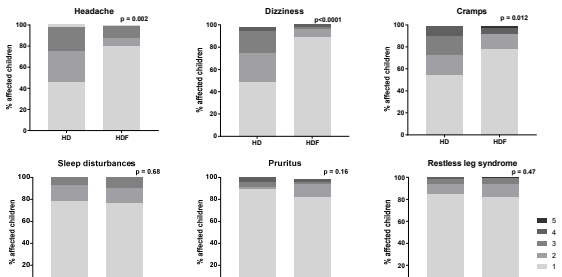


HD → HDF - SWITCH STUDY



Patient related outcomes

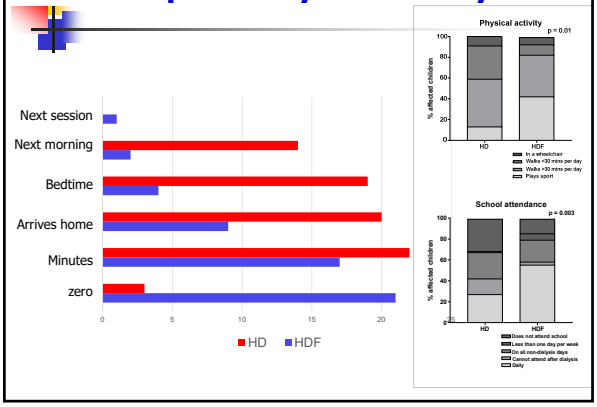
Self-reporting on 6-monthly questionnaires



Correlations:
- ultrafiltration volume per session
- hemoglobin

NO correlations with:
- 24-hr ABPM / systolic or diastolic BP
- Residual renal function

PROMs – post-dialysis recovery time



Conclusions (for HDF)

- In children, HDF halts the progression of vascular changes compared to conventional HD
- HDF is associated with an early and sustained improvement in:
  - fluid status and BP
  - Bone health and growth
  - Reduced inflammation and oxidative stress
  - Improved patient outcomes
- Frequent / daily HD improves growth and QoL

HDF for all in-centre patients?

- We need a randomised trial….. but until this is done, HDF could be used in children based on:
  - Safe and well tolerated
  - Biological plausibility
  - Data from adult RCTs
  - 3H study in children
- Early benefits of HDF – use even if short period on dialysis anticipated
- HDF is beneficial even in those with residual renal function

MCQ 1 – Which one of these patients is least likely to benefit from HDF?

A. An incident dialysis patient
B. A child receiving dialysis 5 days a week
C. A child receiving dialysis for 2 years with urine output of 300ml/day
D. A child receiving incremental dialysis (2 days / week) for 2 years

MCQ 1 – Which one of these patients is least likely to benefit from HDF?

A. An incident dialysis patient
B. A child receiving dialysis 5 days a week
C. A child receiving dialysis for 2 years with urine output of 300ml/day
D. **A child receiving incremental dialysis (2 days / week) for 2 years**

MCQ 2 – Which one of these is not a technical requirement for HDF in children?

A. Ultrapure water
B. High-flux dialyzer
C. Anticoagulation of the circuit
D. Dialysis machines with accurate pressure control
E. Dialysis machines with accurate ultrafiltration control

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MCQ 3 – Which one of the following is seen with high-vol HDF?

A. Albumin losses in the dialysate
B. IgG losses in the dialysate
C. Reduction in inflammatory cytokines (IL6 & TNF-α)
D. Reduction in indoxyl sulphate
E. Improved clearance of urea compared to HD

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MCQ 4 – Which one of the following actions can you take to optimise the convention volume in high-volume HDF?

A. Increase the ultrafiltration rate
B. Increase the dialyser size
C. Increase the needle-size for AVF cannulation
D. Perform pre-dilution HDF
E. Perform expanded haemodialysis (HDx)

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MCQ 5 – Which one of the following statements is true?

A. Post-dialysis recovery time is longer in HDF than in HD
B. Uncontrolled hypertension is more common in children on HDF compared to HD
C. HDF has a catabolic effect
D. HDF leads to a rapid loss of residual urine output
E. In children a target convective volume of 13-15 L/m^2/session is aimed for in post-dilution mode

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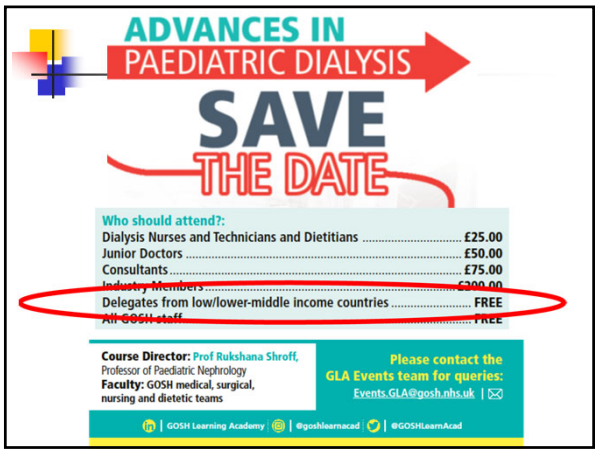
ADVANCES IN
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SAVE
THE DATE
Who should attend?:
Dialysis Nurses and Technicians and Dietitians £25.00
Junior Doctors £50.00
Consultants £75.00
Industry Members £200.00
Delegates from low/lower-middle income countries ..... FREE
All GOSH staff ..... FREE
Course Director: Prof Rukshana Shroff,
Professor of Paediatric Nephrology
Faculty: GOSH medical, surgical,
nursing and dietetic teams
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Kidney Replacement Therapy in Pediatric ICU: Challenges and Opportunity

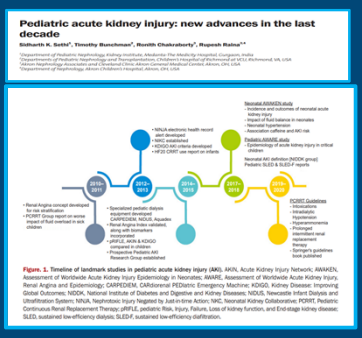
Rupesh Raina, MD, FAAP, FACP, FASN,FISN and FNKF

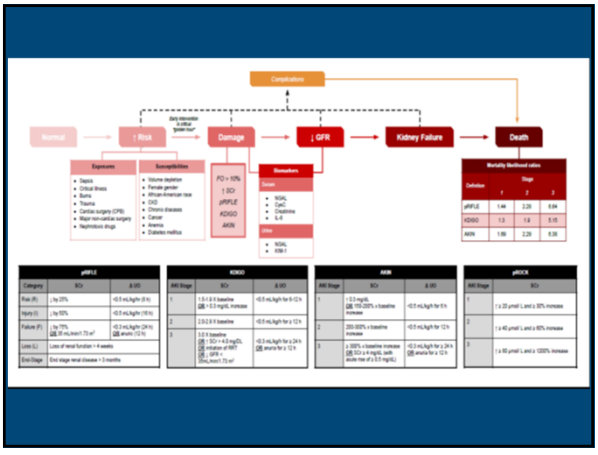
Adult-Pediatric Kidney Disease/Hypertension
Professor of Medicine and Professor of Pediatrics
Director of Research Akron Nephrology Associates
AGMC, Cleveland Clinic, Cleveland, Ohio
Staff Medical Research, Rebecca D. Considine Research Institute
Staff at Akron Children's Hospital, Akron, Ohio
Council of Dean M-4 Director - Northeast Ohio Medical University, Rootstown, Ohio
Faculty Staff at Case Western Reserve University School of Medicine, Cleveland, Ohio

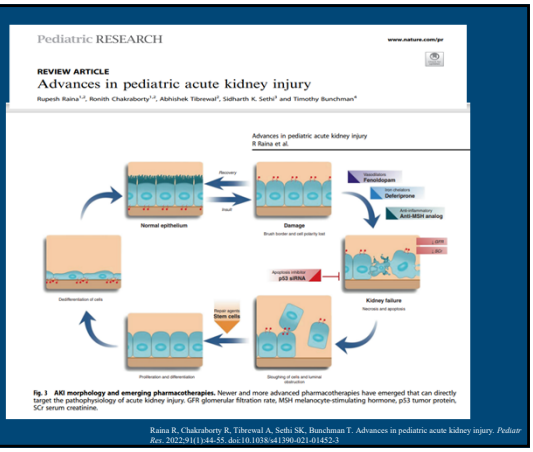
Advances in AKI

- AKI in critically ill patients is associated with increased morbidity and mortality
- Emerging data support that the incidence of AKI in the ICU is rising
- For children with severe AKI, KRT can provide a lifesaving supportive therapy
- The optimal timing to deliver and modality by which to deliver KRT remain a point of discussion within adult literature

How Pediatric AKI with Sepsis Evolving? Call for Action?







Economic Burden of Pediatric AKI:Is It real?

JAMA Network Open.

Research Letter | Pediatrics

Patterns in the Economic Burden of Acute Kidney Injury in Hospitalized Children, 2019-2021

Rupesh Raina, MD; Anvitha Soundararajan, MBBS; Natalie Menassa, MD; Aadi Pandya; Carla Nemer; Abhishek Tibrewal, PhD; Sidharth Kumar Sethi, MD

Introduction

Pediatric acute kidney injury (AKI) is common, especially in hospitalized children, its incidence being 18.7% overall and 24.4% among critically ill patients.[1] Children with AKI have increased odds of higher length of stay (LOS), death, hypertension, proteinuria, and chronic kidney disease.[2-4] Development of AKI increases health care costs and resource use burden. Despite the increasing incidence of pediatric AKI,[5] few studies have evaluated its US economic burden. We used the Pediatric Health Information System (PHIS) to assess the financial burden associated with AKI. The PHIS provides data on treatment costs for pediatric diseases, which were used to evaluate patterns in the economic burden of AKI and variables correlated with mortality and LOS among hospitalized children with AKI.

Supplemental content

Author affiliations and article information are listed at the end of this article.

Table 2. Correlation of Variables With Mortality Rate and Length of Stay

	Mortality rate		Length of stay	
Variable	Pearson r (95% CI)	P value	Pearson r (95% CI)	P value
CHCMI	0.371 (0.335-0.594)	.008	0.596 (0.378-0.751)	<.001
MCC cases of total AKI cases	0.372 (0.102-0.591)	.008	0.517 (0.276-0.697)	<.001
No. of diagnosis codes per AKI case	NA	NA	0.402 (0.136-0.614)	.004
No. of procedure codes per AKI case	0.410 (0.146-0.620)	.003	0.647 (0.448-0.786)	<.001
Mortality rate	NA	NA	0.432 (0.171-0.636)	.002
Length of stay	0.432 (0.171-0.636)	.002	NA	NA

Table 1. Summary of Variables Assessed Across 49 Hospitals With Pediatric Acute Kidney Injury Cases

Variable	Weighted mean (range)
CHCMI	1.08 (0.95-1.21)
MCC cases of total AKI cases, %	40.1
No. of diagnosis codes per AKI case	11.7 (10.2-13.8)
No. of procedure codes per AKI case	1.2 (0.8-1.6)
Mortality rate, %	0.44
Length of stay, d	6.2 (5.2-7.2)
Adjusted charges per AKI case, $	72 460 (51 060-93 860)

Abbreviations: AKI, acute kidney injury; CHCMI, children's hospitals case mix index; MCC, major

APS European Society for Paediatric Research SPR Society for Pediatric Research www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Epidemiology data on the cost and outcomes associated with pediatric acute kidney injury

Rupesh Raina[1,2✉], Sidharth Sethi[3], Varun Aitharaju[4], Ananya Vadhera[3] and Imad Haq[4]

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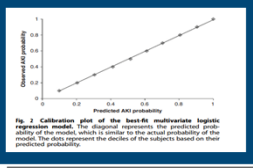


Fig. 2 Calibration plot of the best-fit multivariate logistic regression model. The diagonal represents the predicted probability of the model, which is similar to the actual probability of the model. The dots represent the deciles of the subjects based on their predicted probability.

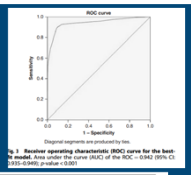


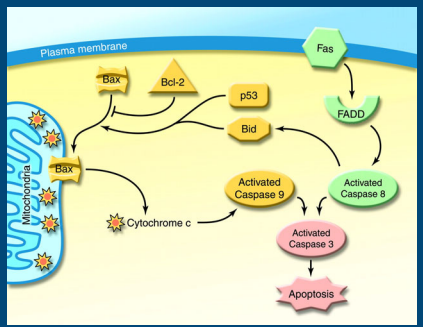
Fig. 3 Receiver operating characteristic (ROC) curve for the best-fit model. Area under the curve (AUC) of the ROC = 0.942 (95% CI: 0.933–0.949). p-value < 0.001

Table 3. Different outcomes among children with and without AKI.

Outcomes	AKI [yes]		AKI [no]		Odds ratio (95% CI)	p-value
Mechanical ventilation [Yes]	79 (3.3%)		18 (0.7%)		4.49 (2.68–7.52)	<0.001
Died during hospitalization [Yes]	11 (0.5%)		1 (0%)		11.01 (1.42–85.34)	0.004
Duration of stay (days)	2424	3 (2–6)	2418	2 (1–3)	NA	<0.004
Total charges ($)	2378	23,900 (12,400–49,600)	2387	19,600 (9891–35,200)	NA	<0.005

AKI –Sepsis: Syndrome and Multifactorial?

Major apoptotic pathways in human ischemic AKI. The extrinsic pathway requires activation of plasma membrane Fas receptor, with signal transduction via FADD resulting in activation of caspase 8

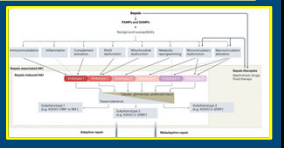


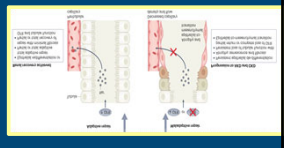
JASN

Devarajan P. Update on mechanisms of ischemic acute kidney injury. *J Am Soc Nephrol*. 2006;17(6):1503-1520. doi:10.1681/ASN.2006010017

Systemic Inflammatory Response Index (SIRI) and Acute Kidney Injury AKI

- SIRI was estimated as a neutrophil monocyte lymphocyte ratio
- The higher SIRI value (≥ 0.59) had a greater risk of AKI (adjusted odds ratio, OR, 3.95, 95% confidence interval, 95%CI, 2.91-5.36, P<0.001) and in-hospital mortality (hazard ratio, HR, 5.01, 95%CI 2.09-12.03, P<0.001).
- SIRI is a pretty good predictor of AKI and fatality in pediatric ICU patients, and the proposed nomogram based on SIRI yields an appropriate prediction value for critically sick pediatric patients





J Int Med Res. 2024 Mar; 52(3)

CKRT Prescription

CKRT

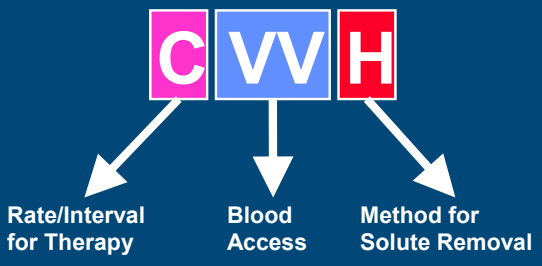
- CKRT in the ICU requires a multidisciplinary team approach that is facilitated by a pediatric nephrologist in conjunction with intensivists and skilled nursing staff
- Although mortality rates for children on dialysis remain high, outcomes are improving with the support of the multidisciplinary team and dialysis technology advancements

Table 1. Comparison of RRT modalities

Modality	CRRT	SLED	HD (standard or high flux)	PD
BFR	3–5 mL/kg/min access dependent	3–5 mL/kg/min access dependent	3–5 mL/kg/min access dependent	10–20 mL/kg/pass[a]
Dialysis flow rate (liter/hr)	0–4	6	30–50	0.5–2
Convective flow rate (liter/hr)	0–4	0	0	0
Systemic anticoagulation	Heparin or citrate	Heparin or citrate	Heparin or none	None
Thermic control	Yes	Yes	Yes	Partial
Ultrafiltration control	Yes	Yes	Yes	Partial
Solutions	Industry made	On line production	On line production	Industry made
Drug clearance	Continuous	Intermittent	Intermittent	Continuous
Nutritional clearance	Continuous	Intermittent	Intermittent	Continuous
Solute clearance	2	3	1	4
UF with hemodynamic stability	1	3	4	2

BFR, blood flow rate; CRRT, continuous renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SLED, sustained lower-efficiently dialysis; UF, ultrafiltration.
[a]This is pass per volume per kg not blood flow but gives an idea of the PD prescription.

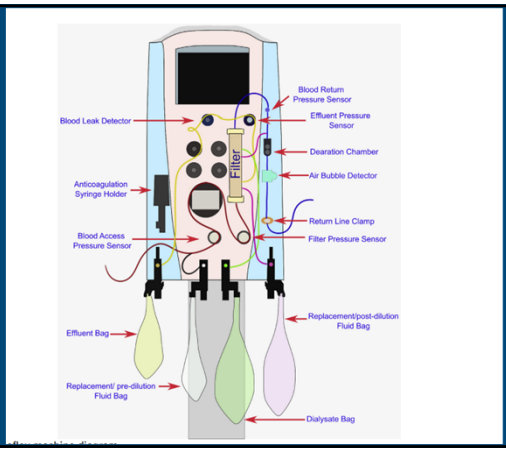
Basis for CKRT Nomenclature



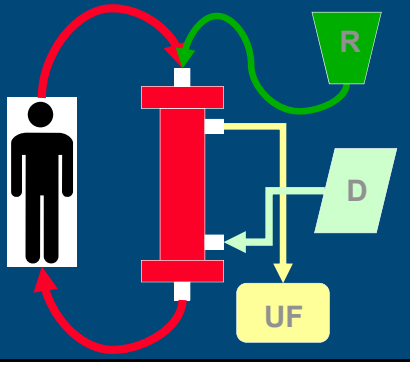
What CKRT Modality?

CKRT Terminology and Physiology: Summary

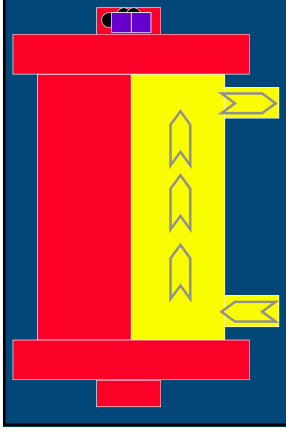
- **CKRT comes in several flavors**
  - **SCUF, CVVH, CVVHD, CVVHDF and PIRRT**
- **Solute transport: diffusion/convection**
- **UF approximates 1-compartment model**
- **Membrane characteristics affect therapy**
- **Fluid composition, rates drive clearance**



CKRT Schematic

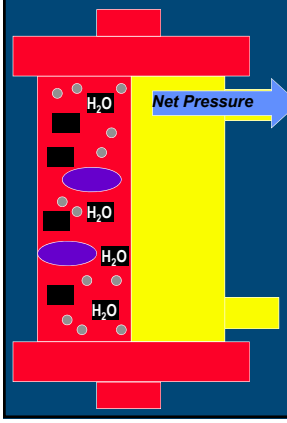


- SCUF
- CVVH
- CVVHD
- CVVHDF



Diffusion

- Small molecules diffuse easily
- Larger molecules diffuse slowly
- *Dialysate* required
  - Concentration gradient
  - Faster dialysate flow increases mass transfer



Convection

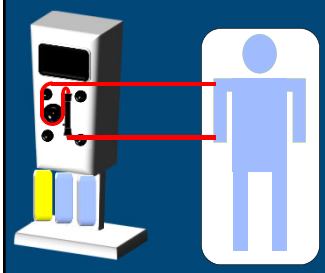
- Small/large molecules move equally
- Limit is cut-off size of membrane
- Higher UF rate yields higher convection *but* risk of hypotension
- May need to *Replace* excess UF volume

Solute Molecular Weight and Clearance

Solute (MW)	Convective Coefficient	Diffusion Coefficient
Urea (60)	1.01 ± 0.05	1.01 ± 0.07
Creatinine (113)	1.00 ± 0.09	1.01 ± 0.06
Uric Acid (168)	1.01 ± 0.04	0.97 ± 0.04
Vancomycin (1448)	0.84 ± 0.10	0.74 ± 0.04
Cytokines (large)	adsorbed	minimal clearance

•Drug therapy can be adjusted by using frequent blood level determinations or by using tables that provide dosage adjustments in patients with altered renal function

Patient's Chemical Balance on CKRT Approximates Delivered Fluids



- Diffusion: blood equilibrates to dialysate
- Convection: loss is isotonic; volume is "replaced"
- Consider large volumes for other fluids (IVF, feeds, meds, etc.)
- Watch for deficits of solutes not in fluids

Mode dialysis in sepsis: CVVH vs CVVHD

Acute Kidney Injury (OMAKI) Canadian Trial group
CVVH vs CVVHD n=78 adults (80% sepsis)
Same dialysis dose of 35ml/kg/hr effluent rate

No difference mortality
CVVH 12/35 35%
CVVHD 10/38 27%

Table 2 Feasibility and safety data

	CVVH (n = 35)	CVVHD (n = 38)	P-value
Duration RRT prescribed, hrs	146 ± 240	145 ± 156	0.88
Duration RRT received, hrs	130 ± 222	128 ± 142	0.87
Mean RRT dose, mL/kg/hr	33.6 ± 7.4	34.7 ± 4.4	0.50
Prescribed dose delivered, %	84.7 ± 16.3	87.8 ± 13.7	0.73
Net ultrafiltration, L/day	1.7 ± 2.2	0.8 ± 4.1	0.98
Days on study therapy	5 (3-7)	4.50 (3.00-10.25)	0.79
Primary reason for CRRT withdrawal			0.75
Death while on CRRT	12 (35%)	10 (27%)	
Kidney function recovery	7 (21%)	7 (19%)	

Wald R, Friedrich JO, Bagshaw SM, et al. Optimal Mode of clearance in critically ill patients with Acute Kidney Injury (OMAKI)--a pilot randomized controlled trial of hemofiltration versus hemodialysis: a Canadian Critical Care Trials Group project. *Crit Care*. 2012;16(5):R205. Published 2012 Oct 24. doi:10.1186/cc11835

Initial CKRT Prescription

Prescription for CKRT

- BFR of 3 to 5 mL/kg/min, a dialysate or a replacement rate of 2,000 mL/1.73 m^2/hour, and a net ultrafiltration rate of 0.5 to 2 mL/kg/hour
- The greater the BFR lesser the risk of clotting
- Contraindication - risk for rapid osmolar shift (dialysis disequilibrium) with associated high BUN, sodium, or glucose levels
- The dialysate of replacement flow rates range from that noted above to Ronco's concept of 40 mL/kg/hour
- These are starting points, and the amount of solution exposure (i.e., dialysate or replacement) can be increased or decreased based upon the solute clearance required

Prescription for CKRT

Prescribed CRRT dose = total prescribed effluent flow rate/h/weight (kg)
Delivered CRRT dose = total achieved effluent flow rate/d (or per hour)/weight (kg)/24 hours (if necessary)
Ratio of delivered dose/prescribed dose = total daily effluent volume achieved (in 24 hours)/total effluent volume prescribed
Time between CRRT circuit exchanges (required and/or unplanned)
Effective CRRT treatment time (in 24-hour period) = 24—number of downtime hours or 1440—number of downtime minutes
Vascular access site, size, length, and depth—is the access of appropriate length?
Mortality (or survival)—specifically in those with AKI requiring RRT
Kidney functional recovery to dialysis liberation

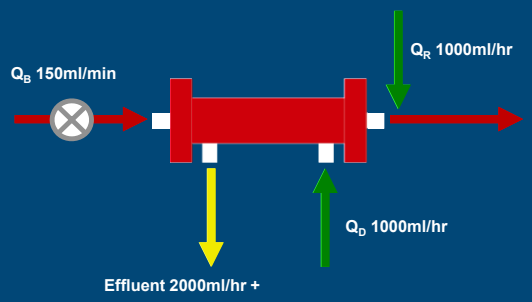
CKRT Urea Kinetics

Calculating Solute Clearance

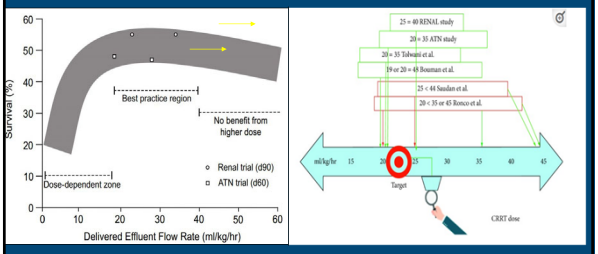
- Generic clearance =
  - Mass removal rate / blood concentration
  - Effluent flow rate x effluent concentration / blood concentration
- $K = Q_E \times C_E/C_B$
- Using urea as solute
  - $Q_E << Q_B$ (17-50 ml/min vs. 150-200 ml/min)
  - Equilibrium achieved ($C_E = C_B$)
- $C_E/C_B = \sigma$ = sieving coefficient
- Sieving coefficients for small MW molecules such as urea = 1

What Effluent dose?

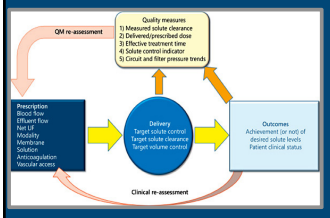
Solution/Effluent Flow Rate is Limiting Factor in CKRT



Blood flow rate vs solute clearance



Precision Continuous Renal Replacement Therapy and Solute Control



CRRT dose identifies the amount of blood cleared of solute by unit of time

Effluent flow is an acceptable surrogate for prescribing CRRT dose for solute clearance.

Default prescribed CRRT dose should be 20-25 ml/kg/h for representative small molecular weight solutes

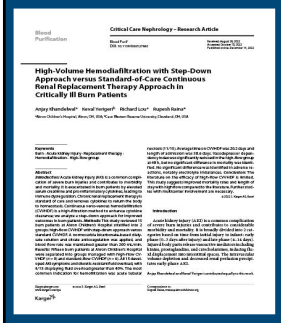
Prescribed dose is dynamic. Prescribed dose should be evaluated at least once every 24 h and more often according to patient needs

Dose delivery can be estimated as intensity (ml/kg/h times the number of treatment hours) or as time-averaged (average ml/kg/h over 24 h or other duration

Dose delivery should be routinely reassessed and modified based on iterative evaluation of quality measures

2022 Dec 14;1-4

High-Volume Hemodiafiltration with Step-Down Approach versus Standard-of-Care Continuous Renal Replacement Therapy Approach in Critically Ill Burn Patients



Fifteen burn patients at Akron Children's Hospital were separated into groups managed with high-flow CVVHDF (n = 9) and standard-flow CVVHDF (n = 6).

All 15 developed AKI symptoms and diuretic-resistant fluid overload, with 4/15 displaying fluid overload greater than 40%.

The most common indication for hemofiltration was acute tubular necrosis (11/15). Average time on CVVHDF was 20.2 days and length of admission was 58.6 days.

Vasodepressor dependency index was significantly reduced in the high-flow group at 48 h, but no significant difference in mortality was identified.

No significant difference was identified in adverse reactions, notably electrolyte imbalances.

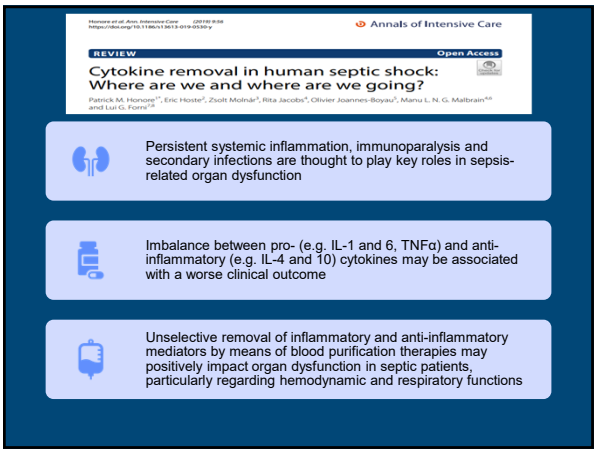
Khandelwal A, Yerigeri K, Lou R, Rama R. High-Volume HemodiaFiltration with Step-Down Approach versus Standard-of-Care Continuous Renal Replacement Therapy Approach in Critically Ill Burn Patients [published online ahead of print, 2022 Dec 14]. *Blood Purif*. 2022;1-4. doi:10.1159/000527681

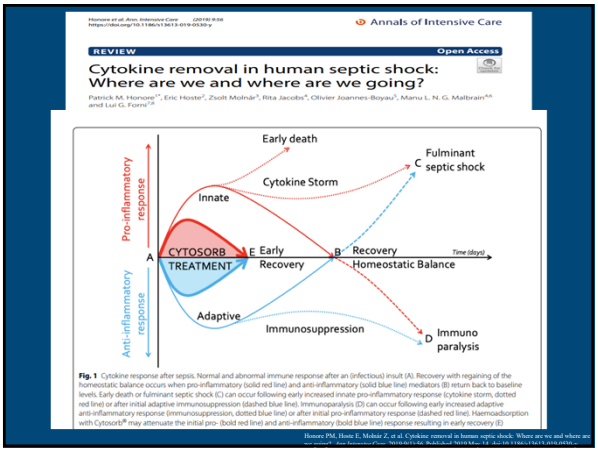
CKRT in MODS?

CYTOKINE REMOVAL IN HUMAN SEPTIC SHOCK: WHERE ARE WE AND WHERE ARE WE GOING?

CKRT in MODS

- The most common causes leading to CKRT were cardiocirculatory failure (56%) and sepsis (20%)
- Overall survival rate was 49.5%
- Mean arterial pressure was significantly lower for non-survivors versus survivors (50.6±1.9 vs 59.7±1.9 mmHg) at initiation of CRRT,
- Patients with a FO 20% of body weight, and patients on vasopressor support had mortality rates of 73.7 and 65%, respectively
- Despite CRRT, persisting MODS results in a high mortality rate.
- A low mean arterial pressure, vasopressor support and a fluid overload >20% of body weight at initiation of CRRT are also associated with a significantly higher mortality rate

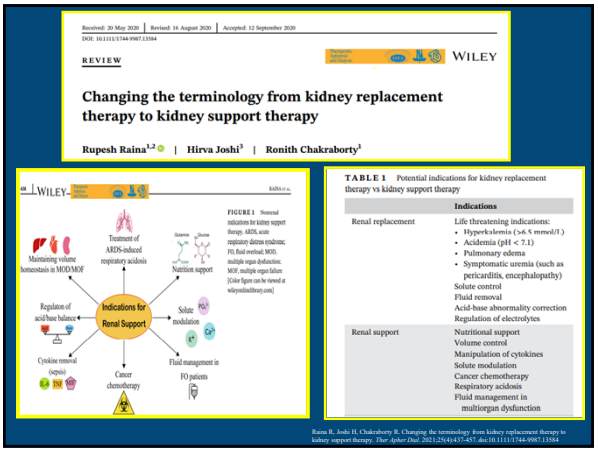




Early vs Late CKRT

Early vs Late CKRT

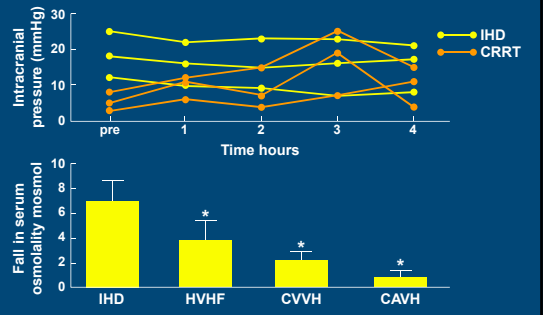
- RCT's have not demonstrated any mortality benefit in starting RRT early vs late, but there is emerging evidence that starting therapy early may improve outcomes
- There is a need to develop and validate biomarkers that can predict the need for initiating and stopping dialysis



Key Point

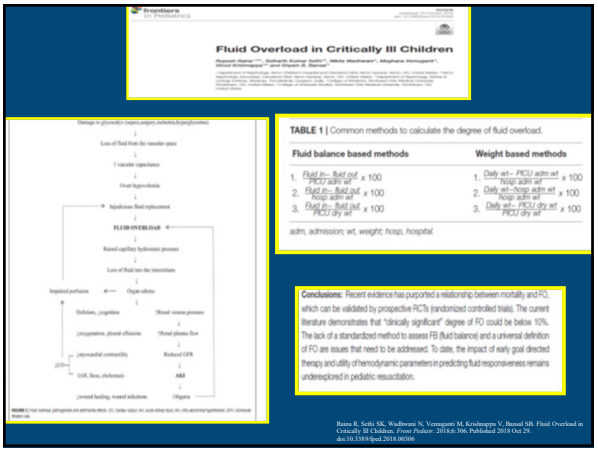
- We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)

CRRT in Management of ICP



Davenport, A. *Sem Dialysis* 2009

Fluid Overload Is Real ICD Code in Sepsis and AKI



Fluid Overload in Critically Ill Children

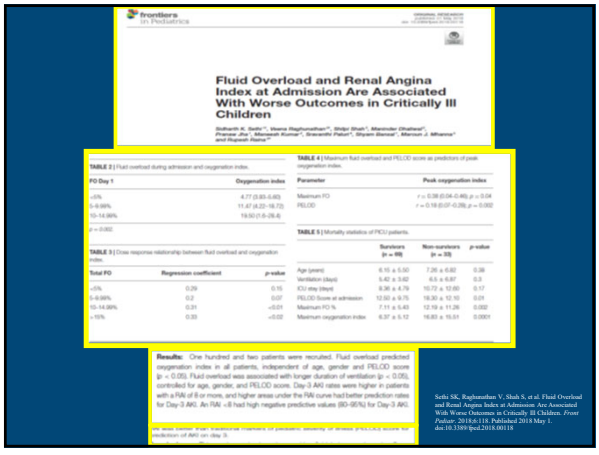
TABLE 1 | Common methods to calculate the degree of fluid overload.

Fluid balance based methods	Weight based methods
1. (Fluid in − fluid out / PICU adm wt) × 100	1. (Daily wt − PICU adm wt / hosp adm wt) × 100
2. (Fluid in − fluid out / hosp adm wt) × 100	2. (Daily wt − hosp adm wt / hosp adm wt) × 100
3. (Fluid in − fluid out / PICU dry wt) × 100	3. (Daily wt − PICU dry wt / PICU dry wt) × 100

adm, admission; wt, weight; hosp, hospital.

Conclusions: Recent evidence has purported a relationship between mortality and FO, which can be validated by prospective RCTs (randomized controlled trials). The current literature demonstrates that "clinically significant" degree of FO could be below 10%. The lack of a standardized method to assess FB (fluid balance) and a universal definition of FO are issues that need to be addressed. To date, the impact of early goal directed therapy and utility of hemodynamic parameters in predicting fluid responsiveness remains underexplored in pediatric resuscitation.

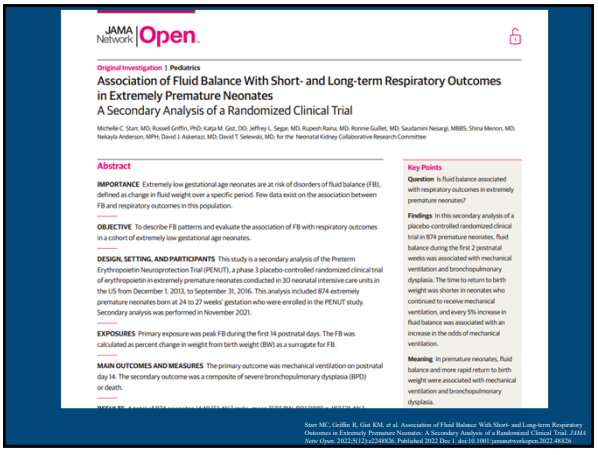
Raina R, Sethi SK, Wudhwani N, Vennapusti M, Krishnappa V, Bansal SB. Fluid Overload in Critically Ill Children. *Front Pediatr.* 2018;6:306. Published 2018 Oct 29. doi:10.3389/fped.2018.00306



Fluid Overload and Renal Angina Index at Admission Are Associated With Worse Outcomes in Critically Ill Children

Results: One hundred and two patients were recruited. Fluid overload predicted oxygenation index in all patients, independent of age, gender and PELOD score ($p = 0.05$). Fluid overload was associated with longer duration of ventilation ($p < 0.05$), controlled for age, gender, and PELOD score. Day-3 AKI rates were higher in patients with a RAI of 8 or more, and higher areas under the RAI curve had better prediction rates for Day-3 AKI. An RAI >8 had high negative predictive values (80–95%) for Day-3 AKI.

Sethi SK, Raghunathan V, Shah S, et al. Fluid Overload and Renal Angina Index at Admission Are Associated With Worse Outcomes in Critically Ill Children. *Front Pediatr.* 2018;6:118. Published 2018 May 1. doi:10.3389/fped.2018.00118



JAMA Network Open.

Original Investigation | Pediatrics

Association of Fluid Balance With Short- and Long-term Respiratory Outcomes in Extremely Premature Neonates
A Secondary Analysis of a Randomized Clinical Trial

Abstract

IMPORTANCE Extremely low gestational age neonates are at risk of disorders of fluid balance (FB), defined as change in fluid weight over a specific period. Few data exist on the association between FB and respiratory outcomes in this population.

OBJECTIVE To describe FB patterns and evaluate the association of FB with respiratory outcomes in a cohort of extremely low gestational age neonates.

DESIGN, SETTING, AND PARTICIPANTS This study is a secondary analysis of the Preterm Erythropoietin Neuroprotection Trial (PENUT), a phase 3 placebo-controlled randomized clinical trial of erythropoietin in extremely premature neonates conducted in 3D neonatal intensive care units in the US from December 1, 2013, to September 31, 2016. This analysis included 874 extremely premature neonates born at 24 to 27 weeks' gestation who were enrolled in the PENUT study. Secondary analysis was performed in November 2021.

EXPOSURES Primary exposure was peak FB during the first 14 postnatal days. The FB was calculated as percent change in weight from birth weight (BW) as a surrogate for FB.

MAIN OUTCOMES AND MEASURES The primary outcome was mechanical ventilation on postnatal day 14. The secondary outcome was a composite of severe bronchopulmonary dysplasia (BPD) or death.

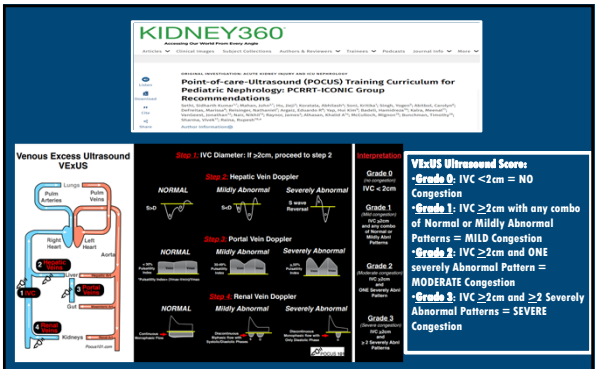
Key Points

Question Is fluid balance associated with respiratory outcomes in extremely premature neonates?

Findings In this secondary analysis of a placebo-controlled randomized clinical trial in 874 premature neonates, fluid balance during the first 2 postnatal weeks was associated with mechanical ventilation and bronchopulmonary dysplasia. The time to return to birth weight was shorter in neonates who continued to receive mechanical ventilation, and every 5% increase in fluid balance was associated with an increase in the odds of mechanical ventilation.

Meaning In premature neonates, fluid balance and more rapid return to birth weight were associated with mechanical ventilation and bronchopulmonary dysplasia.

Starr MC, Griffin R, Gist KM, et al. Association of Fluid Balance With Short- and Long-term Respiratory Outcomes in Extremely Premature Neonates: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open.* 2022;5(12):e2248826. Published 2022 Dec 1. doi:10.1001/jamanetworkopen.2022.48826



Key Points: Updates Volume Status and AKI

- Fluid therapy is integral to the acute resuscitation of critically ill patients
- A threshold may exist beyond which the perceived benefit of additional fluid therapy after resuscitation may contribute to harm
- Prevention of fluid overload may be an important and under-appreciated determinant of survival
- Prevention of early control of fluid overload is evolving as a primary trigger for initiation of RRT

Drug Dosing in CKRT

Drug Dosing recommendations based on Sieving Coefficient (SC)

- $Clearance_{total} = Cl_{CRRT} + Cl_{residual\ renal} + Cl_{non\text{-}renal}$
- SC equations only account for Cl_{CRRT}
- What about other clearances?
  - $Cl_{residual\ renal}$ usually not an issue in CRRT patients
  - $Cl_{non\text{-}renal}$ not always available for drugs

When in doubt, start here…

- **Blood flow, filter type are not very important.**
- **Find out**
  - **In CVVHD: Dialysate flow rate (ml/hr)**
    - **Usually 2 L/1.73m2/hr (33 mL/1.73m2/min)**
  - **In CVVH: Substitution Fluid rate (ml/hr)**
    - **Usually 2L/1.73m2/hr (33 mL/1.73m2/min)**
- **Add this to patient's native Cr Cl (ml/1.73m2/min)**
- **This is patient's new Cr Cl → dose accordingly**
- **Works in most cases…is good enough for initial estimates. Follow up with drug level monitoring.**

Anticoagulation in CKRT?

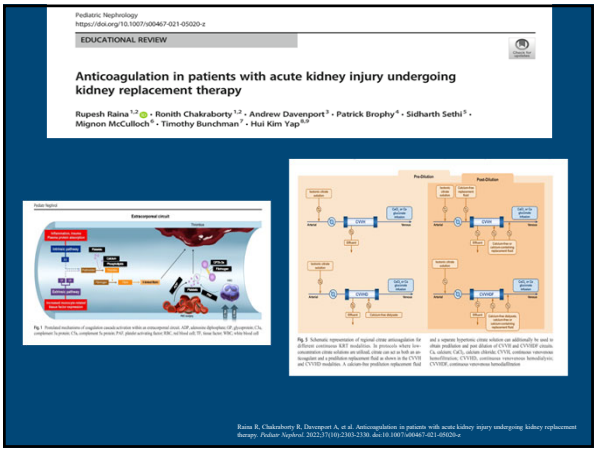

Analytic Reviews

A Meta-Analysis of Extracorporeal Anticoagulants in Pediatric Continuous Kidney Replacement Therapy

Rupesh Raina, MD[1,2], Nirav Agrawal, MBBS[1,3], Kirsten Kusumi, MD[3], Avisha Pandey, BA[1], Abhishek Tibrewal, PhD[1], and Alexander Botsch, MSN, APRN-CNP[3]

- RCA vs UFH circuit life of 50.65 hours vs. 42.10 hours. Tw
- Metabolic alkalosis and electrolyte imbalance seen more commonly in RCA vs UFH
- Risk of systemic bleeding RCA= UFH
- RCA is the preferred anticoagulant over UFH due to its significantly longer circuit life,
- Vigilant circuit monitoring is required due to the increased risk of electrolyte disturbances.

Raina R, Agrawal N, Kusumi K, Pandey A, Tibrewal A, Botsch A. A Meta-Analysis of Extracorporeal Anticoagulants in Pediatric Continuous Kidney Replacement Therapy. *J Intensive Care Med*. 2022;37(5):577-594. doi:10.1177/08850666211992751

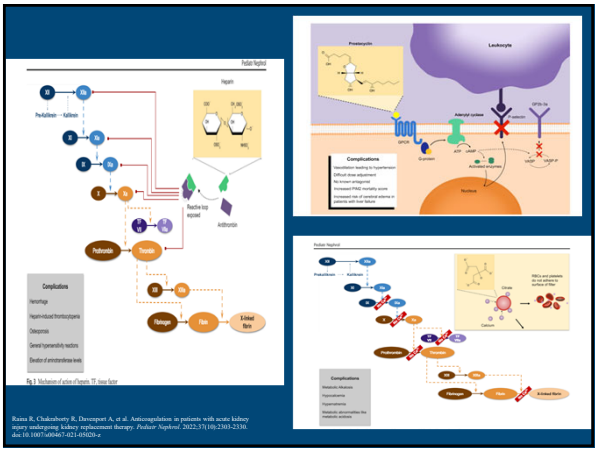

Pediatric Nephrology
https://doi.org/10.1007/s00467-021-05020-z

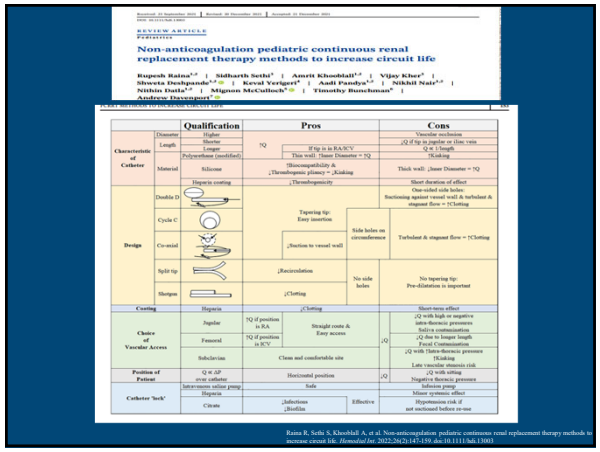
EDUCATIONAL REVIEW

Anticoagulation in patients with acute kidney injury undergoing kidney replacement therapy

Rupesh Raina[1,2] · Ronith Chakraborty[1,2] · Andrew Davenport[3] · Patrick Brophy[4] · Sidharth Sethi[5] · Mignon McCulloch[6] · Timothy Bunchman[7] · Hui Kim Yap[8,9]

Raina R, Chakraborty R, Davenport A, et al. Anticoagulation in patients with acute kidney injury undergoing kidney replacement therapy. *Pediatr Nephrol*. 2022;37(10):2303-2330. doi:10.1007/s00467-021-05020-z


Raina R, Chakraborty R, Davenport A, et al. Anticoagulation in patients with acute kidney injury undergoing kidney replacement therapy. *Pediatr Nephrol*. 2022;37(10):2303-2330. doi:10.1007/s00467-021-05020-z


REVIEW ARTICLE

Non-anticoagulation pediatric continuous renal replacement therapy methods to increase circuit life

Rupesh Raina[1,2] | Sidharth Sethi[3] | Amrit Khoobhali[1,2] | Vijay Kher[3] | Shweta Deshpande[1,2] | Keval Yerigeri[4] | Aadi Pandya[1,2] | Nikhil Nair[1,2] | Nithin Datla[1,2] | Mignon McCulloch[5] | Timothy Bunchman[6] | Andrew Davenport[7]

		Qualification	Pros	Cons
Characteristic of Catheter	Diameter	Higher	↑Q	Vascular occlusion
	Length	Shorter		↓Q if tip in jugular or iliac vein
		Longer	If tip is in RA/ICV	Q ∝ 1/length
	Polyurethane (modified)		Thin wall: ↑Inner Diameter = ↑Q	↑Clotting
	Material	Silicone	↓Biocompatibility & ↓Thrombogenic potency = ↓Clotting	Thick wall: ↓Inner Diameter = ↑Q
		Heparin coating	↓Thrombogenicity	Short duration of effect
Design	Double D		Tapering tip: Easy insertion	One-sided side holes: Suctioning against vessel wall & turbulent & stagnant flow = ↑Clotting
	Cycle C			
	Co-axial		↓Suction to vessel wall	Side holes on circumference: Turbulent & stagnant flow = ↑Clotting
	Split tip		↓Recirculation	No side holes: No tapering tip: Pre-dilution is important
	Shorgun		↓Clotting	
Coating		Heparin	↓Clotting	Short-term effect
Choice of Vascular Access		Jugular	↑Q if position in RA	↓Q with high or negative intra-thoracic pressures: Infection
		Femoral	↑Q if position in ICV	↓Q due to longer length: Femoral Contamination
		Straight route & Easy access		↓Q with Hemothorax pressure: ↑Clotting: Late vascular stenosis risk
		Subclavian	Clean and comfortable site	
Position of Patient		Q ∝ ΔP over catheter	Horizontal position	↓Q with sitting: Negative thoracic pressure
Catheter 'lock'		Intravenous saline pump	Safe	Infusion pump
		Heparin	↓Infections ↓Biofilm	Effective: Minor systemic effect
		Citrate		Hypomagnesia risk if not anticoagulated before re-use

Raina R, Sethi S, Khooblall A, et al. Non-anticoagulation pediatric continuous renal replacement therapy methods to increase circuit life. *Hemodial Int*. 2022;26(2):147-159. doi:10.1111/hdi.13003

Non-anticoagulation pediatric continuous renal replacement therapy methods to increase circuit life

- The most-effective CRRT catheter would be made of nonthrombogenic material, noncuffed and nontunneled with separate lumens for arterial and venous blood
- Blood flow during the process is optimized at 200 ml/min, which can be lowered in the pediatric population due to more narrow catheters.
- Platelet count and hematocrit need to be closely monitored as levels above 450,000 106 /L and 0.40, respectively, increase risk of clotting.
- Predilution is a non-anticoagulation technique to reduce the risk of clotting by returning replacement solution to the blood before it reaches the filter.
- Also, biocompatible membranes such as polyacrylonitrile or polysulfone activate the coagulation cascade significantly less than the conventional cellulose-based membranes, thereby reducing clotting chances

Metabolic Complication in CKRT in Sepsis?

· Metabolic complications of citrate utilization with continuous RRT

Complication	Mechanism	Diagnosis	Management
Citrate excess	Metabolic conversion of citrate to bicarbonate resulting in excess buffer	Metabolic alkalosis	Decrease blood flow rate
		Total Ca^{++}/iCa^{++} <2.5	Increase dialysate flow rate, or decrease buffer concentration in other CRRT solutions
Citrate toxicity	Decreased metabolic conversion of citrate resulting in accumulation of citrate-calcium complexes in blood	Anion gap metabolic acidosis	Decrease blood flow rate, or increase dialysate flow rate, or discontinue citrate
		Total Ca^{++}/iCa^{++} >2.5	
		Escalating Ca^{++} infusion rate	
Citrate deficit	Metabolic conversion of citrate to bicarbonate resulting in insufficient buffer	Metabolic acidosis	Increase blood flow rate
		Total Ca^{++}/iCa^{++} <2.5	Decrease dialysate flow rate
			Increase buffer concentration in other CRRT solutions

Ca^{++}, calcium; iCa^{++}, ionized calcium; CRRT, continuous RRT.

CRRT and Rapid Sodium Correction in Hyponatremia

- **Challenges in Hyponatremic Patients on CRRT:**
  - **Risk of Osmotic Demyelination Syndrome (ODS) with rapid correction of serum sodium**
  - **CRRT increases serum sodium less rapidly than HD but can still exceed safe correction limits (≤8 mEq/L)**
- **Expected Rise in Serum Sodium at 24 Hours:**

- **Expected Rise in Serum Sodium at 24 Hours:**
  - **Sodium Kinetic Model:**
    - Equation:

$$Na_{24hr} = Na_0 + \left(\frac{Nadial/RF - Na_0}{V} \times D \times t \right)$$

    - **Parameters:**
      - Na_0: Initial serum sodium (119 mEq/L)
      - $Nadial/RF$: Dialysate/replacement fluid sodium concentration (140 mEq/L)
      - D: Effective sodium dialysance (4 L/h)
      - t: Time since CRRT initiation (24 hours)
      - V: Total body water (60 L)
    - **Predicted Serum Sodium:**
      - Estimated increase to **136 mEq/L** within 24 hours, exceeding safe correction limits.

Strategies to Prevent Overcorrection of Serum Sodium

- Adjusting CRRT to Control Sodium Correction:
  - Hyponatremic CRRT Solutions:
    - Prepare custom CRRT solutions with lower sodium concentrations.
    - Use commercial CRRT fluids diluted with sterile water to achieve desired sodium levels.
  - Simulation Example:
    - Using 129 mEq/L CRRT solution versus standard 140 mEq/L
    - Frequent laboratory monitoring is crucial for adjustments.
- Avoiding Excessive Clearance:
  - Reduce CRRT dose while managing other solute abnormalities like hyperkalemia.
  - Gradual stepwise increase in CRRT solution sodium concentration to prevent overcorrection.

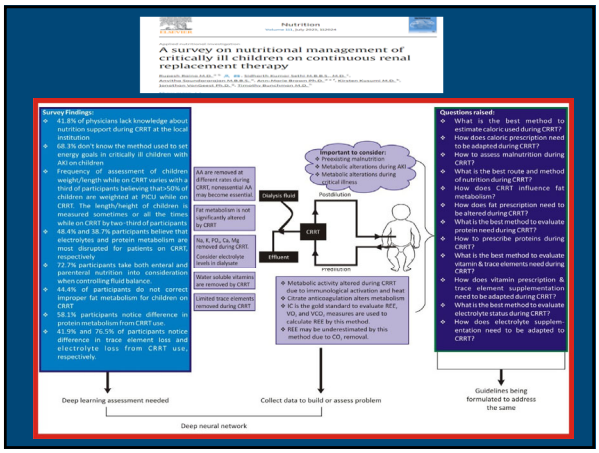
Using D5W to Manage Sodium Correction When Dilution is Not Available

- Application of D5W:
  - Infuse 5% Dextrose Water (D5W) to slow sodium correction when dilution is not possible.
  - Example Calculation:
    - Desired Serum Sodium Change:
      - Target serum sodium ≤127 mEq/L from 119 mEq/L.
    - D5W Infusion Rate:
      - Rate required: 314 ml/h to maintain target sodium levels.
    - Additional Considerations:
      - Monitor for risks: Filter clotting, worsening hyponatremia, rapid correction if D5W runs out.
      - Adjust net ultrafiltration rate to account for D5W infusion.

Nutrition In Critically ill Children with CKRT?

CKRT Can Improve the Energy Balance in Septic AKI

- Metabolic adaptation in septic AKI results in decreased levels of intracellular ATP and stimulates inflammation in the kidney, but the excessive inflammation is harmful
- CKRT as the most common treatment in septic AKI can remove inflammatory cytokines and neutralize the exaggerated inflammation to reduce kidney injury and promote kidney recovery
- The clearance of inflammatory cytokines, especially MIF, promises to play an important role in reducing kidney injury and promote recovery



Protein Requirements for Critically Ill Patients New Insight to AKI and KRT in ICU

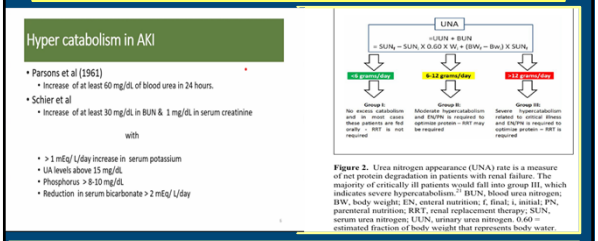


Figure 2. Urea nitrogen appearance (UNA) rate is a measure of net protein degradation in patients with renal failure. The majority of critically ill patients would fall into group III, which indicates severe hypercatabolism.[7] BUN, blood urea nitrogen; BW, body weight; EN, enteral nutrition; f, final; i, initial; PN, parenteral nutrition; RRT, renal replacement therapy; SUN, serum urea nitrogen; UUN, urinary urea nitrogen. 0.60 = estimated fraction of body weight that represents body water.

- AAs MW 140 Da (range: 75–215 Da) lost in CRRT (pre siz 20,000 Da)
- AA loss was greater (7.9 g over 24 hours) with a flow rate of 1000 mL/h, as compared with a flow rate of 500 mL/h (2.4 g over 24 hours)
- Convection, as opposed to diffusion techniques, induces greater AA loss at 1.2–7.5 g/d
- Diffusion techniques increase protein catabolism and decrease protein synthesis
- AA loss ranges from 10–15 g/d with CRRT

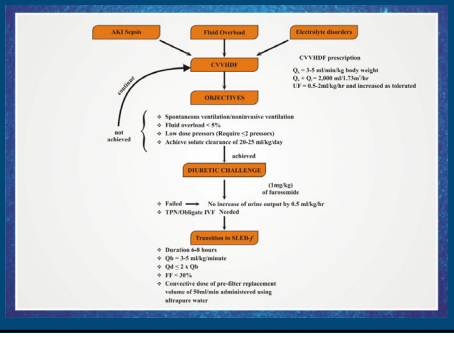
I want to Stop CKRT?

Summary Discontinuation of CKRT

- **No consensus in nephrology or critical care literature**
- **<u>UOP most important predictor of successful discontinuation</u>**
  - **Greater than 400 mL/24 hrs without diuretics or > 2300 mL/24 hrs with diuretics, ≥ 80% chance of success**
  - **Currently, 24-h creatinine clearance greater than 20 ml/min combined with spontaneously decreasing serum creatinine concentrations in the context of fixed RRT**
  - **The 2-h CrCl was a better predictor of remaining CRRT-free than urine output, serum creatinine or age. A 2-h CrCl value of 23 ml/min had a positive predictive value of 88.8%.**
  - **6-h creatinine clearance was greater than 15–20 ml/ min (mean 22+2 ml/min), serum creatinine concentrations decreased spontaneously and increased urine output was associated with a balanced fluid status**

Uchino S *Crit Care Med* 2009 Sep;37(9):2576-82:International Urology and Nephrology (2018) 50:1845–1851

Switching from continuous veno-venous hemodiafiltration to intermittent sustained low-efficiency daily diafiltration (SLED-f) in pediatric acute kidney injury: A prospective cohort study



What is New in CKRT?

High-Dose CKRT Prescription

High dose CKRT may be performed as CVVH or CVVH-D or CVVH-DF:

Clearance (replacement and/or dialysate flow rate to total at least 8000 ml/1.73m^2/hour or 90 ml/kg/hr)

High dose CKRT will be transitioned to regular CRRT once the serum ammonia level is consistently <200 µmol/L for at least 2 measures

Net ultrafiltration rate will be matched to or below the patient's intake since these patients are often polyuric and dehydrated

Add maximum amount of phosphorus to replacement solution/dialysate as these patients do not have hyperphosphatemia. If heparin-based anticoagulation used, supplement PO4 IV or enterally

Measure ammonia level at 30 minutes and then at least every 2 hours

Follow routine lab orders for anticoagulation (iCa or ACT)

Step-down CKRT prescription

Step-down CRRT will be initiated after HD or after high dose CRRT is completed, to prevent rebound of ammonia above 200 µmol/l

A. Clearance (replacement and/or dialysate flow rate will be total at least 2500 ml/1.73m^2/hour).
B. CRRT will be continued at least until serum ammonia level is < 100 µmol/l during at least 4 hours on at least two measurements.
C. Net ultrafiltration rate will be matched to or below the patient's intake since these patients are often polyuric and dehydrated.

OPEN

Consensus guidelines for management of hyperammonaemia in paediatric patients receiving continuous kidney replacement therapy

Table 3 | Dialysis ammonia clearance and filtration fractions

Number of patients	Dialysis modality	Qb (ml/min)	Qd (ml/min)	Ammonia clearance (ml/min/kg body weight)	Ammonia filtration fraction (%)
3	CAVHD	10–20	8.3 (0.5 l/h)	0.87–0.97	12.5–14.3
3	CVVHD	20–40	33.3–83.3 (2–5 l/h)	2.65–6.80	53.0–58.0
2	HD	10–15	500	3.95–5.37	95.0–96.0

CAVHD, continuous arteriovenous haemodialysis; CVVHD, continuous venovenous haemodialysis; HD, haemodialysis; Qb, blood flow rate; Qd, dialysis fluid flow rate. Based on data from REF.[34].

Raina R, Bedoyan JK, Lichter-Konecki U, et al. Consensus guidelines for management of hyperammonaemia in paediatric patients receiving continuous kidney replacement therapy. *Nat Rev Nephrol*. 2020;16(8):471-482. doi:10.1038/s41581-020-0267-8

Correspondence — Kidney Medicine

RESEARCH LETTER

Kidney Replacement Therapy and Mortality in Children With Inborn Errors of Metabolism: A Meta-analysis

To the Editor:

Inborn errors of metabolism, prominently urea cycle defects and organic acidemias, are common etiologic bases for hyperammonemic disorders. Delays in the clearance of ammonia in young children and newborns increase the risk of adverse outcomes, such as cell swelling, metabolic decompensation, coma, and mortality.[1] Initial medical management of hyperammonemia relies on restricting protein intake, maximizing nonprotein caloric intake from intravenous glucose and/or intralipid infusions, and sequestering ammonia through nitrogen scavengers (such as glycerol phenylbutyrate, sodium phenylbutyrate, sodium phenylacetate, and sodium benzoate).[2,3] In cases of severe hyperammonemia, kidney replacement therapy (KRT) accelerates the clearance of excess ammonium to alleviate its toxic effect, preserve neurocognitive functions, and improve survival rates.[2,4]

Before the 1990s, peritoneal dialysis (PD) was primarily used for ammonia clearance due to the technical challenges and risks associated with extracorporeal techniques.[3] Currently, PD largely remains an alternative option in the absence of other extracorporeal detoxifications or in newborns requiring timely vascular access.[2,4,5] Over the past few decades, hemodialysis (HD) and continuous kidney replacement therapies (CKRTs) have become preferred modalities because of higher flow rates for optimal rapid ammonium clearance. After discontinuation, patients treated by HD often experience complications, including hypotension and transiently increased ammonia levels.[2,3] Comparatively, CKRT decreases serum ammonia levels with a reduced risk of hemodynamic instability or ammonia rebound.[6] Despite advancements in CKRT technology, overall KRT-associated mortality rates remain high in children with inborn errors of metabolism and even greater in newborns.[5-7] This meta-analysis aimed to identify KRT-related mortality across a global cohort of children with inborn errors of metabolism.

This retrospective study considered eligible children diagnosed with an inborn error of metabolism and receiving any KRT treatment modality. All children aged <18 years were included in this review. Results were reported on the efficacy of KRT measured via survival rate and sensitivity analysis on source heterogeneity. Publication bias for the survival analysis was measured with Egger's test ($P < 0.05$). A complete methodology is provided in Item S1.

Our integrative review of KRT-associated mortality in children with inborn errors of metabolism identified 249 articles, of which 14 studies published after 2000 met the inclusion criteria for survival analysis (Table S1). We identified a total of 231 patients with inborn errors of metabolism, and the mean age of this population was 2.3 years (ranging from 3 days to 12.5 years), with the proportion of various inborn errors of metabolism disorders shown in Table S2.

Pooled survival among children who received KRT was 63.4% (95% confidence interval [CI], 52.4%-73.7%) (Fig 1 and Table S3), with no visual indication of publication

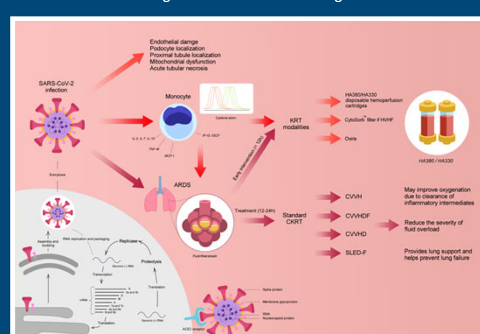
Kidney Medicine — Correspondence

Table 1. Sensitivity Analyses for Survival Among Children With Inborn Errors of Metabolism Treated With Kidney Replacement Therapy

Criteria	Number of Studies (n)	Number of Children (n)	% Proportion (95% CI)	I^2 (95% CI); *P* value	Egger's Test *P* Value
Overall	14	231	63.4 (52.4-73.7)	63.2% (34.5%-79.3%); *P* < 0.001	0.31
Age (>0.7 y[a])	7	96	59.8 (38.5-79.3)	78.4% (55.4%-89.6%); *P* < 0.001	0.19
Sample size (>15[a])	6	162	50.9 (35.8-65.9)	74.3% (41.4%-88.7%); *P* = 0.002	0.08
Geography (United States)	5	105	59.2 (49.4-68.5)	57.7% (20.0%-80.8%); *P* = 0.01	0.77
Study Quality (Good)	12	192	62.3 (49.4-74.4)	67.1% (39.7%-82.1%); *P* < 0.001	0.30

Note: Values were reported either as mean, median, or range; range was converted into mean by averaging min and max values.
Abbreviations: CI, confidence interval.
[a]Median across the studies.

New Paradigm Shift in AKI Following COVID-19



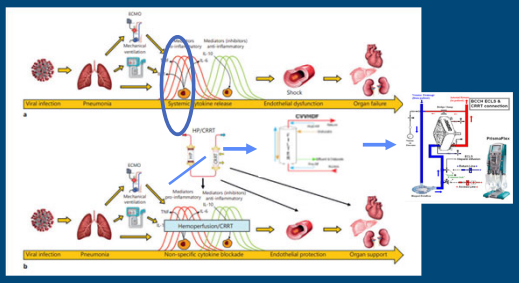
Raina R, Chakraborty R, Sethi SK, Bunchman T. Kidney Replacement Therapy in COVID-19 Induced Kidney Failure and Septic Shock: A Pediatric Continuous Renal Replacement Therapy [PCRRT] Position on Emergency Preparedness With Resource Allocation. *Front Pediatr*. 2020;8:413. Published 2020 Jul 3. doi:10.3389/fped.2020.00413

Cytokine Storm Syndrome

- Mechanism in causing Multi Organ Dysfunction, including renal function impairment.
- Various studies have suggested the occurrence of cytokine storm in critically ill COVID-19 patients due to higher plasma circulating:
  - -Cytokine levels (interleukin [IL] -2, IL-7, IL-10
  - -Interferon-inducing protein-10 [IP-10], granulocyte-colony stimulating factor [GSCF],
  - -Macrophage inflammatory protein-1a [MIP1]
  - -Tumor Necrosis factor alpha [TNF-α])

Raina R, Chakraborty R, Sethi SK, Bunchman T. Kidney Replacement Therapy in COVID-19 Induced Kidney Failure and Septic Shock: A Pediatric Continuous Renal Replacement Therapy [PCRRT] Position on Emergency Preparedness With Resource Allocation. *Front Pediatr*. 2020;8:413. Published 2020 Jul 3. doi:10.3389/fped.2020.00413

PCRRT RECOMMENDATION FOR KRT IN COVID-19 SEPSIS/ARF/MODS



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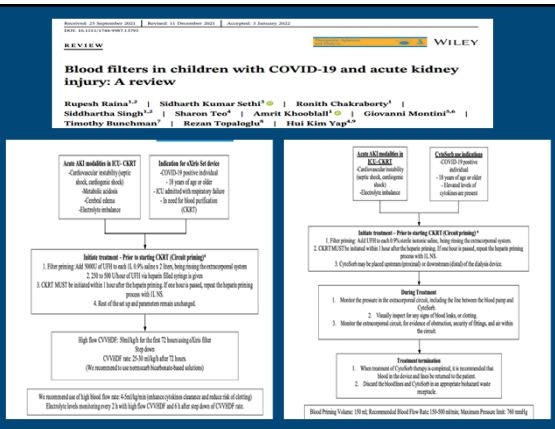
CytoSorb®: Our Solution

- CytoSorb® is the only specifically approved extracorporeal cytokine filter in the E.U.
- Specifically targets the prevention or treatment of organ failure by reducing cytokine storm and controlling potentially deadly inflammation
- Broad approved indication for use: To be used in any situation where cytokines are elevated
  - ✓ Allows for extensive "on-label" use for many different applications
- Safe: More than 1,000 human treatments with no serious device related adverse events

CytoSorbents.

Coming Soon
On April 10, 2020, CytoSorb has received FDA Emergency Use Authorization in the United States for use in critically-ill COVID-19 patients with imminent or confirmed respiratory failure in defined circumstances.



REVIEW — WILEY

Blood filters in children with COVID-19 and acute kidney injury: A review

Rupesh Raina[1,2] | Sidharth Kumar Sethi[3] | Ronith Chakraborty[1] | Siddhartha Singh[1,2] | Sharon Teo[4] | Amrit Khoobiali[1] | Giovanni Montini[5,6] | Timothy Bunchman[7] | Rezan Topaloglu[8] | Hui Kim Yap[4,9]

Raina R, Sethi SK, Chakraborty R, et al. Blood filters in children with COVID-19 and acute kidney injury: A review. *Pediatr Nephrol*. 2022;38(3):566-582. doi:10.1111/1744-9987.13793

CONSENSUS CONFERENCE

Concurrent use of continuous kidney replacement therapy during extracorporeal membrane oxygenation: what pediatric nephrologists need to know—PCRRT-ICONIC practice points

Rupesh Raina · Nikhil Nair · Jonathan Pelletier · Matthew Nied · Tarik Whitham · Kush Doshi · Tara Beck · Geeta Dantes · Sidharth Kumar Sethi · Yap Hui Kim · Timothy Bunchman · Kshitil Alhasan · Lisa Lima · Isabella Guzzo · Dana Fuhrman · Matthew Paden

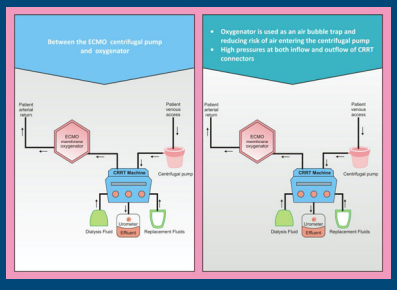
Received: 20 November 2023 / Revised: 15 January 2024 / Accepted: 27 January 2024

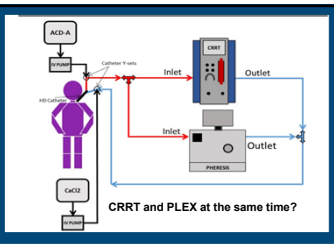
The blood flow rate in the CVVHDF machine should be independent from the ECMO device

The machine's venovenous access should be adjusted to tolerate positive pressures since the arterial access of the ECMO will allow for a very low-resistant circuit.

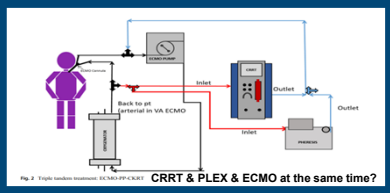
Set the alarms to allow for a positive pressure reading.

The ECMO pressure may be above the machine's programmed alarms and may need for a flow resistor.





CRRT and PLEX at the same time?



CRRT & PLEX & ECMO at the same time?

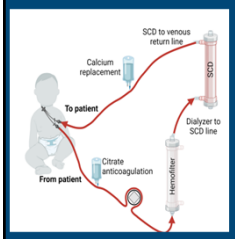
Pediatric Nephrology (2023) 38:927–931
https://doi.org/10.1007/s00467-022-05692-1

BRIEF REPORT

Use of extracorporeal immunomodulation in a toddler with hemophagocytic lymphohistiocytosis and multisystem organ failure

Stuart L. Goldstein[1] · Lenar T. Yessayan[2] · Kelli A. Krallman[1] · Michaela Collins[1] · Stefanie Benoit[3] · Angela Westover[2] · H. David Humes[2]

Received: 27 April 2022 / Revised: 7 July 2022 / Accepted: 8 July 2022 / Published online: 23 July 2022



- In severe forms, HLH presents with signs and symptoms of hyperinfammation that progress to life-threatening multiorgan failure.
- Intervention with an extracorporeal immunomodulatory treatment utilizing a selective cytopheretic device (SCD) could be benefcial.
- The SCD with regional citrate anticoagulation selectively binds the most highly activated circulating neutrophils and monocytes and deactivates them before release to the systemic circulation.
- Multiple clinical studies, including a multicenter study in children, demonstrate SCD therapy attenuates hyperinfammation, resolves ongoing tissue injury and allows progression

Goldstein SL, Yessayan LT, Krallman KA, et al. Use of extracorporeal immunomodulation in a toddler with hemophagocytic lymphohistiocytosis and multisystem organ failure. *Pediatr Nephrol*. 2023;38(3):927-931. doi:10.1007/s00467-022-05692-1

ACKD

Advances in Kidney Replacement Therapy in Infants

Rupesh Raina, Mignon McCulloch, Peter Nourse, Sidharth K. Sethi, and Hui Kim Yap

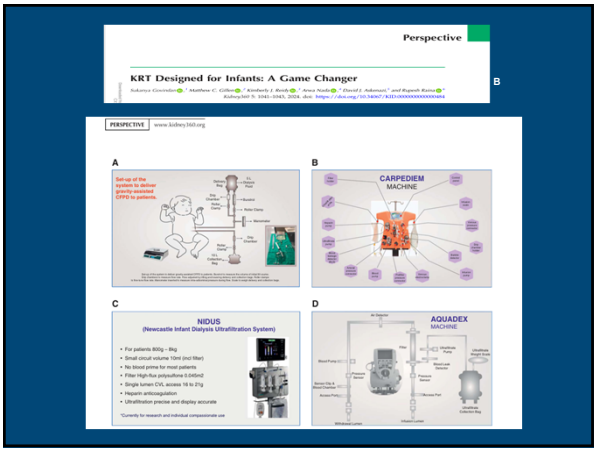
Acute kidney injury continues to be a highly occurring disease in the intensive care unit, specifically affecting up to a third of critically ill neonates as per various studies. Although first-line treatments of acute kidney injury are noninvasive, kidney replacement therapy (KRT) is indicated when conservative management modes fail. There are various modalities of KRT which can be used for neonatal populations, including peritoneal dialysis, hemodialysis, and continuous KRT. However, these KRT modalities present their own challenges in this specific patient population Thus, it is the aim of this review to introduce each of these KRT modalities in terms of their challenges, advances, and future directions, with specific emphasis on new technology including the Cardio-Renal Pediatric Emergency Dialysis Machine, Newcastle infant dialysis and ultrafiltration system, and the Aquadex system for ultrafiltration.

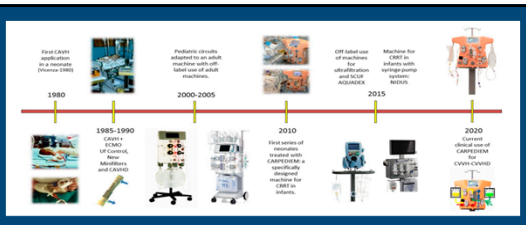
Key Words: Acute kidney injury, Kidney replacement therapy, Infants

Table 6. Characteristics of Novel Modalities of KRT

Characteristic of the System	CARPEDIEM	NIDUS	Aquadex	SLEDD-F
Priming volume Surface area Blood flow rates	27.2, 33.5, 41.5 mL 0.075, 0.147 and 0.245 m^2 10, 20, 30 mL/min	<10 mL 0.045 m^2 20-45 mL/min	33 mL 0.12 m^2 10-40 mL/min	Depends on size of filter used Qb [3-5 mL/kg/minute, minimum 50 mL/minute]
Dialysate flow rate	5, 10, 15 mL/min	-	Prefilter convective clearance – 30 mL/min	<2x Qb
Ultrafiltration rate	-	0-60 mL/hr controlled in 3.2 µL steps	Up to 500 mL/hr	Minimum 25 mL/minute

Abbreviations: CARPEDIEM, Cardio-Renal Pediatric Dialysis Emergency Machine; NIDUS, Newcastle infant dialysis and ultrafiltration system; SLEDD-f, sustained low efficiency daily diafiltration.





CKRT device	Modality	Mode of clearance	Filters	ECV in ml	Surface area in m^2	Membrane type
Prismaflex/Prismax	CVVH, CVVHD CVVHDF, SCUF	Diffusion Convection	HF20	58	0.2	Polyarylethersulfone
CARPEDIEM™	CVVH, CVVHD, SCUF	Diffusion Convection	D50 D100 D150	26 32 41	0.075 0.15 0.25	Polyether sulfone
NIDUS®	CVVHD SCUF	Diffusion	Neofl ux1	15	0.045	Polysulfone
Aquadex™	CVVH SCUF	Convection	UF 500	33	0.12	Polysulfone

APS · European Society for Pediatric Research · SPR Society for Pediatric Research
www.nature.com/pr

CORRESPONDENCE

Caregiver burden in pediatric acute kidney injury and chronic kidney disease

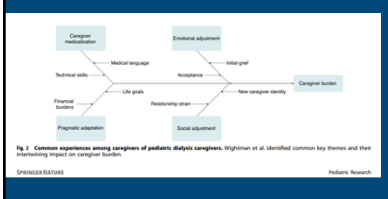


fig. 2 **Common experiences among caregivers of pediatric dialysis caregivers.** Wightman et al. identified common key themes and their interwining impact on caregiver burden.

SPRINGER NATURE
Pediatric Research

Rupesh Raina[1,2,3,4] · Archana Mymeni[2,4] and Sidharth K. Sethi[5]
[1]Department of Nephrology, Akron Children's Hospital, Akron, OH, USA. [2]Department of Nephrology, Akron Children's Hospital, Cleveland Clinic Akron General Medical Center, Akron, OH, USA. [3]Department of Pediatric Nephrology, Kidney Institute, Medanta, The Medicity, Gurgaon, Haryana, India. [4]These authors contributed equally: Rupesh Raina, Archana Mymeni. ✉email: RRaina@akronchildrens.org

CKRT ADVANCES

- Modality: No overall benefit to CRRT compared to IHD, though CRRT may be better for patients at risk of increased ICP and for volume control
- Dose: No benefit to “intensive” therapy, but delivered dose of both CRRT and IHD must be monitored to ensure minimum adequate dose
- Anticoagulation: Citrate is gaining wider acceptance as the preferred anticoagulation for CRRT
- Buffer: Bicarbonate should be the buffer in dialysate and replacement fluid for KRT in patients with AKI, especially with liver failure and/or lactic acidemia

Close Collaboration Between CCM and Nephrology

- Define the primary goal of CRRT daily (ie, fluid removal, acid/base control, small solute clearance, etc) Daily goal informs individualized CRRT prescription
- Keep CRRT running—maximize delivered vs prescribed CRRT ratio Establish and maintain high functioning dialysis vascular access
- Anticoagulation—regional citrate anticoagulation vs heparin vs other
- Review appropriateness medication dosing daily (especially antimicrobial agents) Large changes in effluent flow rates should prompt consideration to increase or decrease medication dosing
- Ensure appropriate nutrition support for CRRT—augmented protein intake recommended
- Avoid CRRT-related complications Severe hypophosphatemia (ie, <2.0 meq/L)
- Frequent CRRT circuit failures → increased blood transfusion needs
- Minimize risk of CRRT therapy errors through standardization and consistency of machine, modality, anticoagulation strategies, and education

Close Collaboration Between CCM and Nephrology

Prescribed CRRT dose = total prescribed effluent flow rate/h/weight (kg)

Delivered CRRT dose = total achieved effluent flow rate/d (or per hour)/weight (kg)/24 hours (if necessary)

Ratio of delivered dose/prescribed dose = total daily effluent volume achieved (in 24 hours)/total effluent volume prescribed

Time between CRRT circuit exchanges (required and/or unplanned)

Effective CRRT treatment time (in 24-hour period) = 24—number of downtime hours or 1440—number of downtime minutes

Vascular access site, size, length, and depth—is the access of appropriate length?

Mortality (or survival)—specifically in those with AKI requiring RRT

Kidney functional recovery to dialysis liberation

What is Needed?

- Newer criteria for adequacy of treatment were implemented in clinical routine, avoiding under-dosing of treatment and favoring the achievement of therapy targets such as fluid balance control, restoration of homeostasis and correction of biochemical derangements with excellent blood purification, thereby making CRRT a well-established form of therapy in intensive care

MCQs

Rupesh Raina, MD, FAAP, FACP, FASN,FISN and FNKF

Adult-Pediatric Kidney Disease/Hypertension
Professor of Medicine and Professor of Pediatrics
Director of Research Akron Nephrology Associates
AGMC, Cleveland Clinic, Cleveland, Ohio
Staff Medical Research, Rebecca D. Considine Research Institute
Staff at Akron Children's Hospital, Akron, Ohio
Council of Dean M-4 Director - Northeast Ohio Medical University, Rootstown, Ohio
Faculty Staff at Case Western Reserve University School of Medicine, Cleveland, Ohio

MCQ 1: CRRT Dosing and Management in a Pediatric Patient with Multiple Comorbidities

- Case: A 14-year-old adolescent (weight: 55 kg) with type 1 diabetes mellitus, obesity, and acute kidney injury secondary to diabetic ketoacidosis (DKA) is started on CRRT. The patient has a high serum potassium level of 6.5 mEq/L and severe metabolic acidosis with a pH of 7.1.

MCQ 1: CRRT Dosing and Management in a Pediatric Patient with Multiple Comorbidities

Considering the patient's underlying condition and the need for urgent correction of hyperkalemia and acidosis, which of the following CRRT strategies should be employed?

A) Prescribe CVVHDF with an effluent rate of 35 ml/kg/hr and a dialysate potassium concentration of 0 mEq/L

B) Use CVVHD with an effluent rate of 25 ml/kg/hr and a bicarbonate-buffered dialysate with a potassium concentration of 2 mEq/L

C) Initiate CVVH with an effluent rate of 40 ml/kg/hr and replacement fluid containing 4 mEq/L of potassium

D) Administer intermittent hemodialysis (IHD) instead of CRRT for faster correction of potassium and acidosis

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D) Administer intermittent hemodialysis (IHD) instead of CRRT for faster correction of potassium and acidosis

MCQ 2: CRRT Management in a Pediatric Patient on ECMO with Complicated Fluid Balance

- Case: A 9-year-old child (weight: 30 kg) with acute respiratory distress syndrome (ARDS) is on veno-venous ECMO and develops oliguric acute kidney injury requiring CRRT. The patient has severe fluid overload, with a positive fluid balance of 3 liters over 48 hours and is hemodynamically unstable on high-dose vasopressors.

MCQ 2: CRRT Management in a Pediatric Patient on ECMO with Complicated Fluid Balance

Which CRRT prescription is most appropriate to manage this patient's fluid balance without compromising hemodynamic stability?

A) CVVHDF with an effluent dose of 30 ml/kg/hr, a net ultrafiltration rate of 2 ml/kg/hr, and blood flow rate of 200 ml/min

B) CVVH with an effluent dose of 25 ml/kg/hr, a net ultrafiltration rate of 1 ml/kg/hr, and blood flow rate of 150 ml/min

C) CVVHD with an effluent dose of 20 ml/kg/hr, a net ultrafiltration rate of 0.5 ml/kg/hr, and blood flow rate of 100 ml/min

D) CVVHDF with an effluent dose of 35 ml/kg/hr, no net ultrafiltration, and blood flow rate of 250 ml/min

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D) CVVHDF with an effluent dose of 35 ml/kg/hr, no net ultrafiltration, and blood flow rate of 250 ml/min

MCQ 3: Complications of Citrate Anticoagulation in Pediatric CRRT

- Case: A 7-year-old girl (weight: 20 kg) with liver failure and acute kidney injury is started on CRRT with regional citrate anticoagulation. After 24 hours, she develops worsening metabolic acidosis, with a total calcium to ionized calcium ratio of 3.0, and an escalating requirement for calcium chloride infusion.

MCQ 3: Complications of Citrate Anticoagulation in Pediatric CRRT

What is the most likely cause of this complication, and what is the best management strategy?

A) Hypercalcemia due to citrate toxicity; stop citrate anticoagulation and switch to systemic heparin

B) Citrate accumulation due to liver failure; decrease the blood flow rate and adjust the citrate infusion rate

C) Hypocalcemia due to inadequate calcium replacement; increase the calcium chloride infusion rate

D) Metabolic acidosis due to citrate overdose; reduce the CRRT dose and increase the bicarbonate concentration in the dialysate

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D) Metabolic acidosis due to citrate overdose; reduce the CRRT dose and increase the bicarbonate concentration in the dialysate

MCQ 4: Antibiotic Dosing Adjustments in Pediatric CRRT

- Case: A 13-year-old boy (weight: 45 kg) on CRRT for sepsis-induced acute kidney injury is being treated with meropenem. The CRRT is running at an effluent rate of 30 ml/kg/hr. The initial dosing was based on estimated clearance, but the patient has since become hemodynamically unstable and volume overloaded.

MCQ 4: Antibiotic Dosing Adjustments in Pediatric CRRT

How should the meropenem dosing be adjusted in this scenario?

A) Increase the meropenem dose to compensate for reduced clearance due to volume overload

B) Maintain the current dose of meropenem but increase the dosing frequency to every 6 hours

C) Decrease the meropenem dose as the patient's hemodynamic instability may reduce drug clearance

D) Maintain the current dosing schedule but monitor drug levels closely for potential accumulation

MCQ 4: Antibiotic Dosing Adjustments in Pediatric CRRT

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MCQ 5: Nutritional management in critically ill patients undergoing Continuous Renal Replacement Therapy (CRRT)

Which of the following is the most appropriate nutritional strategy for a critically ill patient undergoing Continuous Renal Replacement Therapy (CRRT)?

A) High-protein diet with standard caloric intake.

B) Low-protein diet with fluid restriction.

C) Standard-protein diet with low-fat content.

D) High-protein diet with increased caloric intake.

E) Low-protein diet with high carbohydrate content.

MCQ 5: Nutritional management in critically ill patients undergoing Continuous Renal Replacement Therapy (CRRT)

Which of the following is the most appropriate nutritional strategy for a critically ill patient undergoing Continuous Renal Replacement Therapy (CRRT)?

A) High-protein diet with standard caloric intake.

B) Low-protein diet with fluid restriction.

C) Standard-protein diet with low-fat content.

D) High-protein diet with increased caloric intake.

E) Low-protein diet with high carbohydrate content.

MCQ 5: Nutritional management in critically ill patients undergoing Continuous Renal Replacement Therapy (CRRT)

- Explanation: Critically ill patients undergoing CRRT often experience increased protein catabolism and energy expenditure. Therefore, a high-protein diet with increased caloric intake is recommended to meet the metabolic demands, prevent malnutrition, and support recovery. Nutritional needs should be carefully monitored and adjusted based on the patient's ongoing clinical status and the efficiency of the CRRT.

THE UNIVERSITY OF MELBOURNE

Northern Health

Alport syndrome: what's new

Judy Savige, Adult physician
The University of Melbourne
(Melbourne Health and Northern Health)

Conflicts of Interest

- I have no financial or non-financial Conflicts of Interest to declare

Acknowledgements

- The many patients and clinicians who have supported and encouraged us
- Joel Gibson, Mary Huang and many other students
- The ophthalmologists who have collaborated with us
- Alport Foundation Australia

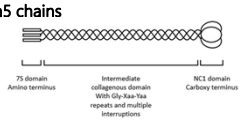
Classification of Alport syndrome - *Kashtan, 2017*

- **XL** Alport syndrome – haematuria; **kidney failure in males by the age of 40 and 20% of females by the age of 60**; hearing loss and ocular abnormalities
- **AR** Alport syndrome – kidney failure in males and females; hearing loss and ocular abnormalities, all often in childhood
- **Digenic** Alport syndrome – variants in two ***COL4A3 – COL4A5*** genes
- **AD** Alport syndrome – **haematuria lifelong;** kidney failure is uncommon, and hearing loss and ocular abnormalities are rare – ***Furlano 2021***

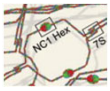
- **Alport spectrum**

Pathogenic variants in Alport syndrome

- ***COL4A3, 4*** **and** ***5*** **code for collagen IV a3, a4 and a5 chains**
- **Collagen IV α3α4α5 heterotrimer**
- Normally forms **cross-links** rather than fibrils



Same types of variants for all 3 genes
- **Large deletions – 10%**
- **Null (frameshift, termination) – 15%**
- Splicing variants – 15%
- **Missense variants (mostly Gly substitutions) – 50%**
- **Gly-Xaa-Yaa** repeats in intermediate collagenous region



Predicted population frequency of XL and AD Alport syndrome in the general population

	COL4A3	***COL4A4***	***COL4A5***
Nonsense	33 (6%)	48 (8%)	
Frameshifts	110 (20%)	42 (7%)	1
Canonical splice site changes	36 (6%)	29 (5%)	6
Position 1 Gly substitutions	380 (68%)	458 (79%)	51
Number of excluded Gly substitutions	N= 15	N=22	N=13
	N=559 in 245,889 or 0.45% of people	N=577 in 233,916 or 0.49% of people	N=59 in 136,920 or 0.04% one in 2320
	0.9% people or one in 106 have a pathogenic variant in *COL4A3* or *COL4A4*		**One in 2,320 have a pathogenic variant in *COL4A5***

- Gibson 2021

Predicted population frequency of XL and AD Alport syndrome in the general population

AD Alport syndrome is the commonest genetic kidney disease, affecting one % of the population

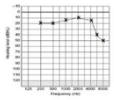
XL Alport syndrome is the second commonest genetic cause of kidney failure

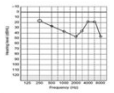
AD:XL Alport syndrome = 20:1

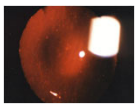
These are still underestimates because
- Some Position 1 Gly were excluded including p.Gly695Arg
- WES does not detect deletions, intronic splicing variants

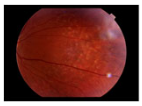
XL Alport syndrome in males

- Haematuria, proteinuria, kidney cysts, progressive kidney failure
- Hearing loss
- Corneal ulcers, lenticonus, fleck retinopathy. Usually normal vision
- Thinned, later lamellated GBM
- Pathogenic variants in *COL4A5*







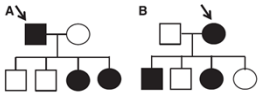


Recommendations for males with XL Alport syndrome

- Affected boys should generally be treated with RAAS blockade and SGLP2 inhibitors from the time of diagnosis
- All first degree family members should undergo genetic testing
- Affected family members should not be kidney donors – Savige 2021, ERKNET review

XL Alport syndrome in females

- Twice as common in females as in males. For every male with XL disease, there are two affected females
- Generally milder disease but 20% risk of kidney failure at 60 years. Hearing loss is common. Peripheral retinopathy is also common
- Proteinuria is a risk factor for kidney failure, hearing loss and ocular abnormalities - *Gibson 2022*
- Offspring of an affected woman have a greater risk of kidney failure than the offspring of an affected male



- Savige, 2016

Recommendations for females with XL Alport syndrome

- Affected individuals should be treated with RAAS blockade, SGLP2 inhibitors from the onset of microalbuminuria – *Kashtan 2021*
- First degree family members should undergo genetic testing
- Affected family members should not be kidney donors – *Savige 2013*

AR Alport syndrome

- Disease is identical in males and females
- Identical clinically to XL disease in males
- Much rarer than XL disease
- Mean age at kidney failure onset is 21 years compared with 26 years for males with XL disease
- Lenticonus in a girl or woman suggests AR disease

- Parents and offspring will usually be heterozygotes and have AD disease
- Siblings may have AR disease

- Recommendations: RAAS blockade, SGLP2 inhibitors from the time of diagnosis

Digenic Alport syndrome

	Genes affected	**Clinical features**	**Inheritance pattern**
Autosomal recessive (AR)	*COL4A3* or *COL4A4*	Males and females have haematuria, kidney failure equally often and equally severe in both, hearing loss, lenticonus and fleck retinopathy	AR
Digenic	***COL4A5*** plus *COL4A3* or *COL4A4*	Males: Phenotype resembles XL Alport syndrome in males	XL plus AD
	COL4A5 plus *COL4A3* or *COL4A4*	Females: Phenotype resembles XL Alport syndrome in females	XL plus AD
	COL4A3* plus *COL4A4 (on the same chromosome)	Males and females: Phenotype generally more severe than AD Alport syndrome	Digenic
	COL4A3* plus *COL4A4 (on opposite chromosomes)	Males and females: Phenotype generally more severe than AD Alport syndrome	AD

Digenic Alport syndrome

- **Commoner than AR** Alport syndrome
- Usually pathogenic variants in ***COL4A3*** **plus** ***COL4A4***
- Disease severity for this combination is intermediate between AD and AR
- Where *COL4A5* plus *COL4A3* or *COL4A4,* severity is more like XL
- Second variant may be missed, and digenic disease explains some apparent AD inheritance with severe features
- Disease in the next generation depends on whether genes affected are on the same chromosome and inherited together (AD) or on different chromosomes (like AR)

AD Alport syndrome

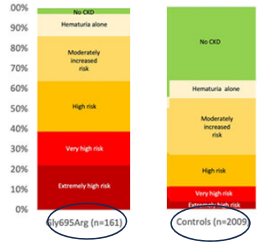
- Features range from no urinary abnormalities (30%), **haematuria,** proteinuria only (10%), kidney cysts, to progressive kidney failure (up to 30%)
- Normal hearing
- No eye abnormalities
- **Thinned GBM**
- Heterozygous pathogenic variants in *COL4A3* or *COL4A4*

Formerly known as

- 'Benign Familial Haematuria' – but not necessarily benign, nor familial, nor associated with haematuria
- 'Benign Persistent Haematuria'
- 'Thin basement membrane nephropathy'
- Carriers of AR Alport syndrome'

AD Alport syndrome: same variant, different phenotypes

- **Same variant (p.Gly695Arg) results in variable features – haematuria, haematuria plus proteinuria, renal impairment, kidney failure in 97%**
- 65% of hospital patients also had a renal phenotype



- Solanki 2023

AD Alport syndrome: same variant and different age at kidney failure

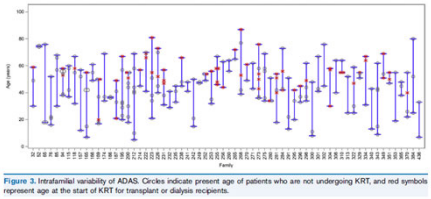


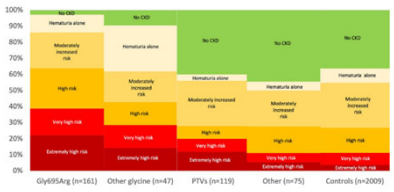
Figure 3. Intrafamilial variability of ADAS. Circles indicate present age of patients who are not undergoing KRT, and red symbols represent age at the start of KRT for transplant or dialysis recipients.

Red symbols – age at kidney failure
Circles – ages of people without kidney failure

- Furlano 2021

AD Alport syndrome: variant type affects severity of clinical features

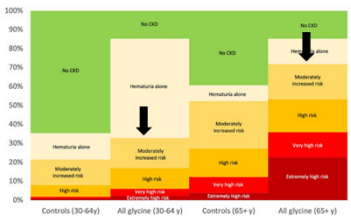
- **Missense variants have a more severe phenotype than null variants**
- 97% of those with a severe variant (p.Gly695Arg) had a renal phenotype
- 60% with a milder variant (null) had a renal phenotype (haematuria alone etc)



-Solanki 2023

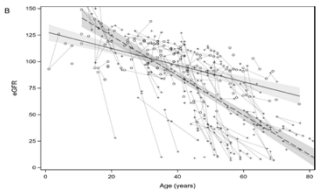
AD Alport syndrome: age affects proteinuria, eGFR

- Haematuria alone more common in younger people
- Overall 85% with Gly variants have haematuria, proteinuria or impaired eGFR
- With increasing age, 85% have features but more severe (30% to 70%, worse proteinuria, eGFR)
- Worse renal features in controls too



- Solanki 2023

AD Alport syndrome: worse than expected kidney function over time



Differences in eGFR measurements over time

____expected eGFR trajectory over time

------ eGFR for AD Alport syndrome

- Furlano 2021

Risk of kidney failure in AD Alport syndrome

- 14 – 39% in different hospital-based series – *Pierides 2009, Furlano 2021, Solanki, 2023, Bada-Bosch 2022*
- But hospital-based series are biased towards severe disease

- **Calculated risk of kidney failure in relatively unbiased populations**
- In many cohorts of ESKF *COL4A5* and *COL4A3/COL4A4* variants occur about equally often
- However pathogenic *COL4A3/COL4A4* variants occur 20 x as often as *COL4A5* normally
- Thus the likelihood of ESKF for a *COL4A3/COL4A4* variant is about 1/20 of that of *COL4A5* variants – < 5% - *Savige 2022*

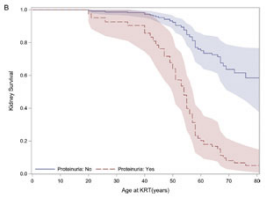
- **However individuals with *COL4A3/COL4A4* variants who have been referred to a nephrologist often have more severe disease**

Risk factors for kidney failure in AD Alport syndrome

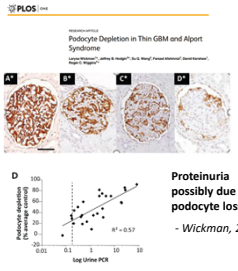
- Better prognosis variants (large deletions, null, splicing)
- Worse prognosis variants – 'dominant negative'. Opposite of XL Alport syndrome. Earlier age at kidney failure (missense, Gly substitutions) - *Solanki 2023, Hoefele, 2024*
- Some Gly substitutions (Glu, Asp, Arg) result in more severe disease than others

- Proteinuria – *Furlano 2021*
- Kidney cysts parallel impaired kidney function –***Bada-Bosch 2022***

Proteinuria and kidney failure in AD Alport syndrome



Kidney survival with proteinuria worse than without proteinuria *- Furlano, 2021*



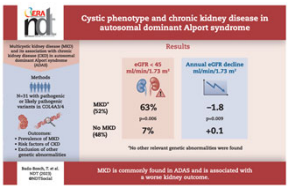
Proteinuria possibly due to podocyte loss

- Wickman, 2016

Kidney cysts in AD Alport syndrome

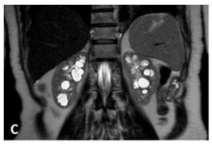
- Kidney cysts are common in Alport syndrome due to all *COL4A3-5* variants
- Mainly **normal sized kidneys**, sometimes normal kidney function

– *Sevillano 2014; Gulati 2020*



Kidney cysts in AD Alport syndrome

- Overall associated with a **worse kidney outcome**
- **Kidney function loss is determined by time-averaged proteinuria and the presence of multiple cysts**



- 31 patients with AD AS; age 57 ± 12 years
- Cysts also occur in children
- **Half had kidney cysts;** 13 per kidney
- Mainly cortical, subcortical; 65% ≥ 5 mm
- More cysts occurred with greater proteinuria and more advanced kidney failure
- **Associated with more rapid eGFR decline**
- Not associated with hypertension
- More cysts than in matched patients with IgA nephropathy
- No pathogenic variants in other haematuria, cystic kidney or proteinuria genes

- Bada-Bosch 2024

Hypomorphic variants in *COL4A3* and *COL4A4* may worsen kidney failure

- Variants that in themselves do not even result in haematuria but which may, in association with another mild pathogenic variant in *COL4A3* or *COL4A4,* result in kidney failure eg p.Leu1474Pro in *COL4A3*

Managing AD Alport syndrome

- Haematuria is the clue found most often in AD Alport syndrome
- Genetic testing distinguishes between AD and XL disease
- Not possible to predict likelihood of being affected from testing for haematuria alone. Genetic testing is worthwhile in first degree relatives
- Disease severity varies in different affected family members
- Patients who are referred to Nephrology clinic usually have more severe disease

- Monitor every one - three years
- Aim to minimise proteinuria with RAAS blockade and SGLP2 inhibitors and optimise BP and lifestyle issues. Treat from the onset of microalbuminuria.
- Give patient a copy of their results. Explain to the patient the risk for other family members. Undertake cascade testing in first degree family members
- Preferably do not use an affected family member as a kidney donor (ERKNet guidelines expected soon)

Treatment

- RAAS blockade. ACE inhibitors and ARBs – to minimise albuminuria as much as BP allows. Antifibrotic too. For all modes of inheritance - *Zeng 2023.* Delays kidney failure by up to 13 years – *Gross 2011; Gross 2020*
- SGLT2i - *Mabillard 2020*
- Mineralocorticoid Receptor Antagonist or Finerenone – *Song 2023*
- Better BP control, weight control, smoking cessation
- Newer agents
- Sparsentan- orally- active dual endothelin- angiotensin receptor antagonist reduces proteinuria in FSGS – *Rheault 2023*
- R3RO1 – reduces cholesterol esters – *Wright 2021*
- ELOX-02 – novel aminoglycoside for reading through 'truncating' variants, decreased proteinuria and improved kidney morphology

Alport syndrome in children

- Genetic testing in children
- Generally not possible to identify affected status from haematuria alone
- Generally not possible to distinguish between XL and AR disease clinically

- Can look in mother for haematuria, peripheral retinopathy and genetic variant

- All children with haematuria are recommended to be tested for XL, AR, digenic and AD Alport syndrome
- Those with XL, AR Alport syndrome should undergo RAAS blockade
- Those with AD Alport syndrome should start RAAS blockade from onset of microalbuminuria

- Often useful to undertake genetic testing in the mother first

- New guidelines coming soon from ERKNET – on using AD Alport donors

How often are pathogenic variants found in children with haematuria or adults with TBMN?

- 60 children referred for haematuria
- **35 (58%) had a genetic diagnosis (5 gene panel)**
- *COL4A3 or COL4A4* (18,30%), *COL4A5* (13,22%), *COL4A1* (2, 3%), *MYH9* (1, 2%), *CLCN5* (2, 3%)
- AD Alport syndrome (13, 22%), XL (12, 20%), AR (2, 3%)
- **Highest diagnostic yield with highest levels of haematuria (>500,000 x 10^6/L)**
- **Proteinuria (UPC> 20 increased the diagnostic yield from 31 to 65%**

- Shanks, 2023

- 13 patients with TBMN
- Tested with Sanger sequencing, MLPA and WES
- **7 (54%) had a P or LP variant in *COL4A3* or *COL4A4* or a digenic variant, others in FSGS gene**

– Hirabayashi, 2022

Missing variants in Alport syndrome

- Even when there is a strong suspicion of Alport syndrome, no variant may be found
- More common with AD Alport syndrome - 70% found; 50% with haematuria, 54% with GBM thinning - *Shanks, 2023; Hirabayashi 2022*
- VUS or no variant at all
- Otherwise Intronic splicing changes, large deletions, IgA nephropathy etc

What's on the horizon?

- Better algorithms for genetic diagnosis
- Better understanding of genotype-phenotype correlation for pathogenic variants – UKBB, trimerization assays, minigene assays and more precise computational tools
- Better understanding of hypomorphic variants and their modifying effect on disease
- New treatments
- Biomarkers to predict renal deterioration
- More accurate advice on kidney donation from affected donors

Summary

- AD Alport syndrome is commonest genetic kidney disease and occurs 20 times as often as XL disease
- Clinical features for AD Alport syndrome vary even within a family
- XL disease – null variants have a worse prognosis
- AD disease – missense variants have a worse prognosis
- Proteinuria is a risk factor for progression

- AD Alport syndrome is so common that it can coexist with other kidney diseases

Which of the following are False?

1.Haematuria in Alport syndrome is

- Demonstrated reliably by dipstick
- Found in nearly all males and females with XL or AR Alport syndrome
- Found in two thirds of people with AD Alport syndrome
- Always persistent
- May predict impaired kidney function
- Sometimes proteinuria occurs without haematuria

Which of the following are False?

1.Haematuria in Alport syndrome is

- Demonstrated reliably by dipstick
- Found in nearly all males and females with XL or AR Alport syndrome
- Found in two thirds of people with AD Alport syndrome
- **Always persistent**
- May predict impaired kidney function
- Sometimes proteinuria occurs without haematuria

Which of the following are False?

2.An 11 year old boy has a lamellated GBM or pathogenic *COL4A5* variant consistent with XL Alport syndrome

- He should be tested for microalbuminuria
- He should be tested for a hearing loss
- He should be tested for lenticonus and a fleck retinopathy
- His mother, brothers and sisters should be tested for haematuria and proteinuria
- His father should be tested for haematuria

Which of the following are False?

2.An 11 year old boy has a lamellated GBM or pathogenic *COL4A5* variant consistent with XL Alport syndrome

- He should be tested for microalbuminuria
- He should be tested for a hearing loss
- He should be tested for lenticonus and a fleck retinopathy
- His mother, brothers and sisters should be tested for haematuria and proteinuria
- **His father should be tested for haematuria**

Which of the following are False?

3.Microalbuminuria in a boy with XL Alport syndrome

- All boys with XL Alport syndrome should be treated even before they develop microalbuminuria
- Ramipril is the best agent in children
- Albuminuria should be minimised using the tolerated highest dose
- SGLT2 inhibitors are not yet proven to be effective in children

Which of the following are False?

3.Microalbuminuria in a boy with XL Alport syndrome

- All boys with XL Alport syndrome should be treated even before they develop microalbuminuria
- **Ramipril is the best agent in children**
- Albuminuria should be minimised using the tolerated highest dose
- SGLT2 inhibitors are not yet proven to be effective in children

Which of the following are False?

4.An 11 yo boy with haematuria but without a renal biopsy or genetic diagnosis of Alport syndrome

- Does not need to be tested for microalbuminuria or treated
- Should be tested for a hearing loss
- Should be tested for lenticonus and a fleck retinopathy (non-mydriatic retinal camera)
- Should have his first degree relatives tested for haematuria

Which of the following are False?

4.An 11 yo boy with haematuria but without a renal biopsy or genetic diagnosis of Alport syndrome

- **Does not need to be tested for microalbuminuria or treated**
- Should be tested for a hearing loss
- Should be tested for lenticonus and a fleck retinopathy (non-mydriatic retinal camera)
- Should have his first degree relatives tested for haematuria

Which of the following are False?

5.An 11year old girl with haematuria and a hearing loss

- Should be tested for microalbuminuria and kidney function
- Does not need to be tested for lenticonus and a fleck retinopathy
- May have AR Alport syndrome
- May have another cause for the hearing loss
- May come from a consanguineous family

Which of the following are False?

5.An 11year old girl with haematuria and a hearing loss

- Should be tested for microalbuminuria and kidney function
- **Does not need to be tested for lenticonus and a fleck retinopathy**
- May have AR Alport syndrome
- May have another cause for the hearing loss
- May come from a consanguineous family

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Anemia in CKD
- The Great Debate -

Sharon Teo
Consultant Paediatric Nephrologist
National University Hospital

Disclosures

No disclosures to declare

Anemia in children with CKD

- What we know
  - Definitions
  - Etiologies
- Management
  - Iron
  - ESAs
  - HIF-PHI

Renal Anemia

Definition: ADULTS

Men < 13 g/dL
Women < 12 g/dL

KDIGO 2012

Renal Anemia

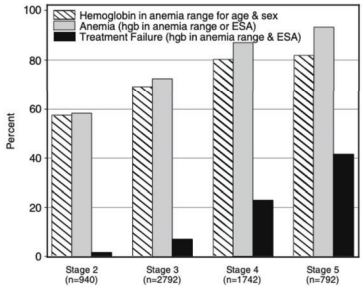
Definition: PAEDIATRICS

AGE (YEARS)	HAEMOGLOBIN (g/dL)
0.5 - 5	< 11.0
5 - 12	< 11.5
12 - 15	< 12.0
> 15	
Male	< 13.0
Female	< 12.0

WHO, KDIGO 2012

How common is paediatric renal anemia?

Prevalence:



NAPRTCS:
- CKD 3 = 73%
- CKD 4 = 87%
- CKD 5 = > 93%

Atkinson et al, Pediatr Neprol 2010

Patient Case 1

- 16 year old boy presents with tiredness and a 2 month history of weight loss and decreased appetite.
- Creatinine on admission was 614 umol/L (urea 27 mmol/L)
- No hypertension
- USS showed small, dysplastic kidneys

Labs:
- SCr 614, bicarb 17
- **Hb 9.6 g/dl**, MCV 86.9 fl
- Iron 4.4 umol/L, Ferritin 150 ug/L, **TSATs 8.9**
- Folate 15.3, Vit B12 632
- **PTH 49.8**

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Question 1

Which of the following is **NOT** a cause of anemia in children with CKD ?

a. Acidosis
b. Hyperparathyroidism
c. Inflammation
d. Malnutrition
e. Uraemia

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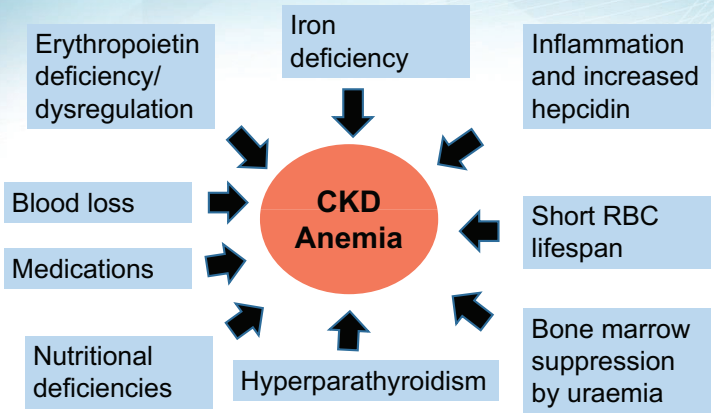
CKD Anemia – Why does it happen?



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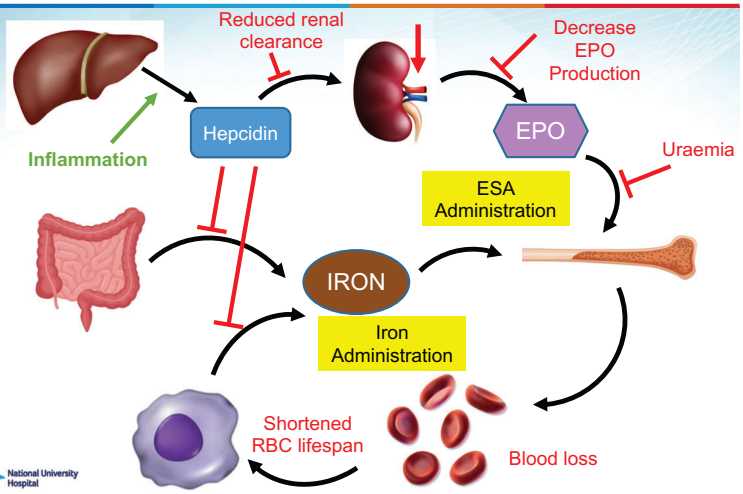
CKD Anemia



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CKD Anemia – Why does it matter?

CKD Anemia

- ↑ risk of mortality
- ↑ hospitalization
- ↑ risk of developing LVH
- ↑ risk of progression of CKD
- Quality of Life
  - Neurocognitive development
  - Exercise tolerance
  - Growth

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Atkinson et al, Nat Rev Nephrol, 2011

CKD Anemia – What can we do?

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Question 2

Which of the following is **NOT** a cause of iron deficiency in patients with CKD.

a. Erythropoetin Stimulating Agent (ESA) use
b. Sleep deprivation
c. Haemodialysis
d. Poor nutrition
e. Menstruation

Patient Case 2

- 15 year old girl with ESRD secondary to FSGS on regular haemodialysis
- Her haemoglobin continues to drop despite regular darbepoeitin (highest dose allowed for weight)
- Heavy menses every month
- IV iron was withheld as per HD facility protocol (ferritin > 800)

Labs:
- **Hb 8.6 g/dl → 7.5 g/dl**
- Iron 16.6 umol/L
- **Ferritin 1129**
- **TSATs 20**

Iron Deficiency

Absolute	Functional
Severely reduced or absent iron stores	Adequate iron stores but inability to mobilize iron from storage

TSAT < 20
Ferritin
< 100 ng/ml
< 200 ng/ml

LIMITATIONS

Ferritin:
- Acute-phase reactant

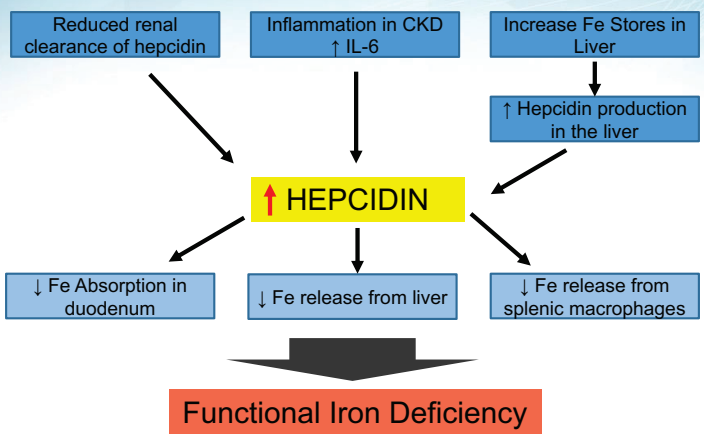
TSAT:
- Diurnal fluctuations
- Reduced in setting of malnutrition and chronic disease

Question 3

Which of the following are **FALSE** about iron regulation in renal anemia?

a. Ferritin is a reflection of iron stores
b. Hepcidin reduces release of iron from macrophages
c. Hepcidin increases absorption of iron from the gut
d. Iron absorption is enhanced by vitamin C

Hepcidin



Iron Supplementation

Oral

VS

Intravenous

Oral Iron

Dosage: 3 – 6 mg/kg/day of elemental iron

Pro

- Inexpensive
- Available
- Safe
- Easier to administer

Con

- Poor enteral absorption
- Poor compliance
- GI side effects

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Oral Iron

Dosage: 3 – 6 mg/kg/day of elemental iron

Iron Formulation	Dose Prescribed (per tablet)	Elemental Iron (%)
Ferrous sulfate (Ferro Gradumet®)	325 mg	65 mg (20%)
Ferrous fumarate	200 mg	66 mg (33%)
Ferrous gluconate	300 mg	36 mg (12%)
Iron polymaltose (Maltofer ®)		
• Tablet	100 mg	100mg (100%)
• Drops	50 mg/ml	50 mg/ml (100%)
• Syrup	10 mg/ml	10mg/ml
Sucroferric oxyhydroxide (Velphoro ®)	2.5 g	500 mg (20%)
Ferric citrate	1 g	210 mg (21%)

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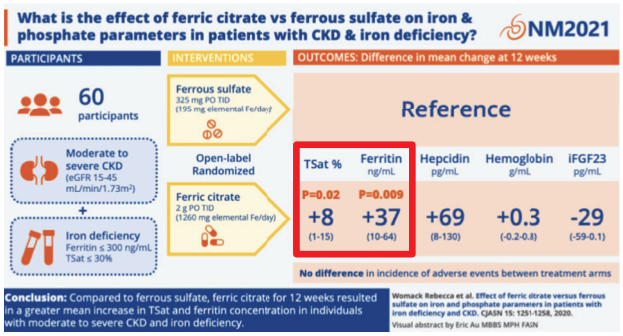
Adult

Randomized Controlled Trial > Clin J Am Soc Nephrol. 2020 Sep 7;15(9):1251-1258.
doi: 10.2215/CJN.15291219. Epub 2020 Jul 21.

Effect of Ferric Citrate versus Ferrous Sulfate on Iron and Phosphate Parameters in Patients with Iron Deficiency and CKD: A Randomized Trial

Rebecca Womack [1], Fabian Berru [1], Bhupesh Panwar [1], Orlando M Gutiérrez [1 2]



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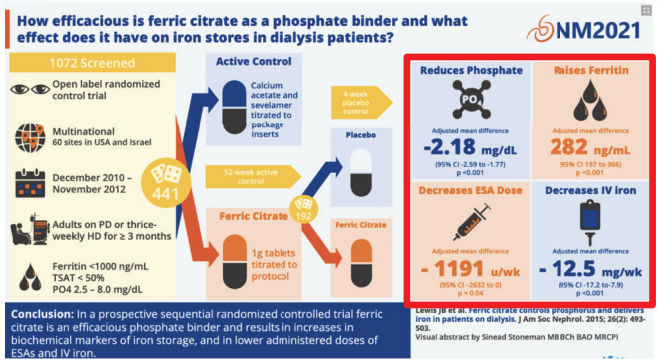
Womack R et al, Clin J Am Soc Neprol, 2020

Adult

J Am Soc Nephrol. 2015 Feb; 26(2): 493–503. PMCID: PMC4310662
Published online 2014 Jul 24. doi: 10.1681/ASN.2014020212 PMID: 25060056

Ferric Citrate Controls Phosphorus and Delivers Iron in Patients on Dialysis

Julia B. Lewis,[1,2] Mohammed Sika,[1] Mark J. Koury,[3] Peale Chuang,[4] Gerald Schulman,[1] Mark T. Smith,[5] Frederick C. Whittier,[6] Douglas R. Linfert,[7] Claude M. Galphin,[7] Balaji P. Athreya,[7] A. Kaldun Kaldun Nossuli,[8] Ingrid J. Chang,[9,10] Samuel S. Blumenthal,[11] John Manley,[11] Steven Zeig,[12] Kotagal S. Kant,[13] Juan Jose Olivero,[14] Tom Greene,[9,10] and Jamie P. Dwyer[1], for the Collaborative Study Group



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Lewis JB et al, J Am Soc Nephrol, 2015

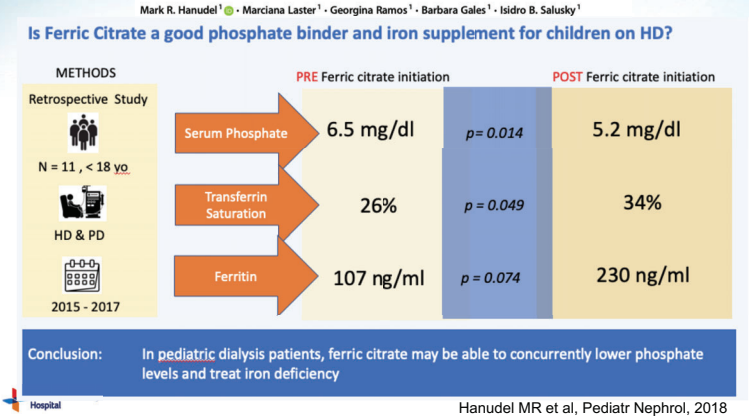
Paed

Pediatric Nephrology (2018) 33:2137–2142
https://doi.org/10.1007/s00467-018-3999-y

ORIGINAL ARTICLE

Clinical experience with the use of ferric citrate as a phosphate binder in pediatric dialysis patients

Mark R. Hanudel[1] · Marciana Laster[1] · Georgina Ramos[1] · Barbara Gales[1] · Isidro B. Salusky[1]



Hospital

Hanudel MR et al, Pediatr Nephrol, 2018

FIT4KID Trial

Pediatric Nephrology (2022) 37:2547–2557
https://doi.org/10.1007/s00467-022-05492-7

REVIEW

A review of ferric citrate clinical studies, and the rationale and design of the Ferric Citrate and Chronic Kidney Disease in Children (FIT4KiD) trial

National University Hospital

Iron Supplementation

Oral

VS

Intravenous

National University Hospital

IV Iron

Pro

- More efficacious
  - ↑ Ferritin levels
  - ↑ Hb levels
  - ↓ ESA use

Con

- Side effects
  - Transient hypotension
  - Nausea & vomiting
  - Hypersensitivity
  - Hypophosphatemia
- Infectious risk

National University Hospital

IV Iron

Iron Formulation	Elemental Iron	Maximum single dose	Infusion time
Iron Sucrose (Venofer®)	20 mg/ml	100 mg	10 mins - 4 hours
Iron Dextran (Dexferrum ®)	50 mg/ml	100 mg	60 mins
Ferric Carboxymaltose (Ferrinject®)	50 mg/ml	15mg/kg (max 750 mg)	15 – 30 mins
Iron isomaltoside (Monoferric®)	100 mg/ml	20 mg/kg	30 – 60 mins

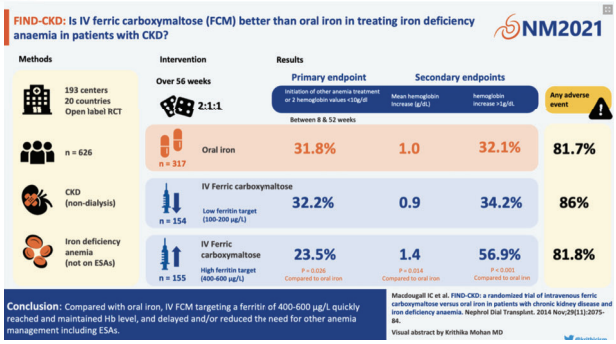
National University Hospital

Adult

Nephrol Dial Transplant (2014) 29: 2075–2084
doi: 10.1093/ndt/gfu231
Advance Access publication 2 June 2014

FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Iain C. Macdougall[1], Andreas H. Bock[2], Fernando Carrera[3], Kai-Uwe Eckardt[4], Carlo Gaillard[5], David Van Wyck[6], Bernard Roubert[7], Jacqueline G. Nolen[7], Simon D. Roger[8] on behalf of the FIND-CKD Study Investigators[9]



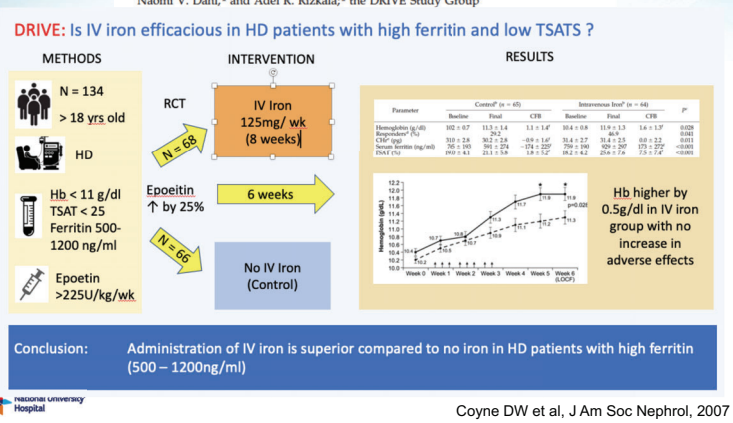
National University Hospital

Macdougall et al, Nephrol Dial Transplant, 2014

Adult

Ferric Gluconate Is Highly Efficacious in Anemic Hemodialysis Patients with High Serum Ferritin and Low Transferrin Saturation: Results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study

Daniel W. Coyne,* Toros Kapoian,† Wadi Suki,‡ Ajay K. Singh,§ John E. Moran,‖ Naomi V. Dahl,¶ and Adel R. Rizkala;¶ the DRIVE Study Group



National University Hospital

Coyne DW et al, J Am Soc Nephrol, 2007

Patient Case 2

- 15 year old girl with ESRD secondary to FSGS on regular haemodialysis
- Her haemoglobin continues to drop despite regular darbepoeitin (highest dose allowed for weight)
- Heavy menses every month
- IV iron was withheld as per HD facility protocol (ferritin > 800)

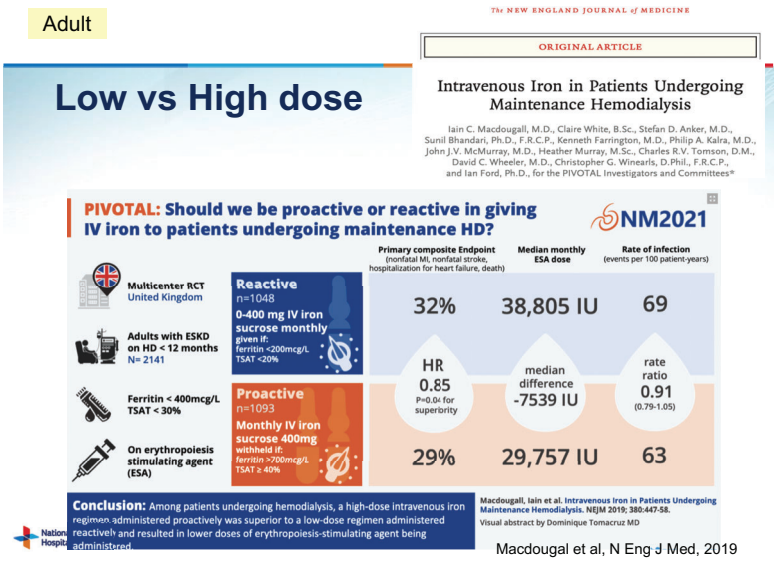
Labs:
- **Hb 8.6 g/dl → 7.5 g/dl**
- Iron 16.6 umol/L
- **Ferritin 1129**
- **TSATs 20**

IV iron recommenced despite high ferritin and her Hb improved

National University Hospital

Adult

Low vs High dose



Macdougal et al, N Eng J Med, 2019

Question 4

Which of the following are **TRUE** about erythropoietin (EPO) and Erythropoeitin stimulating Agents (ESAs)?

a. EPO production is not affected by oxygen levels
b. The primary site for endogenous erythropoietin production are the renal tubular epithelial cells
c. EPO is also produced by hepatocytes
d. ESAs use is NOT associated with increased risk of thrombotic events
e. Route of administration of ESAs can be either oral or intravenous

Erythropoeitin Stimulating Agents (ESAs)

- Erythropoietin (EPO)
  - Product of the *EPO* gene on chromosome 7
  - Produced by interstitial peritubular cells
- ESAs
  - Recombinant EPO (formed by cloning the human *EPO* gene) approved by FDA use in 1989

Erythropoeitin Stimulating Agents (ESAs)

"I started on dialysis in 1966. I don't remember how many transfusions I had. It was many, at least one per month. ***I*** *had to be desperate before the doctor would order blood.*
I was part of the ***phase III clinical trial in 1987****. I was on home dialysis, raising two children, alone. My hematocrit was 11-15 percent; I couldn't walk up the stairs.* ***I had to crawl on my hands and knees because I was so out of breath****. Once I started on the drug, I could tell there was a change within two weeks. Within 30 days, my HCT was 40! My daughter said, 'All of a sudden you were up and going.' Eventually,* ***I could run up the stairs.***
I used to be asked, 'What are you doing?' I answered, 'What can I do? My body has me in prison.' ***Epo changed all of that. What a difference it made in my life!"***

Nancy Spaeth's Story: A little history and a lot of Hope

Erythropoeitin Stimulating Agents (ESAs)

"I started on dialysis in 1966. I don't remember how many transfusions I had. It was many, at least one per month. ***I*** *had to be desperate before the doctor would order blood.*
I was part of the ***phase III clinical trial in 1987****. I was on home dialysis, raising two children, alone. My hematocrit was 11-15 percent; I couldn't walk up the stairs.* ***I had to crawl on my hands and knees because I was so out of breath****. Once I started on the drug, I could tell there was a change within two weeks. Within 30 days, my HCT was 40! My daughter said, 'All of a sudden you were up and going.' Eventually,* ***I could run up the stairs.***
I used to be asked, 'What are you doing?' I answered, 'What can I do? My body has me in prison.' ***Epo changed all of that. What a difference it made in my life!"***

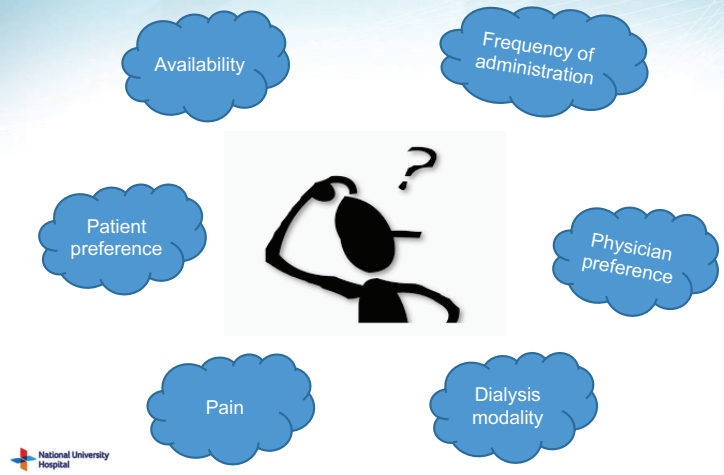
Nancy Spaeth's Story: A little history and a lot of Hope

ESAs - Types

ESA	Half-life	Initial Dose	Maintenance Dose
Epoetin-alfa (Eprex®)	4 – 13 hours (IV)	50 – 75 IU/kg 3 times a week	100 – 200 IU/kg/week
Epoeitin-beta (Recormon®)	4 – 12 hours (IV) 13 – 28 hours (SC)	75 – 150 IU/kg/week 1-3 times per week	1-3 times per week
Darbepoetin-alfa (Aranesp®)	12– 25 hours (IV) 16 – 44 hours (SC)	0.25 – 0.75 mcg/kg Once weekly	Every 2-4 weeks
CERA (Mircera®)	134 hours (IV) 139 hours (SC)	0.6 mcg/kg Every 2 weeks	Every month

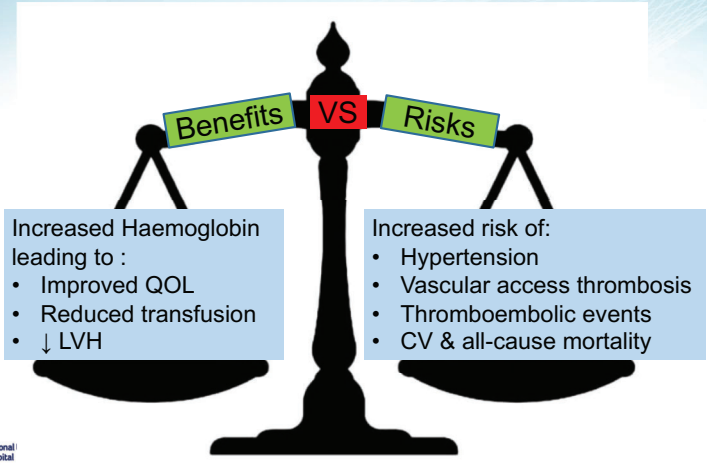
National University Hospital

ESAs - Types



National University Hospital

Erythropoeitin Stimulating Agents (ESAs)



Increased Haemoglobin leading to :
- Improved QOL
- Reduced transfusion
- ↓ LVH

Increased risk of:
- Hypertension
- Vascular access thrombosis
- Thromboembolic events
- CV & all-cause mortality

National University Hospital

Hb target – How high is to high?

Hb
< 11 g/dL

VS

Hb
> 13 g/dL

National University Hospital

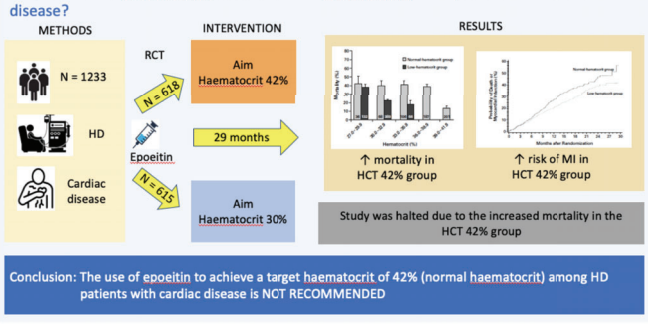
Adult

The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D., ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

NHCT: Is normal haematocrit better than low haematocrit in HD patients with cardiac disease?



Conclusion: The use of epoeitin to achieve a target haematocrit of 42% (normal haematocrit) among HD patients with cardiac disease is NCT RECOMMENDED

National University Hospital

Besarab A et al, N Eng J Med, 1998

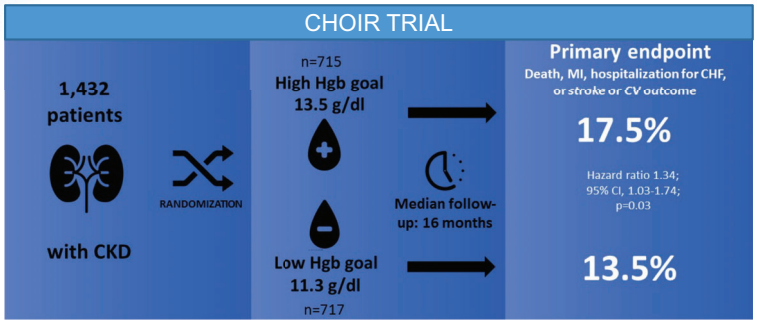
Adult

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*



National University Hospital

Singh AK et al, N Eng J Med, 2006

Hb target – How high is to high?

Hb
< 11 g/dL

VS

Hb
> 13 g/dL

KDOQI: Hb **11 – 12 g/dL** – Adult and Children

KDIGO: Hb **< 11.5 g/dL** (definitely < 13 g/dL) – Adult
Hb **11 - 12 g/dL** - Children

National University Hospital

Paed

www.kidney-international.org clinical investigation

Hemoglobin of 12 g/dl and above is not associated with increased cardiovascular morbidity in children on hemodialysis

see commentary on page 16

Michelle N. Rheault[1], Julia T. Molony[2], Thomas Nevins[1], Charles A. Herzog[2,3] and Blanche M. Chavers[1]

[1]Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota, USA; [2]Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, Minnesota, USA; and [3]Department of Medicine, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota, USA

Is Haemoglobin above 12 g/dl associated with increased cardiovascular morbidity in children on HD?

METHODS

Retrospective Cohort Study

N = 1569 , < 17 yo

HD

2000 - 2008

Haemoglobin

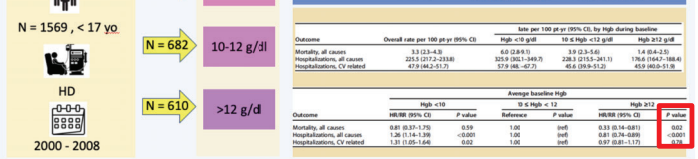
N = 277 → < 10 g/dl

N = 682 → 10-12 g/dl

N = 610 → >12 g/dl

RESULTS

Outcomes: Mortality, Hospitalization, Cardiac events



Conclusion: In children on haemodialysis, haemoglobin 12 g/dl and above is not associated with increased cardiovascular visits, mortality or all-cause and cardiovascular-related hospitalization.

National University Hospital

Rheault et al, Kidney Int, 2016

High Hb

VS

ESA

National University Hospital

Adult

AJKD

Original Investigation

Dose of Erythropoiesis-Stimulating Agents and Adverse Outcomes in CKD: A Metaregression Analysis

Ioannis Kouloridis, MD,[1,2,] Mansour Alfayez, MD,[1,2,*] Thomas A. Trikalinos, MD,[2,3,4] Ethan M. Balk, MD, MPH,[2,3] and Bertrand L. Jaber, MD, MS[1,2]*

Results: 31 trials (12,956 patients) met the criteria. All-cause mortality was associated with higher (per epoetin alfa–equivalent 10,000-U/wk increment) first-3-month mean ESA dose (incidence rate ratio [IRR], 1.42; 95% CI, 1.10-1.83) and higher total-study-period mean ESA dose (IRR, 1.09; 95% CI, 1.02-1.18). First-3-month ESA dose remained significant after adjusting for first-3-month mean hemoglobin level (IRR, 1.48; 95% CI, 1.02-2.14), as did total-study-period mean ESA dose adjusting for target hemoglobin level (IRR, 1.41; 95% CI, 1.08-1.82). Parameter estimates between ESA dose and cardiovascular mortality were similar in magnitude and direction, but not statistically significant. Higher total-study-period mean ESA dose also was associated with increased rate of hypertension, stroke, and thrombotic events, including dialysis vascular access–related thrombotic events.

Conclusions: In patients with CKD, higher ESA dose might be associated with all-cause mortality and cardiovascular complications independent of hemoglobin level.

National University Hospital

Koulouridis I et al, Am J Kidney dis, 2012

Paed

Pediatr Nephrol (2014) 29:2021–2028
DOI 10.1007/s00467-014-2820-9

ORIGINAL ARTICLE

Association of higher erythropoiesis stimulating agent dose and mortality in children on dialysis

Rachel M. Lestz · Barbara A. Fivush · Meredith A. Atkinson

Retrospective cohort study
N = 829 dialysis patients < 18 years old
Mortality in 60 patients (7%)

- Higher proportion receiving ESA dose in the highest category (epo > 350 U/kg/wk or darbepoetin > 1.5 U/kg/wk)
  - 50% vs 28%, *p=0.02*
- Trend to lower Hb levels
  - Hb 11.0 vs 11.4 g/dL, *p=0.05*

Conc: Higher ESA dose is independently associated with mortality in children on chronic dialysis

National University Hospital

Lestz RM et al, Pediatr Nephrol, 2014

Adult

CLINICAL RESEARCH www.jasn.org

Ferric Gluconate Reduces Epoetin Requirements in Hemodialysis Patients with Elevated Ferritin

Toros Kapoian,* Neeta B. O'Mara,† Ajay K. Singh,‡ John Moran,§ Adel R. Rizkala,‖ Robert Geronemus,¶ Robert C. Kopelman,** Naomi V. Dahl,‖ and Daniel W. Coyne††

DRIVE II: Can IV iron reduce epoetin dose in HD patients with high ferritin?

METHODS

N = 134
> 18 yrs old
HD
Hb < 11 g/dl
TSAT < 25
Ferritin 500-1200 ng/ml
Epoetin >225U/kg/wk

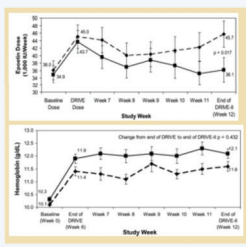
INTERVENTION

DRIVE
IV Iron 125mg/ wk N = 68
RCT 6 weeks
No IV Iron (Control) N = 66

OBSERVATIONAL

DRIVE II
N = 56
Dose adjustment to Epoetin
N = 56
6 weeks

RESULTS



By week 12, epoetin dose has dropped significantly in IV iron group Compared to control group ($p < 0.05$)

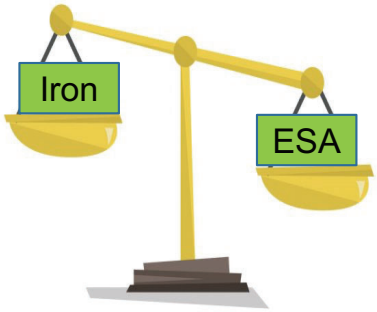
Conclusion: IV iron is maintains haemoglobin and allows lower epoetin doses in anemic HD patients with low TSAT and ferritin up to 1200ng/ml

Hospital

Kapoian T et al, J Am Soc Nephrol, 2008

CKD Anemia – What can we do?

Management



Patient Case 3

- 12 yo boy with Schimke Immuno-Osseus Dysplasia (SIOD) – On PD
- Haemoglobin remains 6 – 7 g/dl despite optimal ESAs and Iron.
- Required blood transfusions when symptomatic anemia

Labs:
- Hb 6.3 g/dl, plt 120, WCC 3.72 x 10^9/L
- Ferritin 400, TSATs 35
- Coombs negative
- Vit B12 and folate normal
- PTH 19
- Stool occult blood neg
- Parvovirus neg

BMA: hypocellular with no dysplasia

ESA resistance / hyporesponsiveness

Do not achieve the desired Hb concentration despite receiving **higher than regular doses** of ESAs or who require **increasingly higher doses** to maintain a target Hb

KDOQI - 450 units/kg per week i.v. EPO or 300 units/kg per week s.c. EPO

KDIGO - No increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing

ESA resistance / hyporesponsiveness

Determining (and treating the cause):

- Iron Deficiency
- Inflammation/ infection
- Chronic blood loss
- Inadequate dialysis
- Non - compliance
- Hemolysis
- Nutritional deficiencies
- Medications (eg. ACEi)
- Hyperparathyroidsim
- Bone marrow defects

New Medications

New therapies

ESAs

VS

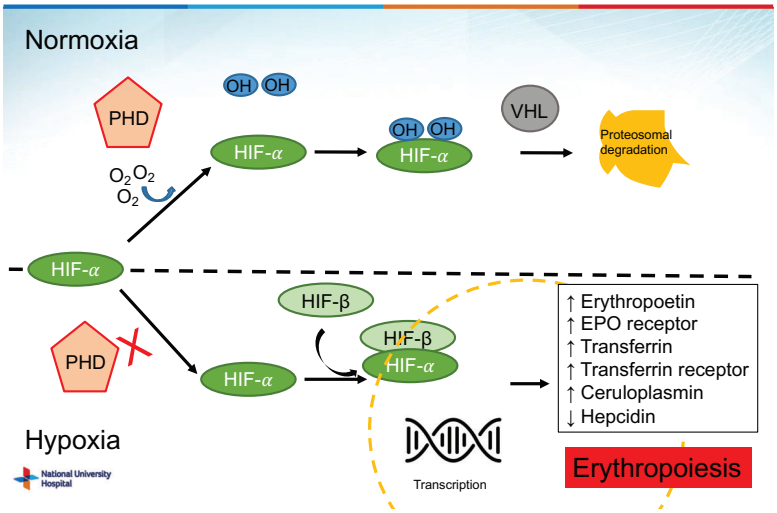
HIF-PHI

Question 5

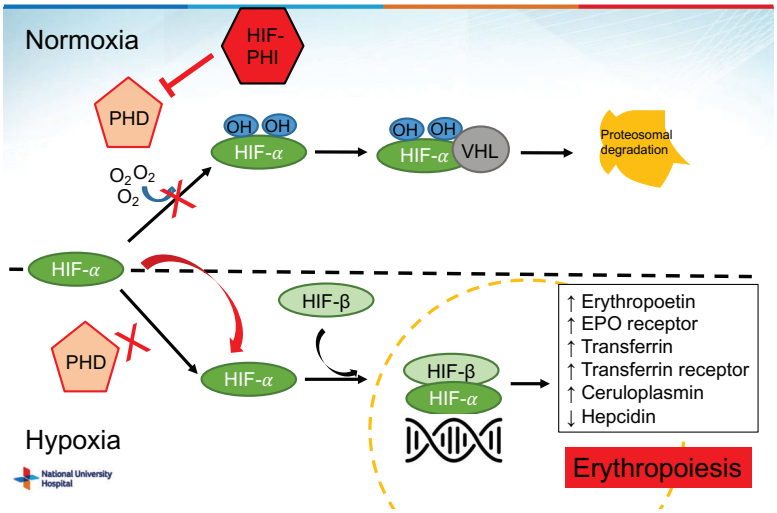
Which of the following are **FALSE** about hypoxic inducible factors (HIF)?

a. Increase endogenous EPO production
b. Upregulates transferrin
c. Upregulates transferrin receptors
d. Upregulates intestinal absorption of iron
e. Increase hepcidin levels

Hypoxia-Inducible Factor

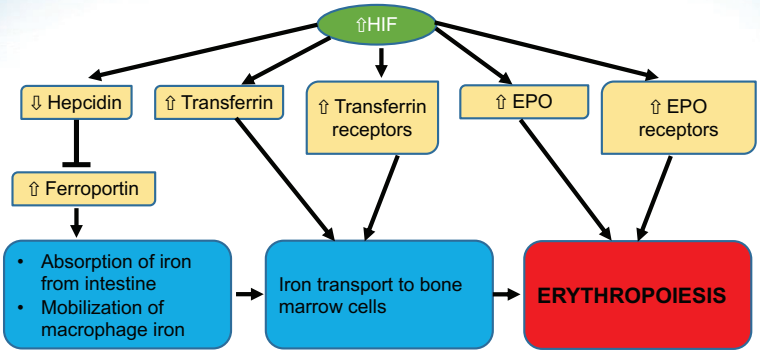


Hypoxia-Inducible Factor

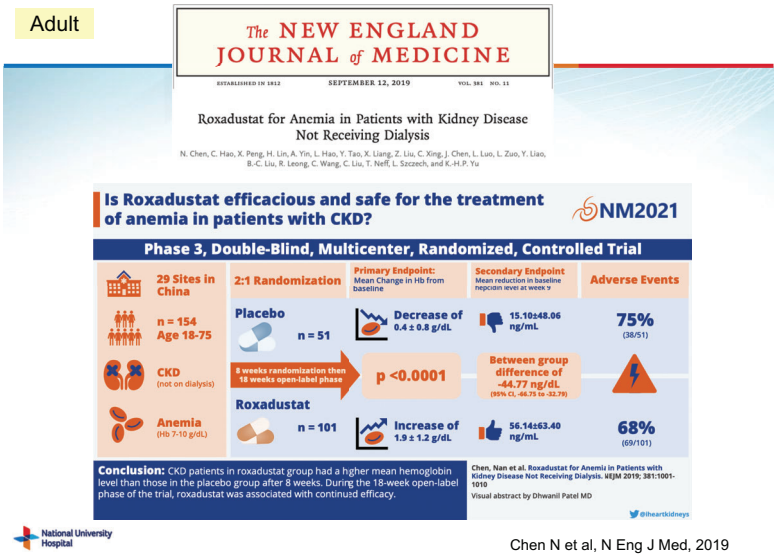


HIF Stabilisers = HIF-PHI

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) activates the HIF pathway and the coordinated response ensures sufficient iron availability for effective erythropoiesis to occur in the presence of physiologic levels of EPO2

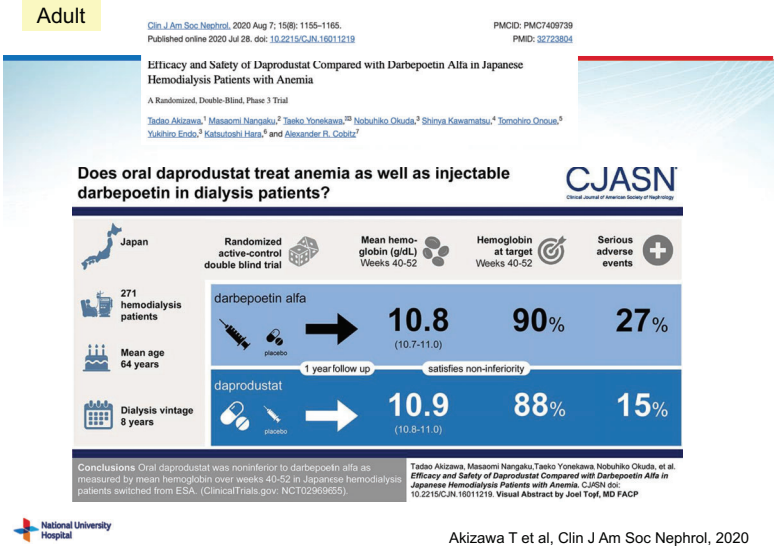


Adult



Chen N et al, N Eng J Med, 2019

Adult



Akizawa T et al, Clin J Am Soc Nephrol, 2020

ESAs

- IV or SC administration
- Directly stimulates erythropoiesis in bone marrow
- Serum erythropoietin levels may exceed normal physioclogical range

HIF-PHI

- Oral administration
- Upregulates erythropoietin production (achieving Hb targets with reduced plasma EPO levels)
- Suppress hepcidin - Increases iron release from storage tissue
- Upregulates transferrin receptor expression in gut (increase iron absorption)

National University Hospital

HIF-PHI

HIF-PHI	Half-life	Dosing	Frequency of dosing
Roxadustat	12 – 13 hours	0.7 – 2.5 mg/kg	3 times a week
Vadadustat	4.5 hours	150 – 600 mg	Daily
Daprodustat	4 hours	5 – 25 mg	Daily

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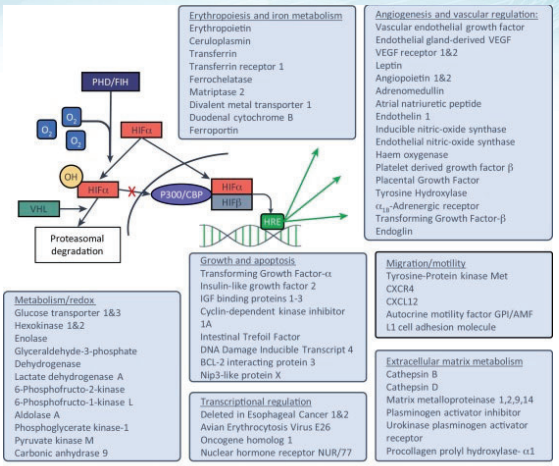
HIF-PHI – Long term effects

Pleiotropic effects of the HIF pathway raise potential concerns regarding safety



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HIF-PHI – Long term effects

Pleiotropic effects of the HIF pathway raise potential concerns regarding safety

- Potential Tumour Promoting Effects
- Cyst growth-promoting Effects
- Proangiogenic effects due to upregulation of VEGF
- Risk of abnormal embryonic and fetal development
- Effects on bone and cartilage growth plate development

National University Hospital

HIF-PHI – Paediatric Use

HIF-PHI has not been approved for paediatric use

Insufficient data to support the use as all phase III trials excluded patients under 18 years old

Several trials are planned in paediatric patients after the completion of phase 3 trials in adults

Pediatric Nephrology (2024) 39:911–914
https://doi.org/10.1007/s00467-023-06240-1

BRIEF REPORT

Compassionate use of roxadustat for treatment of refractory renal anemia in an infant

Yan Yang[1,2,3] · Yan Chen[1,2,3] · Yang Yang[1,2,3] · Haitao Bai[1,2,3] · Bizi He[1,2,3] · Dengli Liu[1,2,3]

National University Hospital

Summary

- The pathophysiology and etiology of CKD anemia is multifactorial requiring a holistic approach.
- Iron repletion is essential in the management of CKD anemia despite difficulty in the assessment in this cohort of patients.
- ESA is efficacious and the dosing needs to be individualised to the patient.
- HIF-PHIs are non-inferior to conventional ESAs in increasing and maintaining Hb concentrations in adult patients with CKD → Currently awaiting paediatric studies

National University Hospital

Thank You

National University Hospital

Infectious complications in Asia

Paul Ananth Tambyah

National University Hospital

NUS National University of Singapore

Email from Epi 2 Nov 06

- Please be informed a case of Chickenpox, who is a Staff Nurse working in ward 46 oncology. Thanks Sr L for alerting Epi.
- 29 yo F had chickenpox before when she was young.
- Rashes on hands and arms appeared on 31 Oct.
- Staff was working on 29 and 30 Oct. She was off on 31 Oct.
- Staff went to see GP near her home on 1 Nov and was given MC from 1 Nov to 12 Nov.
- Positive contact history: her daughter had chickenpox 2 weeks ago.
- Actions: 1. Dear Sr L
  Please identify any **immuno-compromised, pregnant** and **non-immune** patients and staff in contact **on 29 and 30 Oct** and alert EPIU and Infection control nurses.
  Kindly update Staff MC in Staff Sickness Surveillance accordingly.

What proportion of your staff are immune to chickenpox

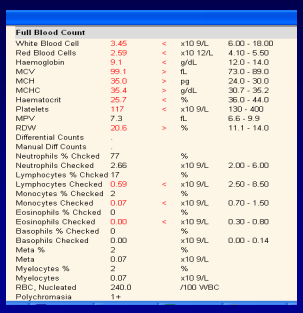
A. 100%
B. 75-99%
C. 50-75%
D. I have no idea

An unfortunate boy (pt D)

- 4 yr old ALL
- Diagnosed 2004, Chemotherapy KKWCH
- Remission Jul 06
- Relapse Oct 06 with thrombocytopenia
- Had i/t MTx and reinsertion of PAC 27 Oct
- Received chemo with L-Asparaginase, iv vincristine, iv daunorubicin and IT MTX on 31 Oct

Readmitted

- Had two more cycles on 7 Nov and 14 Nov
- "The parents told me about the pain on <19 Nov>, but did not tell me about the vesicle, as they thought it rather insignificant. I saw him on <20 Nov> and noticed the vesicle, and admitted him to the iso ward for Acyclovir"
- Adm 20 Nov, diffuse vesicles, unable to walk because of pain



Full Blood Count				
White Blood Cell	3.45	<	x10 9/L	6.00 - 18.00
Red Blood Cells	2.59	<	x10 12/L	4.10 - 5.50
Haemoglobin	9.1	<	g/dL	12.0 - 14.0
MCV	99.1	>	fL	73.0 - 89.0
MCH	35.0	>	pg	24.0 - 30.0
MCHC	35.4	>	g/dL	30.7 - 35.2
Haematocrit	25.7	<	%	36.0 - 44.0
Platelets	117	<	x10 9/L	130 - 400
MPV	7.3		fL	6.6 - 9.9
RDW	20.6	>	%	11.1 - 14.0
Differential Counts				
Manual Diff Counts				
Neutrophils % Chcked	77		%	
Neutrophils Checked	2.66		x10 9/L	2.00 - 6.00
Lymphocytes % Chcked	17		%	
Lymphocytes Checked	0.59	<	x10 9/L	2.50 - 6.50
Monocytes % Checked	2		%	
Monocytes Checked	0.07	<	x10 9/L	0.70 - 1.50
Eosinophils % Chcked	0		%	
Eosinophils Checked	0.00	<	x10 9/L	0.30 - 0.80
Basophils % Checked	0		%	
Basophils Checked	0.00		x10 9/L	0.00 - 0.14
Meta %	2		%	
Meta	0.07		x10 9/L	
Myelocytes %	2		%	
Myelocytes	0.07		x10 9/L	
RBC, Nucleated	240.0		/100 WBC	
Polychromasia	1+			

What is the most likely differential for a vesicular rash in an immunocompromised child?

A. Mpox
B. Disseminated herpes simplex infection
C. Varicella
D. Enterovirus EV71 infection

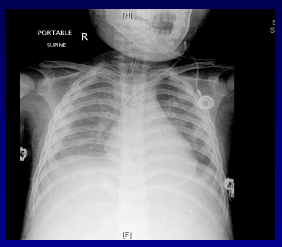
Developed seizures that night

- Treated with iv acyclovir, plts
- Bled from mucosae
- Increasingly drowsy
- Transferred to PICU

Potassium	3.9		mmol/L	3.5 - 5.0
Chloride	96	<	mmol/L	98 - 107
Carbon Dioxide	26		mmol/L	22 - 31
Anion Gap	10		mmol/L	10 - 18
Urea	8.6	>	mmol/L	2.5 - 7.5
Creatinine	35	<	umol/L	66 - 125
Calcium	2.06	<	mmol/L	2.15 - 2.55
Phosphate	0.83	<	mmol/L	0.85 - 1.45
ALP	177	>	U/L	40 - 130
Uric Acid	149	<	umol/L	220 - 540
Verified by: GUAH THUAN CHONG (G2029Z) on Nov 21 2006 11:39AM				
Calcium, Corrected				
Calcium, Corrected	2.28		mmol/L	2.15 - 2.55
Verified by: GUAH THUAN CHONG (G2029Z) on Nov 21 2006 11:39AM				
GGT				
GGT	116	>	U/L	15 - 90
Verified by: GUAH THUAN CHONG (G2029Z) on Nov 21 2006 11:39AM				
Liver Panel				
Albumin	29	<	g/L	38 - 48
Bilirubin, Total	45	>	umol/L	5 - 30
Bilirubin, Conj	25	>	umol/L	0 - 5
Bilirubin, Unconj	20		umol/L	5 - 25
AST	3080	>	U/L	10 - 50
ALT	2971	>	U/L	10 - 70
ALP	177	>	U/L	40 - 130
LDH	8474	>	U/L	300 - 700

In PICU

- Went into multi-system organ failure
- Intubated, put on inotropes DA, NA
- Persistently hypoxic, bradycardic
- Death pronounced at 23/11/06 0958H
  Cause of death :
  Disseminated varicella



Email from Epi 2 Nov 06

- Please be informed a case of Chickenpox, who is a Staff Nurse working in ward 46 oncology. Thanks Sr L for alerting Epi.
- 29 yo F had chickenpox before when she was young.
- Rashes on hands and arms appeared on 31 Oct.
- Staff was working on 29 and 30 Oct. She was off on 31 Oct.
- Staff went to see GP near her home on 1 Nov and was given MC from 1 Nov to 12 Nov.
- Positive contact history: her daughter had chickenpox 2 weeks ago.
- Actions: 1. Dear Sr L
  Please identify any **immuno-compromised, pregnant** and **non-immune** patients and staff in contact **on 29 and 30 Oct** and alert EPIU and Infection control nurses.
  Kindly update Staff MC in Staff Sickness Surveillance accordingly.

Reply from NM

- Dear Epi
  The patients who had direct contact with S/N were:
  1) A SJ 89XXXX
  2) B XB 308XXXX
  3) C SG 920XXXX
  4) **D XI 309XXXX**
  5) E SH 903XXXX

  Thanks
  will update you if any new occurances take place.
  Regards

What is the most appropriate post-exposure prophylaxis for a non-immune child who is immunocompromised and exposed to varicella?

A. Oral acyclovir
B. Valganciclovir
C. Varicella immunoglobulin
D. IVIG

Varicella (chicken pox)

Is transmitted by the:

a. Airborne route
b. Blood borne
c. Contact only
d. Droplets

Original Article

Epidemiology of Skin Diseases in Renal Transplant Recipients in a Tertiary Hospital

Qi Ping Chen,[1]MBBS, MSc, Derrick CW Aw,[1,2]MBBS, MMed, MRCP

Abstract

Introduction: There is no published epidemiological data on skin d
plant recipients in this tropical country, which has multi-ethnic gro
the predominant ethnic group. Materials and Methods: Skin diseases
recipients were studied in a skin clinic of a tertiary institution during a
from June 2006 to March 2009. Results: Our study showed that except t
skin manifestations, sebaceous hyperplasia (56.6%), seborrheic kerato
naevi (76.9%), skin tags (37.1%) and viral (29.4%) and fungal (20.3%)
prevalent skin diseases among renal transplant recipients living in Sin
of pre-malignant and malignant tumours was very low (11.2% actinic
disease, 1.4% squamous cell carcinoma, 0.7% basal cell carcinoma, 0
Male predominance was seen in sebaceous hyperplasia (72.4% vs 3.
(17.2% vs 1.8%), viral (36.8% vs 19.6%) and fungal (27.6% vs 8.9%
also showed increased prevalence of sebaceous hyperplasia with incr
lence was significantly higher than that reported in the age matched
prevalence of seborrheic keratosis, actinic keratosis and viral infecti
with post-transplant duration. Conclusions: Our study provides epid
prevalence of skin diseases in renal transplant recipients. It emphasise
matologic follow-up for renal transplant patients in order to obtain
treatable skin diseases.

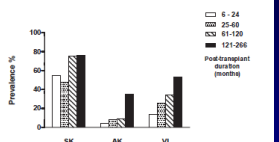


Fig. 3. The correlation of prevalence of skin conditions with post-transplant duration. Among all the skin conditions, only SK, AK and VI were correlated with post-transplant duration with higher prevalence in longer duration. The correlations were statistically significant with P value < 0.05. The other types of skin conditions were not associated with age.
SK: seborrheic keratosis, AK: actinic keratosis, VI: viral infection

Ann Acad Med Singapore 2010;39:904-8

Keywords: Actinic keratosis, Sebaceous hyperplasia, Seborrheic keratosis

Which patients are the highest risk for infectious complications?

- A. A 20 year old living donor renal Tx recipient who is six months post transplant and is well
- B. A 12 year old cadaveric kidney transplant patient who is 3 years post-transplant who has just been treated for rejection
- C. A 4 year old living unrelated donor recipient who is two years post-transplant and has hypertension
- D. A cadaveric kidney transplant who is 10 years post-transplant and is now 15 years old

Case 2 -Background

- 23 year old Malay female
- Well-thrived, developmentally normal
- SLE diagnosed in 2006 at 14 years old
  - Presented with rashes, oral ulcers and polyarthropathy
  - CNS involvement with seizures
  - SLE related neurogenic bladder with Mitrofanoff creation
  - Class IV Lupus nephritis with ESRF
- Crohn's disease involving the colon and terminal ileum
- Received multiple courses IV MP, also cyclophosphamide, IVIg, Rituximab and Belimumab

With thanks to Dr Manu Chhabra

Case 2 -Background

- ESRF:
  - Initially on PD since 2007: PD fluid leak with peritonitis, inadequate UF
  - Commenced on IHD with PD since 2009 via AVF
  - Eventually on full HD since 2014
  - Renal cystic disease complicated by bilateral RCC, nephrectomy in 2014
- Infection history:
  - CONS peritonitis 2009, treated with IV and IP antibiotics
  - Occult Eryisipelothrix rhusopathieae bacteraemia 2013
  - Recurrent chest infections 2014
  - CONS and Enterobacter Clocae exit site infection 2014
  - Urinary bacterial colonisation with recurrent cystitis (E. Faecalis, E. Coli, Pseudomonas)

With thanks to Dr Manu Chhabra

Deceased donor transplantation 2015

- Underwent living unrelated donor transplantation at 23 years old
- CMV +/+, EBV -/+
- Immunosuppression
  - Induction: Basiliximab (anti-CD25), methylprednisolone, IV mycophenolate
  - Maintenance : Prednisolone, Tacrolimus, and Mycophenolate.
- Peri-operative course:
  - Severe delayed graft function from ATN
  - Biopsy POD7 negative for rejection
  - ATG D2-11 (total 11mg/kg)
  - Improvement in urine output and serum creatinine after POD 37
  - Dialysis dependent till 5 weeks post-transplant
- Surveillance CMV and EBV PCR negative
  - IV ganciclovir given POD2 – POD13, then oral valganciclovir
- Uncomplicated Candida and E Coli UTI post-op

With thanks to Dr Manu Chhabra

New fever 11 weeks post transplantation

Presents to clinic:

2 days generalised joint pains and myalgia with nausea and watery diarrhoea

1 day fever max T 38.3C

1 day epigastric and suprapubic abdominal pain

Systems review unremarkable

No joint swelling

No cough or sore throat, no jaundice, no vomiting

no headache, no rash, no hematuria, or retro-orbital pain

Examination

T 37.3
HR 120
BP 99/65 mmHg sitting
BP 89/50 mmHg standing
RR 22
SPO2 100% on air

GCS 15
Lethargic
No rashes
H s1 s2 no murmur
L clear
Abdomen soft and non tender
No hepatosplenomegaly
No graft tenderness
No neurological deficit

What is the most likely pathogen?

A. Rotavirus
B. Dengue
C. Influenza
D. CMV
E. COVID

Investigations

TW 1.9 (chronic post transplant) ANC 1.43 ALC 0.15
Plt 171
Hb 11.3 g/dL Haematocrit 33.6%
CRP 6 mg/L
C3 107 mg/dL, anti-Ds DNA 3
UFE WBC 6 RBC 2 EC <1, urine culture: no growth

Dengue NS1 positive
Dengue Ig M, Ig G **negative**
Dengue Type 3 RNA **positive**

What is the diagnosis?

A. Dengue re-activation
B. Primary dengue infection
C. Dengue re-infection
D. SLE flare
E. None of the above

Investigations

TW 1.9 (chronic post transplant) ANC 1.43 ALC 0.15
Plt 171
Hb 11.3 g/dL Haematocrit 33.6%
CRP 6 mg/L
C3 107 mg/dL, anti-Ds DNA 3
UFE WBC 6 RBC 2 EC <1, urine culture: no growth

Dengue NS1 positive
Dengue Ig M, Ig G **negative**
Dengue Type 3 RNA **positive**

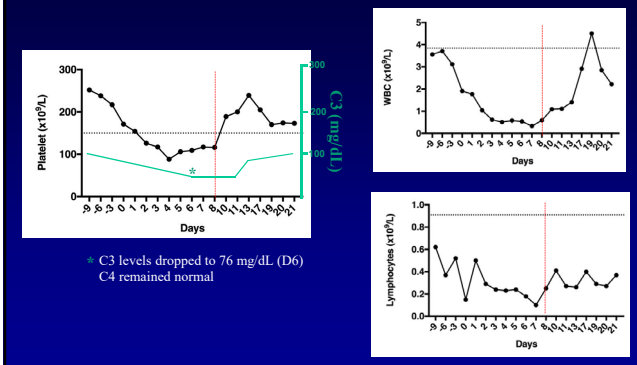
Primary DENV3 infection

How would you manage her immunosuppression?

A. Stop MMF and keep Tacrolimus and Prenisolone
B. Stop MMF and Tacrolimus and keep prednisolone
C. Stop prednisolone and keep MMF and Tacrolimus
D. Stop prednisolone and Tacrolimus and keep MMF
E. Continue all immunosuppression

Subsequent progress

- MMF discontinued, maintained on Tacrolimus and Prednisolone
- Improving AKI : Cr 132 mmol/L (baseline) to 180 mmol/L on D4, improved with hydration to a nadir of 87 mmol/L by D5
- Platelet counts improved by D5 (nadir of 88)
- Improvement in joint and muscle aches, and diarrhoea by day 8
- Persistence of fever
- **WBC, lymphocyte, neutrophil counts and complement remained low**

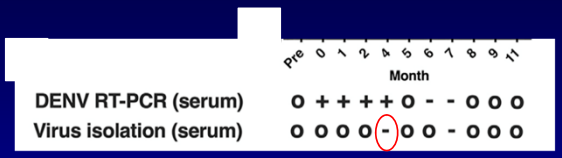


* C3 levels dropped to 76 mg/dL (D6)
C4 remained normal

Subsequent progress

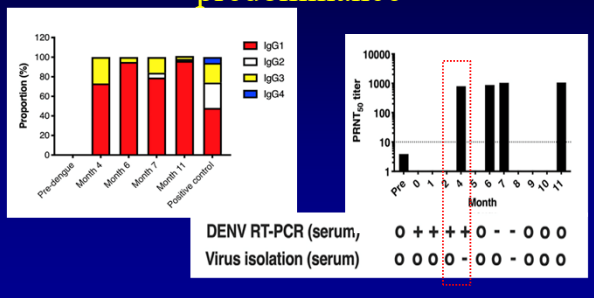
- Serum CMV PCR negative
- Urine cultures grew E. Faecalis with mild pyuria, treated with amoxicillin
- Fever lysed D11, improvement in WBC counts
- **Persistence of dengue RNA by RT-PCR** in serum despite resolution of symptoms on repeat testing

Persistence of dengue RNAaemia



Ng et al Cell Host Microbe. 2019 Nov 13;26(5):601-605.

Seroconversion with IgG1 predominance



Would you treat her?

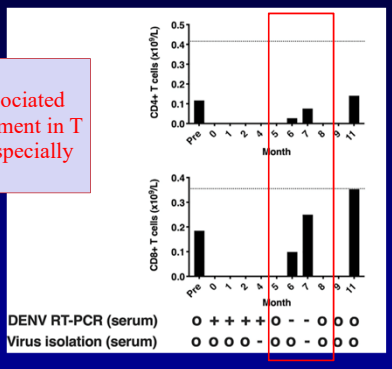
A. No

B. With steroids

C. With IVIg

D. With dengue vaccine

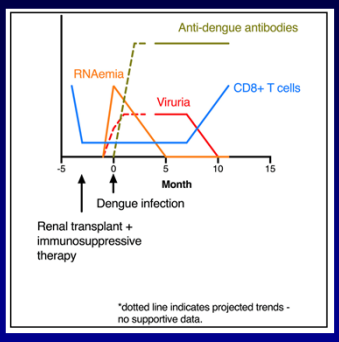
Clearance of RNAemia associated with improvement in T cell counts, especially CD8 T cells



Persistence of dengue virus in urine

	Pre	0	1	2	4	5	6	7	8	9	11
	Month										
DENV RT-PCR (serum)	O	+	+	+	+	O	-	-	O	O	O
Virus isolation (serum)	O	O	O	O	-	O	O	-	O	O	O
Virus isolation (urine)	O	O	O	O	+	O	O	+	O	+	O

Kinetics of dengue virus infection reflect recovery of humoral and cellular immunity



Podocytes a host cell for viral replication?

	Pre	0	1	2	4	5	6	7	8	9	11
	Month										
DENV RT-PCR (serum)	O	+	+	+	+	O	-	-	O	O	O
Virus isolation (serum)	O	O	O	O	-	O	O	-	O	O	O
Virus isolation (urine)	O	O	O	O	+	O	O	+	O	+	O
DENV RT-PCR (podocytes)	O	O	O	O	O	O	+	+	-	O	-

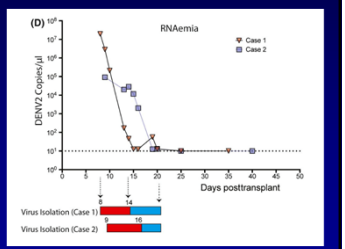
Podocytes a host cell for viral replication?

CASE REPORT

Aviremic organ transplant dengue virus transmission – A case report

Jean X. Y. Sim[1,2] | Esther S. Gan[3] | Hwee C. Tan[3] | Milly M. Choy[3] | Hei M. Wong[1,2] | Ban H. Tan[3,4] | Terence Kee[4,5] | Quan Y. Ho[4,5] | Sobhana Thangarajh[4,5] | Raymond T. P. Lin[6] | Eng E. Ooi[3] | Jenny G.-H. Low[1,3]

Donor tested negative for DENV viremia but positive for **DENV viruria** resulting in the transmission of DENV to two kidney recipients



Am J Transplant. 2021 May;21(5):1944-1947.doi: 10.1111/ajt.16540.

Does your center routinely screen donors for dengue?

A. No

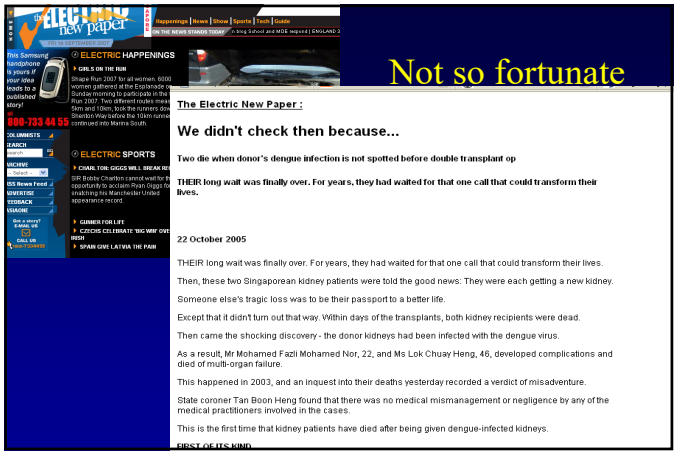
B. Yes with urine PCR

C. Yes with serum NS1 Ag and/or IgM

D. Yes with blood PCR

E. Yes with some combination of the above

Not so fortunate



The Electric New Paper :

We didn't check then because...

Two die when donor's dengue infection is not spotted before double transplant op

THEIR long wait was finally over. For years, they had waited for that one call that could transform their lives.

22 October 2005

THEIR long wait was finally over. For years, they had waited for that one call that could transform their lives.

Then, these two Singaporean kidney patients were told the good news: They were each getting a new kidney.

Someone else's tragic loss was to be their passport to a better life.

Except that it didn't turn out that way. Within days of the transplants, both kidney recipients were dead.

Then came the shocking discovery - the donor kidneys had been infected with the dengue virus.

As a result, Mr Mohamed Fazli Mohamed Nor, 22, and Ms Lok Chuay Heng, 46, developed complications and died of multi-organ failure.

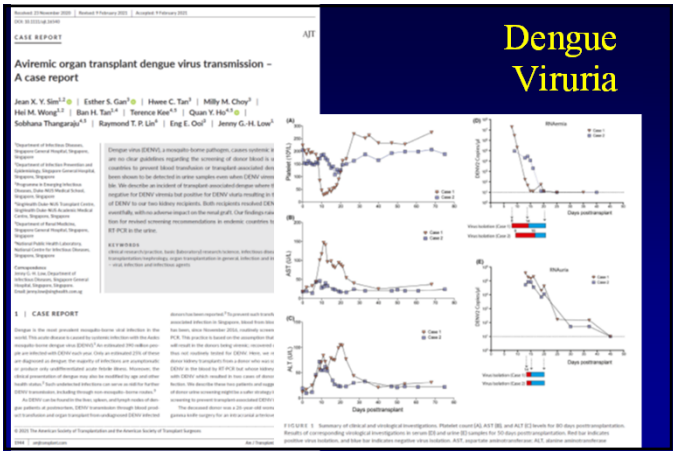
This happened in 2003, and an inquest into their deaths yesterday recorded a verdict of misadventure.

State coroner Tan Boon Heng found that there was no medical mismanagement or negligence by any of the medical practitioners involved in the cases.

This is the first time that kidney patients have died after being given dengue-infected kidneys.

FIRST OF ITS KIND

Dengue Viruria



CASE REPORT

AJT

Aviremic organ transplant dengue virus transmission – A case report

Organs donors are routinely screened for which of the following in your country?

- A. HIV
- B. Hepatitis B
- C. Hepatitis C
- D. CMV
- E. Dengue

Review Article

Singapore Med J 2012; 53(4) : 223

CME ARTICLE

http://smj.sma.org.sg/5304/5304ra1.pdf

Infectious disease trends among immunocompromised hosts

Barnaby Young[1], MB Bchir, MRCP, *Paul A Tambyah*[2], MBBS, MD

ABSTRACT With our rapidly ageing population and advancing treatments for patients with haematological, oncologic and rheumatological diseases, there are increasing numbers of immunocompromised patients presenting to primary care and general hospitals with opportunistic infections. This review considers the trends of these infections across four representative subgroups: fungal infections following haematopoietic stem cell transplant; viral infections post solid organ transplant; mycobacterial infect… a cause of fever in neutropenia. We al… epidemiology and outcomes of these …

Keywords: haematology, immunodeficiency, oncolog…

Singapore Med J 2012; 53(4): 223-230

Fig. 2 Case 2. Esophagogastroduodenoscopy images show (a) severe pangastritis with duodenitis and (b) multiple antral erosions.

Fever and dysphagia
7 mos post-transplant

What is the diagnosis

- A. HSV
- B. Candida
- C. CMV
- D. Ca esophagus

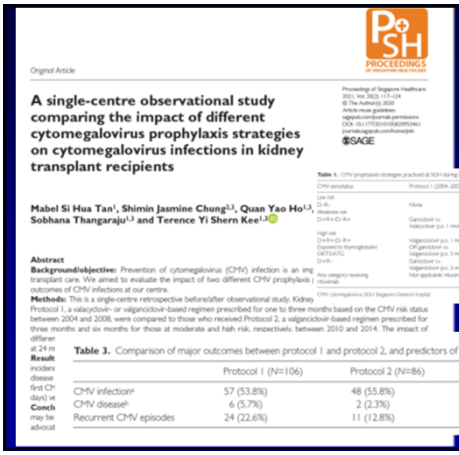
CMV is the most common viral infection post SOT, occurring in 8%–39% of recipients.[21] Diagnosing CMV disease requires distinguishing asymptomatic reactivation from end-organ disease and 'CMV syndrome' with fever and bone marrow suppression.[22] Donor/recipient CMV status, the organ transplanted as well as the choice of immunosuppressive agent significantly affect the incidence rate. CMV disease is also an independent risk factor for other infections and acute/chronic allograft injury due to the immunomodulating effects of CMV disease.

Anti-viral prophylaxis reduces CMV disease and mortality in all CMV-positive (R+) and CMV-negative (R–) recipients from CMV-positive donors (D+).[23] A consequence of prophylaxis is an increase in the rate of late-onset disease, after six months post transplant. This may be due to CMV suppression preventing the development of immunity to CMV.[24] Prolonging prophylaxis with valganciclovir from 100 days to 200 days following high-risk (D+/R–) renal transplants reduces the rates of CMV disease during the treatment period but results in substantially more late-onset disease.[25] A lower dose of maintenance valganciclovir therapy may overcome this problem while reducing cost and adverse effects such as leucopenia.[26]

What does your center do for CMV prophylaxis post-transplant?

A. Universal prophylaxis
B. Targeted prophylaxis with valganciclovir
C. Targeted prophylaxis with acyclovir/valaciclovir
D. Targeted prophylaxis with letermovir
E. No prophylaxis, pre-emptive treatment

SGH Experience



PSH PROCEEDINGS

Original Article

A single-centre observational study comparing the impact of different cytomegalovirus prophylaxis strategies on cytomegalovirus infections in kidney transplant recipients

Mabel Si Hua Tan[1], Shimin Jasmine Chung[1,3], Quan Yao Ho[1,3], Sobhana Thangaraju[1,3] and Terence Yi Shern Kee[1,3]

Abstract

Background/objective: Prevention of cytomegalovirus (CMV) infection is an imp... transplant care. We aimed to evaluate the impact of two different CMV prophylaxis ... outcomes of CMV infections at our centre.

Methods: This is a single-centre retrospective before/after observational study. Kidney ... Protocol 1, a valacyclovir- or valganciclovir-based regimen prescribed for one to three months based on the CMV risk status between 2004 and 2008, were compared to those who received Protocol 2, a valganciclovir-based regimen prescribed for three months and six months for those at moderate and high risk, respectively, between 2010 and 2014. The impact of differer... at 24 m...

Result ... incidenc... disease ... first CM... day(s) wi...

Conch ... may be ... advocat...

Table 3. Comparison of major outcomes between protocol 1 and protocol 2, and predictors of CMV infection.

	Protocol 1 (N=106)	Protocol 2 (N=86)	OR (95% CI)	p-Value
CMV infection[a]	57 (53.8%)	48 (55.8%)	1.09 (0.61–1.92)	0.884
CMV disease[b]	6 (5.7%)	2 (2.3%)	0.40 (0.078–2.02)	0.300
Recurrent CMV episodes	24 (22.6%)	11 (12.8%)	0.50 (0.23–1.09)	0.092

Don't forget tuberculosis

Pediatr Blood Cancer 2009;53:1318–1320

BRIEF REPORT

Pulmonary Tuberculosis Presenting as Fever Without Source in a Pediatric Patient With Acute Lymphoblastic Leukemia

Christina Lancioni, MD,[1]* A. Desiree LaBeaud, MD,[1] Frank Esper, MD,[1] Nazha Abughali, MD,[2] and Jeffery Auletta, MD[1,3]

Children who undergo treatment for malignancies are at high risk for infection with both typical and opportunistic pathogens. Fever in these children prompts extensive evaluation and empiric treatment with broad-spectrum antimicrobials. In the United States (US), tuberculosis is an infrequently reported cause of fever in the pediatric cancer patient and has not been well described. In this report we describe a case of primary pulmonary tuberculosis (TB) in a boy with precursor B-cell acute lymphoblastic leukemia (ALL) and review the pertinent literature. Pediatr Blood Cancer 2009;53:1318–1320. © 2009 Wiley-Liss, Inc.

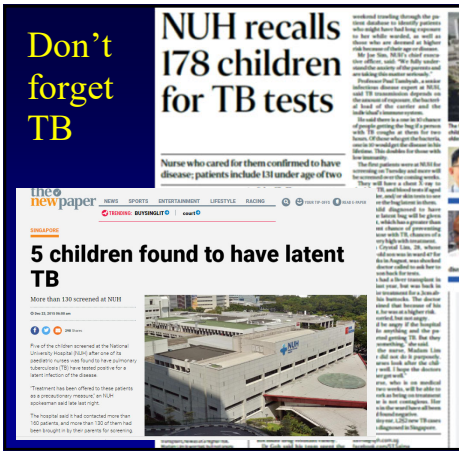
Key words: immunosuppression; leukemia; *Mycobacterium tuberculosis*; pediatric

CASE

A 2½-year-old male with high-risk precursor B-cell acute lymphoblastic leukemia (ALL) in remission, was admitted (hospital day zero, HD 0) for a fever of 39.4°C. One day prior to admission he completed his second round of delayed intensification chemotherapy with vincristine, doxorubicin, cyclophosphamide, cytarabine, and a 21-day course of dexamethasone. No other symptoms were present at the time of admission and his physical examination was unremarkable. The patient was born in the US and had never traveled internationally; however, both parents were born in India and foreign relatives had stayed in the home within the past 3 months. In addition, his mother had a history of a positive ... reaction (PCR) for *Mycobacterium tuberculosis* (MTB) was positive and the LUL mycobacterial culture grew MTB. Azithromycin was subsequently discontinued and rifambutin (RMB) added to the pre-existing three-drug tuberculosis (TB) treatment regimen. EMB was discontinued after AFB cultures from the lobectomy grew pan-sensitive MTB.

The patient was restarted on chemotherapy on HD 41 after demonstrating a full recovery from his lobectomy and tolerance of his TB treatment. He was discharged on HD 46 to continue INH, RIF, and PZA for the first 2 months of therapy and remain on INH and RIF for a total of 9 months. He has tolerated both his TB treatment and continued chemotherapy well; in addition, follow-up CTs of the chest have not demonstrated progressive infection or

Don't forget TB



NUH recalls 178 children for TB tests

Nurse who cared for them confirmed to have disease; patients include 131 under age of two

the newspaper NEWS SPORTS ENTERTAINMENT LIFESTYLE RACING

SINGAPORE

5 children found to have latent TB

More than 130 screened at NUH

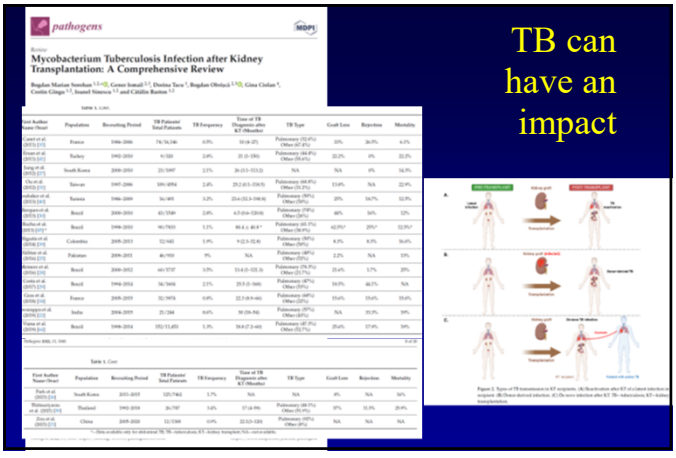
Five of the children screened at the National University Hospital (NUH) after one of its paediatric nurses was found to have pulmonary tuberculosis (TB) have tested positive for a latent infection of the disease.

"Treatment has been offered to these patients as a precautionary measure," an NUH spokesman said late last night.

The hospital said it had contacted more than 150 patients, and more than 130 of them had been brought in by their parents for screening.

How the disease is spread

TB can have an impact



pathogens

MDPI

Review

Mycobacterium Tuberculosis Infection after Kidney Transplantation: A Comprehensive Review

A travelling kidney??

Kalisvar Marimuthu

Tan Tock Seng Hospital and
National University of Singapore Health System

History

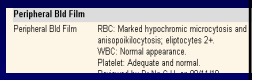
Ms M is a 28 year old Indonesian woman from Sumatra with end stage renal failure secondary to SLE with class IV lupus nephritis:

- Renal transplantation in Guangzhou China on 18/4/08
- Current immunosuppressants:
  - tacrolimus 2mg bd
  - mycophenolate mofetil 500mg bd
  - prednisolone 5mg OM
- Admitted Nov 2010 with dyspepsia and fevers

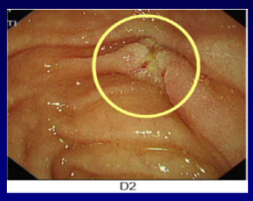
Lab results

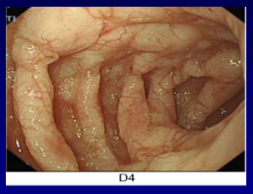
- Full blood count
- WBC 5.75 x 109/L
- HB 6.8 g/dL
- MCV 59.2 fL
- Platelet 178 x 109/L

- Renal panel
- Na 125 mmol/L
- K 2.5 mmol/L
- Urea 32.3 mmol/L
- Creatinine 526 mmol/L



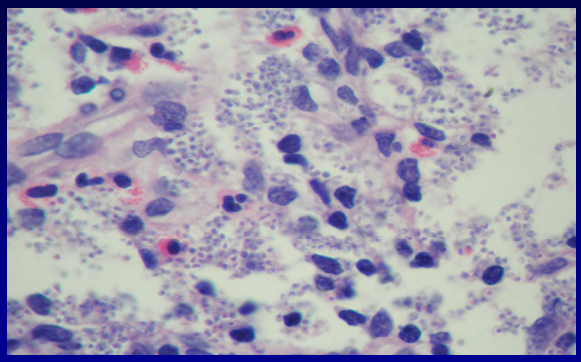
OGD performed on 10 Nov 2010



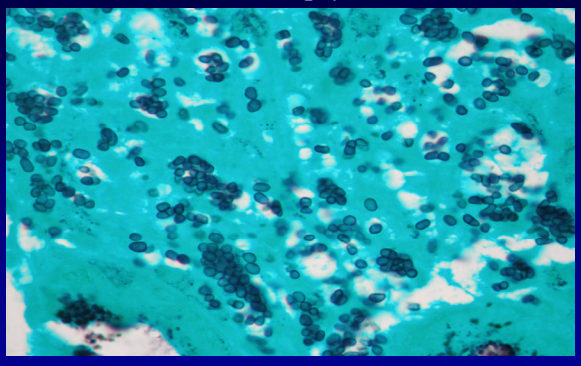


Focal ulceration seen at D2 (biopsy taken). D3, 4 showed pale irregular mucosa (biopsy taken).

Gastric biopsy H&E



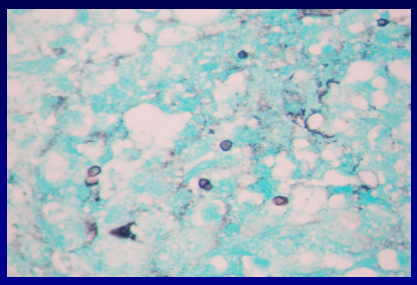
Gastric biopsy GMS



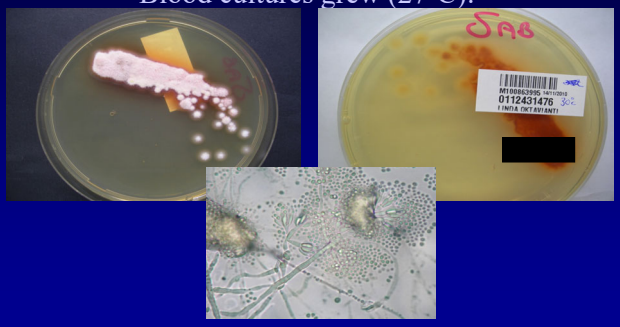
Diagnosis

- A. A fungal infection
- B. A bacterial infection
- C. A viral infection
- D. A mycobacterial infection
- E. A malignancy

Renal biopsy was done



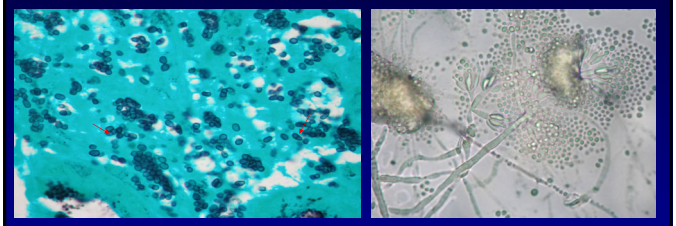
Blood cultures grew (27ºC):



Final diagnosis

- A. *Aspergillus fumigatus*
- B. *Cladosporium balantia*
- C. *Histoplasma capsulatum*
- D. *Penicillium marneffei*
- E. *Cryptococcus neoformans*

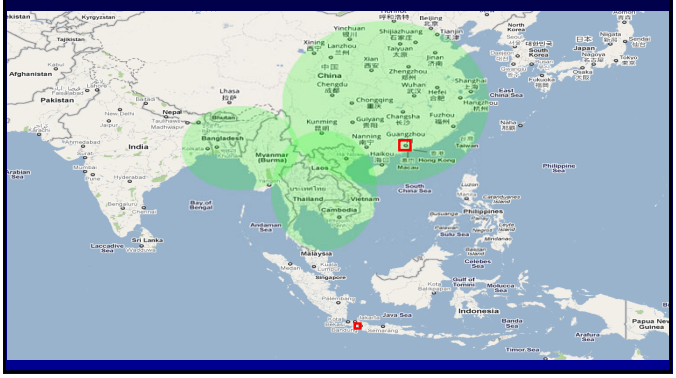
Review : *Penicillium marneffei*



- P. marneffei is the only thermally dimorphic fungus of the genus Penicillium.
- At 25° C on culture plates it forms a mould and at 37° C, a yeast
- *Penicillium marneffei* was first isolated from a bamboo rat (*Rhizomys sinensis*) in VN
- First human case in a lymphoma pt in 1973

Lim et al. J Clin Pathol 2006.

Geographic distribution of *P. marneffi*



Nutritional Requirements in CKD: Focus on Asian Diet and Infants

Wong Chui Ying
Principal Dietitian
National University Hospital

Outline

- Case example
- Nutritional requirements for growth in CKD infants
- Feeding challenges in CKD infants
  - Choice of milk feeds
  - Volume/fluid restriction
  - Vomiting/ GERD
  - Food aversion

[Input data classification]

Question 1

What are the factors for poor growth and inadequate nutritional intake in infants with CKD?

A. GER (gastro- esophageal reflux)

B. Low appetite

C. Dialysate losses

D. All of the above

3

[Input data classification]

Question 1

What are the factors for poor growth and inadequate nutritional intake in infants with CKD?

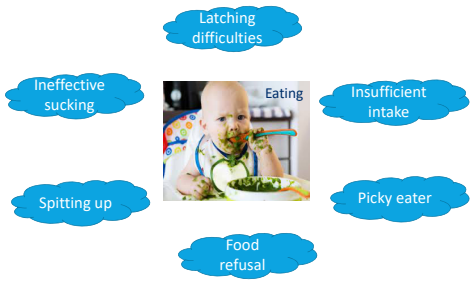
A. GER (gastro- esophageal reflux)

B. Low appetite

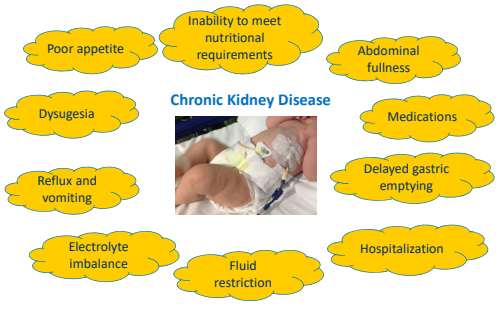
C. Dialysate losses

D. All of the above

4



Nutrition and Growth in Infant with CKD



Case: Baby K

Diagnosis: Congenital Nephrotic Syndrome with genetically-proven Denys-Drash Syndrome (Genotype XY, WT1 mutation)

Born in Jakarta, at 40 weeks at 2735g via Caesarean section due to previous lower segment C-sec

First presented at 3 months of life with intermittent eye swelling twice per week

At 5 months old, proteinuria was first noted and had persistent proteinuria despite completion of antibiotics.

She was progress from oliguria to anuria, with anasarca and stage 2 hypertension.

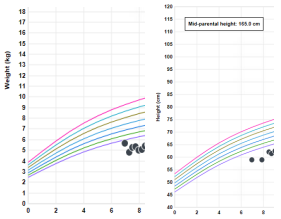
Perm-cath tunneled CDL insertion (8Fr) on the right. Haemodialysis was initiated.

Case: Baby K- Dialysis

- At age of 7 months, she transferred to Singapore for further care.
- She was admitted to NUH Paediatric Intensive Care Unit for commencement of continuous renal replacement therapy.
- 2 weeks later, she was transitioned to intermittent HD.
- Commenced on PD due to the dislodgement and removal of her right Mahukar line after another 2 weeks (8 months old).

Case: Baby K- Feeding History & Growth

- Fully breast fed till 3 months old. (mix of breast and bottle feeding)
- At 4 months, she was hospitalised and had NGT inserted as she was unwell and unable to complete feeds.
- On transfer to NUH at 7 months old, she was on NG continuous feeding @ 20ml/hr.



Case: Baby K- Nutrition

7 months old, on CRRT

weight and length: 5.665kg (~1%ile) and 59cm (<1%ile)

working weight: 6kg

Table 1 Energy and protein requirements for infants, children and adolescents with CKD2–5D aged 0–18 years

SDI for energy and protein: birth[a] to 18 years			
Month	SDI[b] energy (kcal/kg/day)	SDI protein (g/kg/day)	SDI protein (g/day)
0	93–107	1.52–2.5	8–12
1	93–120	1.52–1.8	8–12
2	93–120	1.4–1.52	8–12
3	82–98	1.4–1.52	8–12
4	82–98	1.3–1.52	9–13
5	72–82	1.3–1.52	9–13
6–9	72–82	1.1–1.3	9–15
10–11	72–82	1.1–1.3	9–15
12	72–120	0.9–1.14	11–14

Additional 0.1g/kg/day for HD
→ 1.2-1.4g/kg/day

Adapted from Shaw V, Polderman N, Renken-Terhaerdt J, Pagliardini F, Oosterveld M, Tuokkola J, Andersen C, Desloovere A, Greenbaum L, Haffner D, Nelms C, Qizalbash L, Vande Walle J, Warady B, Shroff R, Rees L. Energy and protein requirements for children with CKD stages 2-5 and on dialysis-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. Pediatr Nephrol. 2020; 35:519-531.

Case: Baby K- Nutrition

Blood results:

calcium: 1.88 Phosphate: 0.97

Urea: 10.3 Creat: 98

Feeding regime:

- NG continuous feeding with Dulac stage 1 (5 hours x 4 cycles)
- Grade up regime 20ml/hr > 30ml/hr > 35ml/hr (117ml/kg/day)
- Fortified formula with Carborie > concentration of 0.8kcal/ml
- Final regime: 35ml/hr Dulac + Carborie (0.8kcal/ml) provides → 572kcal (95kcal/kg), 9.2g protein (1.5g/kg)

Allow 10ml milk via bottle at the start of each cycle, remainder via NGT

[Input data classification]

Question 2

Breast milk is preferable for infants with CKD because it is:

A. High in calories
B. Low in phosphate
C. high in potassium
D. Contains antibodies

[Input data classification]

Question 2

Breast milk is preferable for infants with CKD because it is:

A. High in calories
B. Low in phosphate
C. high in potassium
D. Contains antibodies

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Challenge: Choice of Formula

- In infant, breast milk is the feeding of choice.
- Breast milk provides modest amount of phosphorus and calcium and is gold standard for all infants including those with renal disease.
- If breast milk is not available, standard formula may be appropriate
- When low potassium and phosphorus intake is required, special formula with low renal solute load should be offered
- e.g. Similac PM 60/40, Kindergen, Renastart

Key nutrient composition of human milk, standard formula and special formula (per 100ml)

Nutrient	Human milk	Human milk +HMF	Term formula	Renastart	Kindergen	Similac PM 60/40
Energy,kcal	67	80	68	100	100	67
Protein (g)	0.9	1.9	1.4	1.5	1.5	1.5
Fat (g)	4.2	4.6	3.7	4.8	5.2	3.7
Carbs (g)	7.3	9.1	7.4	12.6	11.6	6.8
Vit D (IU)	2	60	46	96	96	40
Calcium (mg)	28	144	53	24	46	37
Phosphorus (mg)	15	79	29	19	23	19
Magnesium (mg)	3.1	7.0	4.7	8.1	10.9	4.0
Iron (mg)	0.1	0.4	1.2	1.0	1.5	0.5
Sodium (mg)	18	34	17.1	48	46.1	16
Potassium (mg)	58	122	77	22	23.9	53
Zinc (mg)	0.3	1.3	0.6	0.89	0.83	0.5

Special Formula: What to do if you don't have it

When special formula is not available:

- Choose standard formula with lowest phosphate and potassium contents
- Use of medications to reduce phosphorus and potassium contents in the formula

e.g. "decanting" formula milk with phosphate binders

[Input data classification]

Question 3

Select the preferred method to increase calories without increasing feeds volume in infants with CKD?

A. Adding formula powder to EBM
B. Adding glucose polymers to EBM/ formula
C. Concentrating formula by addition of more scoops of powder to a given volume of water
D. All of the above

17

[Input data classification]

Question 3

Select the preferred method to increase calories without increasing feeds volume in infants with CKD?

A. Adding formula powder to EBM
B. Adding glucose polymers to EBM/ formula
C. Concentrating formula by addition of more scoops of powder to a given volume of water
D. All of the above

18

Challenge: Volume Restrictions

- Concentrating formulas by increasing ratio of formula powder to water is not recommended as it also increases electrolytes
- Increase the calories per volume amount- adding energy modules e.g. glucose polymers, fat emulsions

Glucose polymer - Carborie, Polycose

Energy Module	Age (months)	Amount of CHO module (g) added to 100ml formula/ EBM	Final concentration of CHO in formula (g/100ml)
Glucose polymer	< 6	3-5	10-12
	6-12	5-8	12-15

Adapted from Shaw V (ed) *Clinical Pediatric Dietetic*, 4th edition(2015). Chichester: Wiley Blackwell, page 18

Challenge: Volume Restrictions

Fat emulsions – MCT oil

Energy Module	Age (years)	Amount of fat module (ml) added to 100ml formula	Final concentration of fat in formula (g/100ml)
Fat emulsion	< 1	3-5	5-6
	>1	9	9

Adapted from Shaw V (ed) *Clinical Pediatric Dietetic*, 4th edition(2015). Chichester: Wiley Blackwell, page 18

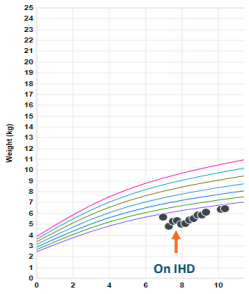
Protein powder - Myotein, Beneprotein, Propass

- To provide specific amount of protein per kg of body wt
- Added in small amount and increase gradually
- Monitor urea levels to detect excessive intake

Case: Baby K – Volume Restrictions

- Start IHD for 2 weeks while waiting for PD
- Fluids restriction = 300ml/day
- Feeds changed to Renastart (1kcal/ml) and Infatrini (0.92kcal/ml).
- Increased feeds concentration further to 1.1-1.2kcal/ml by adding Carborie.
- Renastart (weekends); Infatrini (weekdays) with 15ml/hr then subsequent switch to bolus 50ml Q4H
- MCT oil 0.5ml QDS, extra 3kcal/kg/day

= Total intake: 59-65kcal/kg/day and 0.8-1.3g protein/kg/day



Case- Baby K: Initiation of PD

At 8 months old,

PD initiated and feeds volume increased to ~480ml/day.

Formulas remained the same-

- fortified Renastart & Infatrini with Carborie (1.1-1.2kcal/ml).

Table 1 Suggested dietary intake (SDI) for energy and protein from birth at term to 12 months

Month	SDI energy (kcal/kg/day)	SDI protein (g/kg/day)	SDI protein (g/day)
0	93–107	1.52–2.5	8–12
1	93–120	1.52–1.8	8–12
2	93–120	1.4–1.52	8–12
3	82–98	1.4–1.52	8–12
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5	72–82	1.3–1.52	9–13
6–9	72–82	1.1–1.3	9–14
10–11	72–82	1.1–1.3	9–15
12	72–120	0.9–1.14	11–14

Additional 0.15-0.3g/kg/day for PD
→ 1.25-1.6g/kg/day

Case- Baby K: Frequent vomiting

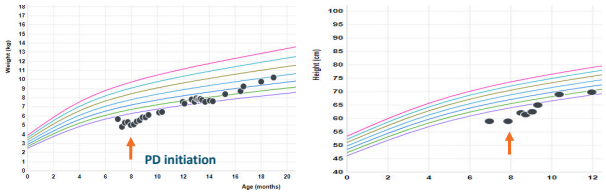
- Feeding regime was adjusted many times to reduce vomiting - tried various methods (timing, feeding volume/rates, delivery route)

At 9 months old,

- discharged after 2 months of hospital stays.
- Final regimen: 480ml/day
  - **Day bolus: 45ml Q3H x 4; Night continuous: 30ml/hr x 5 hrs x 2 cycles**
  - Allow time off from feeding (daytime)- purees via oral
- Biochem results:

Sodium: 131-140 Urea: 9.7-12.6 Phosphate: 1.76-2.6

Potassium: 3.2-4.5 Creat: 260-330

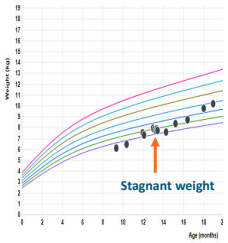


Total intake: **565kcal (94kcal/kg), 10.5g protein (1.8g/kg), 207mg sodium, 299mg K+, 301mg Calcium, 174mg PO4.**

Case- Baby K: Frequent vomiting

- At 10 months onwards,
  - Feeds increased to 550-570ml per day
  - Total intake: 652kcal (100kcal/kg), 11.7g protein (1.8g/kg), 242mg sodium, 324mg K+, 327mg Calcium and 191mg PO4
- Frequent vomiting ++

At 13 months,
- She underwent pH impedance study and laparoscopic Nissen fundoplication with gastrostomy creation
- Switched to HD temporarily (~470ml/day) for 1 month.



[Input data classification]

Question 4

Which of the following is incorrect for complementary feeding (weaning) for infant with CKD?

A. Solid foods should be introduced as recommended for healthy infants.
B. Weaning diet can be delayed as long as growth is good.
C. Oral stimulation is desirable, even if oral intake is limited.
D. Weaning is important for development of oral- motor skills.

26

[Input data classification]

Question 4

Which of the following is incorrect for complementary feeding (weaning) for infant with CKD?

A. Solid foods should be introduced as recommended for healthy infants.
B. Weaning diet can be delayed as long as growth is good.
C. Oral stimulation is desirable, even if oral intake is limited.
D. Weaning is important for development of oral- motor skills.

27

[Input data classification]

Question 5

Reasons for food aversion in infants with CKD:

A. Uremia
B. GER/ vomiting
C. Reduced small and taste sensations
D. All of the above

28

[Input data classification]

Question 5

Reasons for food aversion in infants with CKD:

A. Uremia
B. GER/ vomiting
C. Reduced small and taste sensations
D. All of the above

29

Challenge: Food Aversion

Appetite, taste, GERD (negative association)

Oral Stimulation

- can start by providing positive non-nutritive oral stimulation
- positive experience around infant's face/mouth (e.g kisses, stroking) → infant learns that not all touch is negative.
- Use mouth pacifiers and toys with different textures

Play with food

Do not pressure or force-feed child

Consult speech therapist to offer skill-appropriate

Weaning Diet

- CKD does not change the time of weaning: 4-6 months of age.
- Solids provide extra energy.
- Start with smooth pureed food, progress with lumpy textures as tolerated.
- Is important baby developing chewing skills at this stage
- Take into considerations of dietary restrictions for CKD
- If child has problems with chewing and swallowing foods, may need advice from a speech and swallowing therapist
- Some children with CKD do not eat normally until they have a kidney transplant, keep up messy play and involvement at mealtimes is important even if no food is eaten

Case- Baby K: Oral feeding

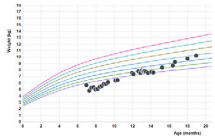
- Her main source of nutrition has been tube feeding
- Regular ST reviews since admission (at 7 months old).
- Short term goal: pleasure and skill development
- **ST recommendations** :
- Allowed to bottle-feed 10ml at a time as tolerated before each NG feed.
- Started purees once a day with different flavours
- Allow meltable baby biscuits
- To increase her interest in food- encourage exposure to the **sights, smells and touch** of food by eating with her and/or in front of her.

Case- Baby K: Oral feeding

19 months old:

- Her growth is stable and progressing well
- Reduced total calories by 8% from tube feeding to stimulate hunger
- Her current regime (570ml/day)

8am	75ml milk (bolus)
11am	75ml milk (bolus)
2pm	75ml milk (bolus)
5pm	Oral feeding- purees
6-7pm	75ml milk (bolus)
11pm – 5am	45ml/hr x 6 hours x 1 cycle



Take Home Message

- Nutrition is a key component in the management of infants with CKD- maintain **normal growth and development**.
- Nutrition therapy needs to be **individualized,** depending on:
  - Stage and progression of CKD
  - Modality of dialysis
  - The needs of the growing and developing child
- There is no one-size-fits all approach.
- **Multidisciplinary team approach** is needed; doctors, dietitian, nurses, speech therapist, play therapist.

[Input data classification]

Thank you.

NUHS National University Health System

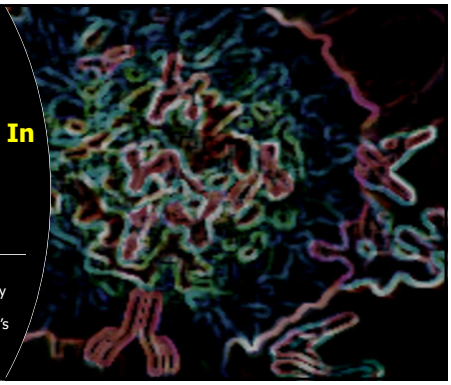
National University Hospital | Ng Teng Fong General Hospital | Alexandra Hospital | Jurong Community Hospital | National University Polyclinics | Jurong Medical Centre

National University Cancer Institute Singapore | National University Heart Centre Singapore | National University Centre for Oral Health Singapore | NUHS Diagnostics | NUHS Pharmacy

NUS Yong Loo Lin School of Medicine | NUS Faculty of Dentistry | NUS Saw Swee Hock School of Public Health

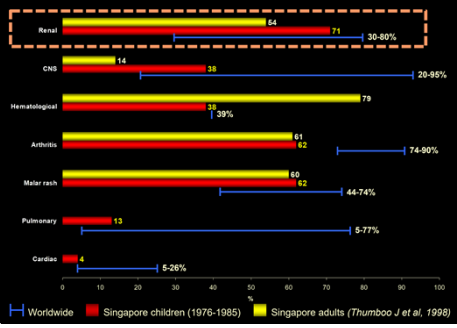
35

Steroid-Free Treatment For Lupus Nephritis In Children: Is It Possible?



Hui-Kim Yap
Shaw-NKF-NUH Children's Kidney Centre
KTP-National University Children's Medical Institute
National University of Singapore

Higher rates of organ involvement: >70% of Singapore children developed lupus nephritis during the course of SLE

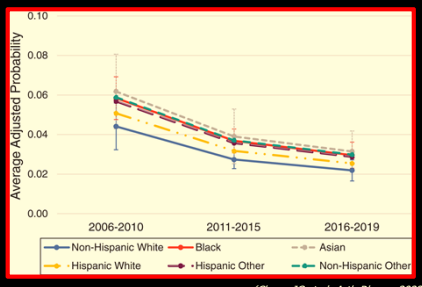


Rate of CKD 5 is reported to be up to 15% in children with lupus nephritis

Study	LN patient number (n)	Follow up (median [range])	Initial kidney involvement (n,%)	CKD stage 5 or kidney failure (n, %)
Groot et al (2019)	111	20 years	67/111 (60%)	16/111 (14%)
Hari et al (2009)	54	10 years	No data	3/54 (6%)
Taheri et al (2011)	60	3 years	No data	9/60 (15%)
Wong et al (2006)	128	5.3 years [1-16.5]	51/128 (40%)	4/128 (3%)
Vachvanichsanong et al (2009)	180	3.9 years [0.02-19.4]	No data	2/180 (1%)

(Oni L et al; Pediatr Nephrol 2021)

In hospitalized children, average adjusted probability of the first occurrence of any adverse renal outcome at a given hospital admission was higher in African American and Asian children



(Chang JC et al; Arth Rheum 2022)

Standardized mortality ratio in adult lupus nephritis is increased

(Multisite international cohort study: 23 centres, 9547 patients)

Cause of death	Standardized mortality ratio	95% CI
All deaths	2.4	2.3-2.5
Heart disease	1.7	1.4-2.0
Stroke	1.1	0.7-1.7
Malignancy	0.8	0.6-1.0
Infections	5.0	3.7-6.7
Respiratory	1.3	0.8-1.6
Renal	**7.9**	**5.5-11.0**

(Bernatsky S et al; Arthritis Rheum 2006)

KEY POINTS

- What are the challenges associated with traditional steroid-based treatment approaches in childhood lupus nephritis?
- Can steroid dose be minimized with current multi-targeted therapy for lupus nephritis?
- Can steroid-free management be achieved with the new biologics and targeted therapies?

What are the challenges associated with traditional steroid-based treatment approaches in childhood lupus nephritis?

Case

A 10-year old boy presented with fever, facial nerve and right 6th nerve palsy and acute nephritic syndrome. Investigations showed neutropenia, thrombocytopenia, low serum complements and positive anti-dsDNA Ab. Renal biopsy showed focal proliferative lupus nephritis (ISN/RPS class III). He was treated with prednisolone, azathioprine and hydroxychloroquine and was apparently in remission. He presented again 3 years later with hypertensive encephalopathy with BP of 200/111, AKI, pulmonary hemorrhage and evidence of TTP. He was given IV phenytoin, intubated and had to be dialyzed. He was also given 12 sessions of plasmapheresis. Renal biopsy then showed diffuse lupus nephritis (ISN/RPS class IV) with 29% fibrocellular crescents and thrombotic microangiopathy. He received 2 courses of IV methylprednisolone, with mycophenolate followed by IV cyclophosphamide during this time and had complications of pneumonia with acute respiratory distress.

He was subsequently transferred to our hospital for initiation of chronic dialysis as his serum creatinine remained at 586 umol/L.

A Tenckhoff catheter was inserted and PD was commenced.

MCQ 1

What immunosuppressive therapy regimen would you recommend at this point?

A. Stop all immunosuppressive therapy
B. Oral prednisolone low dose
C. Oral prednisolone low dose and hydroxychloroquine
D. IV methylprednisolone pulses with tapering oral prednisolone and mycophenolate
E. Monthly low dose IV cyclophosphamide pulse with oral prednisolone

What immunosuppressive therapy regimen would you recommend at this point?

A. Stop all immunosuppressive therapy
B. Oral prednisolone low dose
C. Oral prednisolone low dose and hydroxychloroquine
D. IV methylprednisolone pulses with tapering oral prednisolone and mycophenolate
E. Monthly low dose IV cyclophosphamide pulse with oral prednisolone

He was continued on monthly pulse IV methyl-prednisolone for a total of 6 courses together with mycophenolate as maintenance therapy.

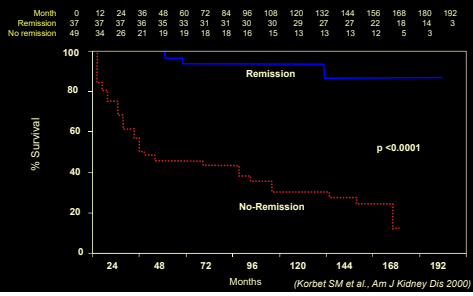
Over the next 2 months, his serological parameters of activity normalized, with recovery of renal function. His serum creatinine reached a baseline of 80 umol/L and proteinuria of 0.29 g/day/1.73m^2.

Sequential immunosuppressive therapy for proliferative lupus nephritis (ISN/RPS class III/IV)

Induction → ACHIEVE REMISSION
- Decrease lupus activity
- Restore kidney function
- Decrease proteinuria

Maintenance → PREVENT PROGRESSION OF CKD
- Decrease proteinuria
- Prevent SLE relapses

Kidney survival rates in severe lupus nephritis worse in those who did not achieve remission after induction therapy: 94% at 10 years in remission group compared with 31% in no remission group



Steroid-based immunosuppression protocols have been the mainstay of treatment of lupus nephritis

MCQ 2

In a recent meta-analysis, which induction immunosuppressive agent(s) ranks as the best to induce complete remission with least side effects?

A. Prednisolone + hydroxychloroquine
B. Prednisolone + IV cyclophosphamide
C. Prednisolone + mycophenolate
D. Prednisolone + calcineurin inhibitor
E. Prednisolone + mycophenolate + calcineurin inhibitor

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E. Prednisolone + mycophenolate + calcineurin inhibitor

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD002922. DOI: 10.1002/14651858.CD002922.pub4.

Immunosuppressive treatment for proliferative lupus nephritis (Review)

Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM

- Unique records identified through updated database searching of MEDLINE, Embase and Cochrane databases through March 2, 2018
- 74 RCTs were included, 67 on induction therapy (n= 4791), 9 on maintenance therapy (n=767)
- Involving adults and children (<18 years, 31 studies)

Cochrane Library

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD002922. DOI: 10.1002/14651858.CD002922.pub4.

Immunosuppressive treatment for proliferative lupus nephritis (Review)

Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM

- Outcomes for induction therapy (**compared to IV cyclophosphamide**):
  - Primary: complete remission, ESKD, all-cause mortality
  - Others: Partial renal remission, doubling of serum creatinine, side effects of therapy

Induction (studies; participants)	MMF (10; 878)	MMF + TAC (2; 402)	IV CYC + MMF (1; 82)	CNI (4; 178)
Complete remission	**1.17 [0.97, 1.42]**	**2.38 [1.07, 5.30]**	1.22 [0.78, 1.89]	**1.35 [0.94, 1.93]**
Partial renal remssion	1.02 [0.89, 1.18]	1.0 [0.78, 1.28]	1.03 [0.55, 1.90]	0.88 [0.61, 1.26]
All cause mortality	1.12 [0.61, 2.06]	0.0 [0.0, 0.0]	0.95 [0.06,14.72]	0.41 [0.06, 2.69]
ESKD	0.71 [0.27, 1.84]		1.48 (0.62-3.53)	1.0 [0.07,14.85]
Doubling Screatinine	0.0	0.98	0.57	0.33
Diarrhea	**2.42 [1.64, 3.58]**	2.33 [0.92, 5.94]		0.35 [0.12, 1.01]
Alopecia	**0.29 [0.19, 0.46]**	0.78 [0.36, 1.72]		0.21 [0.02, 1.76]

The combination of MMF plus calcineurin inhibitor ranked as the best treatment to induce remission with least side effects

MCQ 3

In a recent meta-analysis, which maintenance immunosuppressive agent ranks as the best to prevent relapses in lupus nephritis with least side effects?

A. Prednisolone
B. Hydroxychloroquine
C. Azathioprine
D. Cyclophosphamide
E. Mycophenolate mofetil

In a recent meta-analysis, which maintenance immunosuppressive agent ranks as the best to prevent relapses in lupus nephritis with least side effects?

A. Prednisolone
B. Hydroxychloroquine
C. Azathioprine
D. Cyclophosphamide
E. Mycophenolate mofetil

Cochrane Library

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD002922. DOI: 10.1002/14651858.CD002922.pub4.

Immunosuppressive treatment for proliferative lupus nephritis (Review)

Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM

- Outcomes for maintenance therapy:
  - Primary: All-cause mortality, ESKD, relapse after remission
  - Secondary: Partial renal remission, doubling of serum creatinine, side effects of therapy

Maintenance (studies, participants)	AZA vs MMF (4; 452)	AZA vs CYC (1; 39)	AZA vs CsA (1; 69)	AZA vs TAC (1; 30)
Renal relapse	1.75 [1.20, 2.55]	0.79 [0.34, 1.85]	1.25 [0.51, 3.06]	6.62 [0.35, 123.63]
All cause mortality	1.15 [0.34, 3.87]	0.12 [0.01, 2.03]	0.0 [0.0, 0.0]	
ESKD	1.70 [0.52, 5.54]	0.35 [0.04, 3.09]	0.0 [0.0, 0.0]	
Doubling Screatinine	2.19 [1.03, 4.66]	0.79 [0.34, 1.85]		
Leukopenia	5.61 [1.68, 18.72]		2.73 [0.95, 7.86]	
Major infections	1.08 [0.60, 1.96]		2.18 [1.01, 4.73]	1.26 [0.30, 5.22]
Ovarian failure	0.77 [0.17, 3.42]			
	[0.46, 1.95]			

AZA was associated with more renal relapse, doubling of serum creatinine and leukopenia compared to MMF

Current evidence-based treatment of severe proliferative lupus nephritis in adults

REMISSION INDUCTION

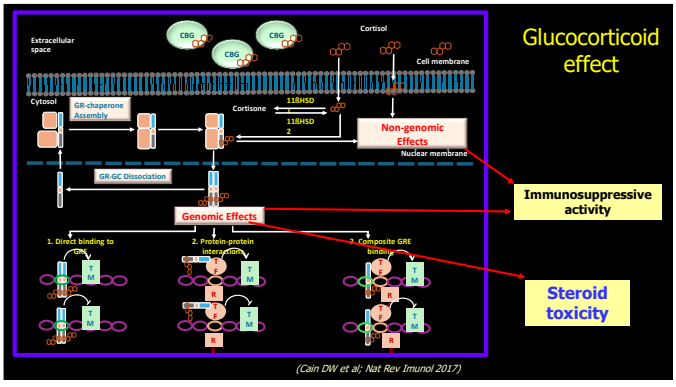
Prednisolone
Hydroxychloroquine

First Line	Refractory or severe
Low dose IV cyclophosphamide for 6 months	High dose IV cyclophosphamide for 6 months + MMF
or	or
Mycophenolate (MMF)	CNI
	or
	CNI + MMF

REMISSION MAINTENANCE

Mycophenolate mofetil or Azathioprine

(American College of Rheumatology Guidelines; Arth Care Res 2012)
(2019 update of the EULAR recommendations for the management of SLE. Ann Rheum Dis 2019)



(Cain DW et al; Nat Rev Imunol 2017)

Is there an optimal steroid dose for immunosuppressive action without increasing toxicity?

- Non-genomic mechanisms must be activated by high dose steroids (prednisolone equivalent ≥100 mg) to realize further immunosuppression without increasing toxicity
- Non-genomic effects increase up to equivalent of methylprednisolone 1 g
- Clinical outcomes may not improve beyond cumulative methylprednisolone dose of 1.5 g but risk of infection does

What is a reasonable steroid dosing strategy for treatment of lupus nephritis?

- Induce genomic and non-genomic effects rapidly with IV methylprednisolone daily for 2-3 days to a maximum of 1 g
- Maintain with moderat-dose prednisolone 0.3-0.5 mg/kg/day
- Prednisolone reduction without antecedent high dose methyl-prednisolone may not be adequate to treat severe lupus npehritis

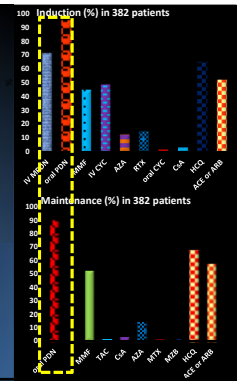
What about in children with lupus nephritis?

International cohort of 382 children with lupus nephritis – presentation, treatment and outcome at 24 months

Chiara De Mutiis[1] · Scott E. Wenderfer[2] · Biswanath Basu[3] · Arvind Bagga[4] · Alvaro Orjuela[2] · Tanmoy Sar[3] · Amita Aggarwal[5] · Avinash Jain[6] · Hui-Kim Yap[7] · Sharon Teo[8] · Shuichi Ito[9] · Ai Ohnishi[9] · Naomi Iwata[10] · Ozgur Kasapcopur[11] · Mehmet Yildiz[11] · Audrey Laurent[12] · Antonio Mastrangelo[13] · Masao Ogura[14] · Yuko Shima[15] · Pornpimol Rianthavorn[16] · Clovis A. Silva[17] · Vitor Trindade[17] · Alessandra Gianviti[18] · Miyazono Akinori[19] · Riku Hamada[20] · Junya Fujimura[21] · Shogo Minamikawa[21] · Naohiro Kamiyoshi[21] · Hiroshi Kaito[21] · Shingo Ishimori[22] · Francesco Iannuzzella[23] · Kjell Tullus[24]

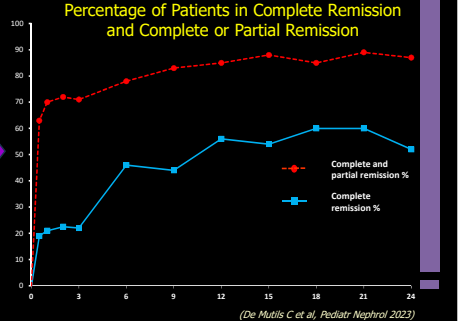
Pediatric Nephrology (2023) 38:3699–3709

All children received high dose steroids either IV or oral for induction therapy followed by maintenance steroids in 90%



(De Mutils C et al, Pediatr Nephrol 2023)

About **50% of children achieved complete remission** while a further 30% achieved partial remission at 6 months



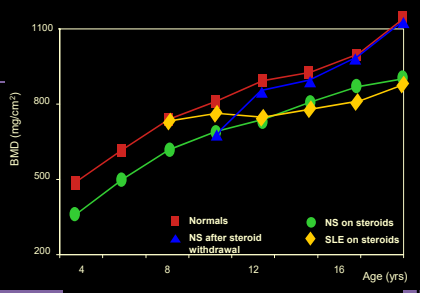
(De Mutils C et al, Pediatr Nephrol 2023)

Major concern in children: cumulative steroid-related toxicities

- Infections
- **Short stature**
- Cosmetic effects
- Osteoporosis
- Cataracts or glaucoma
- Hypertension
- Diabetes mellitus

Growth retardation is a significiant problem in childhood-onset SLE due to daily steroid dosing

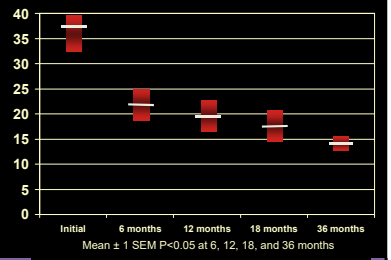
- Long-term steroids decreased spine bone mineral density in children with SLE



(Bianchi ML, Calcif Tissue Int 2002)

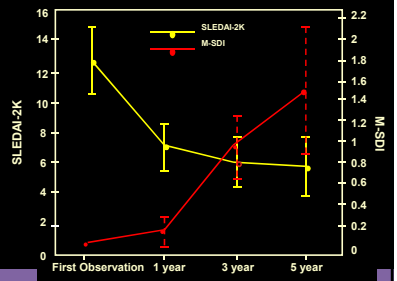
Current therapeutic regimens involved daily steroid dosing

- Intermittent IV cyclophosphamide for 36 months in children with lupus nephritis resulted in a 60% reduction in dosage of prednisolone to a mean of 14 mg **DAILY**



(Lehman TJA et al, J Pediatr 2000)

- Therapy of juvenile-onset SLE resulted in decrease in activity over time **but could not prevent damage scores from increasing**



(Bandeira M et al, Lupus 2006)

Can steroid dose be minimized with current multi-targeted therapy for lupus nephritis?

MCQ 4

Can steroids be discontinued during maintenance therapy of lupus nephritis?

A. Yes
B. No
C. Maybe

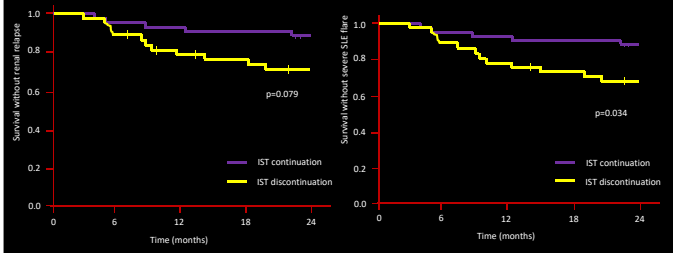
Can steroids be discontinued during maintenance therapy of lupus nephritis?

A. Yes
B. No
C. Maybe

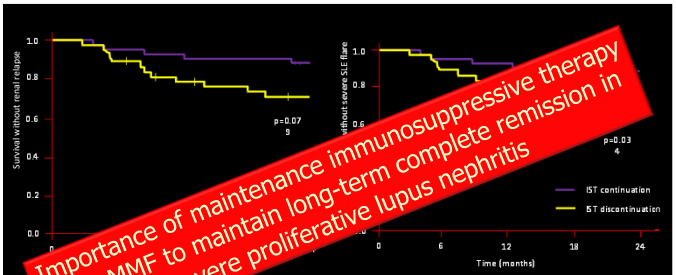
Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial

Jourde-Chiche N, *et al. Ann Rheum Dis* 2022;**81**:1420–1427. doi:10.1136/annrheumdis-2022-222435

- RCT (n=96) of lupus nephritis (LN) patients on maintenance immunosuppression therapy (IST) with AZT or MMF for 2-3 years and hydroxychloroquine + low dose steroids ≤10 mg/day
- Randomized into:
  - IST continuation over 24 months (n=48)
  - IST discontinuation over 3 months (n=48)
- Primary outcome: relapse of proliferative LN at 24 months
- Secondary outcome: Severe lupus flare (renal/extrarenal)

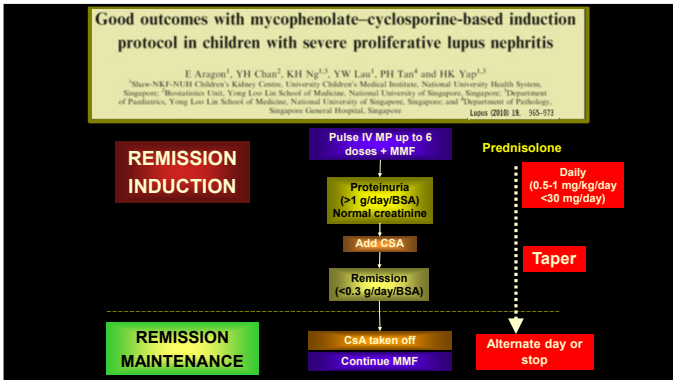


- Patients who discontinued immunosuppression had higher risk of relapse of lupus nephritis and severe flares of lupus despite low dose maintenance steroid therapy



Importance of maintenance immunosuppressive therapy with MMF to maintain long-term complete remission in severe proliferative lupus nephritis

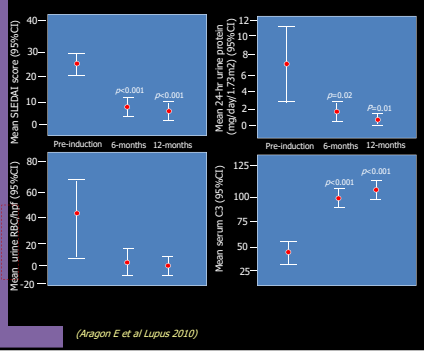
…o discontinued immunosuppression had higher risk of …pse of lupus nephritis and severe flares of lupus despite low dose maintenance steroid therapy



Difference between IV methylprednisolone and oral prednisolone:

- IV methylprednisolone kills plasmacytoid dendritic cells that makes the type 1 interferons which are the major driver of lupus
- Dendritic cells regenerate in a week implying that repeat pulsing may be useful in inducing remission

(Guiducci et al, Nature 2008)



(Aragon E et al Lupus 2010)

Combination of pulse methylprednisolone, mycophenolate and cyclosporine is an effective therapeutic alternative for induction of children with severe proliferative lupus nephritis

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

E Aragon[1], LP Resontoc[1], YH Chan[2], YW Lau[1], PH Tan[4], HL Loh[4], KH Ng[1,3] and HK Yap[1,3]
[1]Shaw-NKF-NUH Children's Kidney Centre, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore; [2]Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [3]Department of Pediatrics Yong Loo Lin School of Medicine, National University of Singapore, Singapore; and [4]Department of Pathology, Singapore General Hospital, Singapore

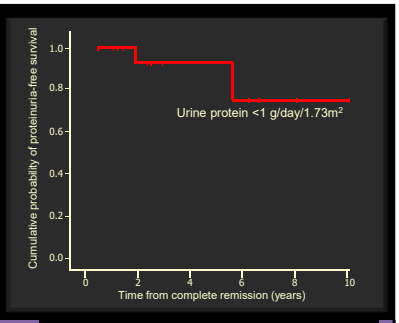
Lupus (2016) 25, 399–406

16 children with proliferative lupus nephritis (III/IV):

- Median duration of follow-up: 9.2 years (range 5.8-14.2 years)
- All children achieved complete remission within 24 months (median 8.7 months, range 4-24 months)

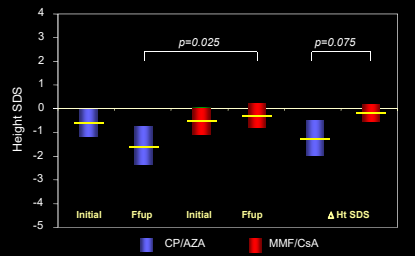
Patient	Induction therapy	Duration of therapy (years)	MMF dose at last followup (mg/m2/d)	Pred dose at last followup (mg/kg/d)
1	IV MP+MMF+CSA	10.2	532.1	NIL
2	IV MP+MMF+CSA	9.5	1291.7	0.12 EOD
3	PRED+MMF+CSA	12.8	1170.5	0.04 EOD
4	IV MP+MMF	12.9	1238	0.17 OD
5	IV MP+MMF+CSA	7.9	751	NIL
6	IV MP+MMF+CSA	9.0	990.6	0.06 EOD
7	IV MP+MMF+CSA	7.8	1107.9	NIL
8	IV MP+MMF+CSA	11.6	1015.8	NIL
9	IV MP+MMF+CSA	6.8	1266.7	0.09 OD
10	PRED+MMF+CSA	14.2	1158.5	0.16 EOD
11	IV MP+MMF+CSA	11.9	1198.5	NIL
12	IV MP+MMF+CSA	6.4	1145.5	0.20 EOD
13	IV MP+MMF+CSA	9.4	1171.5	NIL
14	IV MP+MMF+CSA	5.8	945.5	0.10 EOD
15	IV MP+MMF	5.8	1169.5	0.02 EOD
16	IV MP+MMF+PLEX	6.8	1243	0.04 EOD

- Cumulative relapse free (proteinuria free) survival at 10 years was 73.3%



(Aragon E et al Lupus 2016)

- Patients treated with MMF/CsA fared better in terms of growth as shown by the height SDS compared to CP/AZA group

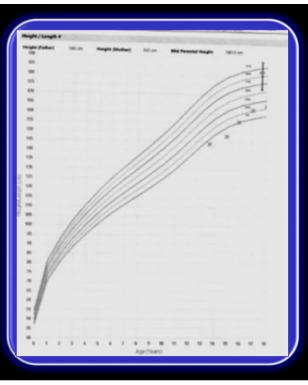


(Singapore 1985-2006)

Case

His steroid dose was gradually tapered over 9 months and he was then changed to alternate day therapy with improvement in his height velocity.

Steroid therapy was discontinued 8 years later and he was maintained on mycophenolate and hydroxychloroquine.



Can steroid-free management be achieved with the new biologics and targeted therapies?

MCQ 5

Which of the following biologics have been shown in clinical trials to be effective in inducing remission in lupus nephritis?

A. Belatacept
B. Belimumab
C. Dupilumab
D. Eternacept
E. Tocilizumab

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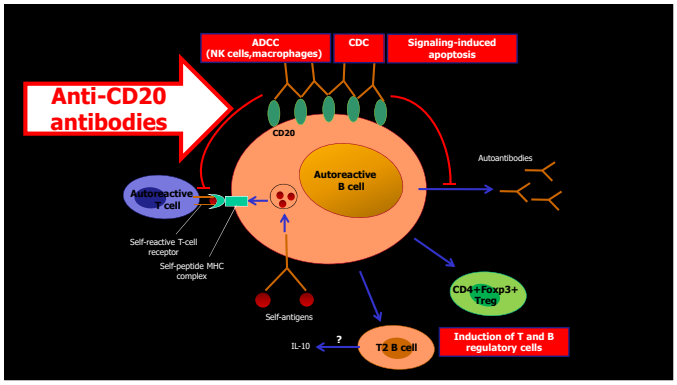


frontiers | Frontiers in Immunology

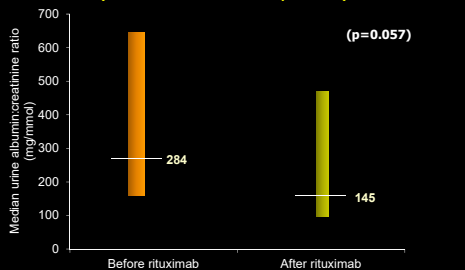
SYSTEMATIC REVIEW

Comparative Effectiveness of Rituximab and Common Induction Therapies for Lupus Nephritis: A Systematic Review and Network Meta-Analysis

*Kang Li, Yanqiu Yu, Yuan Gao, Fei Zhao, Zheng Liang and Junjie Gao**

- Unique records identified through searching of MEDLINE, Embase and Cochrane databases through December 9, 2021 (19 studies, 1566 patients)

Reduction in albuminuria following Rituximab treatment in children with lupus nephritis (UK JSLE cohort study n=31)



(Watson L, et al Lupus 2014)

The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE

L Watson[1,2], MW Beresford[1,3], C Maynes[4], C Pilkington[5], SD Marks[4], Y Glackin[5] and K Tullus[4]

Lupus (2014) 0, 1–8.

- Retrospective study in 63 children with SLE receiving 104 courses of rituximab
- Adverse events:
  - 18% delayed second course
  - 6% allergy
  - 2% reduced Ig level
  - 2% infection including CMV and herpes zoster

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

Ines Mahmoud, PhD[1], Manel Jellouli, MD[2], Imen Boukhris, PhD[3], Rim Charfi, MD[4], Aicha Ben Tekaya, MD[1], Olfa Saidane, MD[1], Maryem Ferjani, MD[2], Yousra Hammi, MD[2], Sameh Trabelsi, PhD[4], Narjess Khalfallah, PhD[2], Rawdha Tekaya, PhD[1], Tahar Gargah, PhD[2], and Leila Abdelmoula, PhD[1]

(J Pediatr 2017;187:213-9)

Objectives To evaluate the efficacy and safety of rituximab for treating pediatric systemic lupus erythematosus (pSLE).

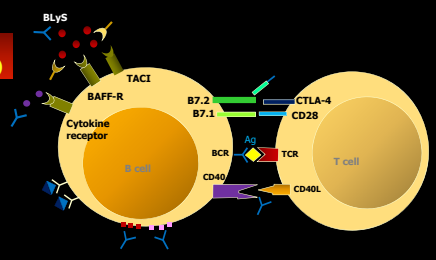
Study design We performed a systematic review to evaluate the efficacy and safety of rituximab in children with pSLE. Data from studies performed before July 2016 were collected from MEDLINE, the Cochrane Library, Scopus, and the International Rheumatic Disease Abstracts, with no language restrictions. Study eligibility criteria included clinical trials and observational studies with a minimal sample size of 5 patients, regarding treatment with rituximab in patients with refractory pSLE (aged <18 years at the time of diagnosis). Independent extraction of articles was performed by 2 investigators using predefined data fields.

Results Twelve case series met the criteria for data extraction for the systematic review with a good quality assessment according to an 18-criteria checklist using a modified Delphi method. Among them, 3 studies were multicenter and 3 were prospective. The total number of patients was 272. Studies collected patients with active disease refractory to steroids and immunosuppressant drugs. Refractory lupus nephritis was the most common indication (33%). Acceptable evidence suggested improvements in renal, neuropsychiatric and haematological manifestations, disease activity, complement and anti-double stranded Desoxy-Nucleo-Adenosine, with a steroid-sparing effect. However, there was poor evidence suggesting efficacy on arthralgia, photosensitivity, and mucocutaneous manifestations of SLE in children. An overall acceptable safety profile with few major adverse events was shown.

Conclusion Rituximab exhibited a satisfactory profile regarding efficacy and safety indicating that this agent is a promising therapy for pSLE and should be further investigated.

B-cell directed therapies

Anti-BLyS (Belimumab)



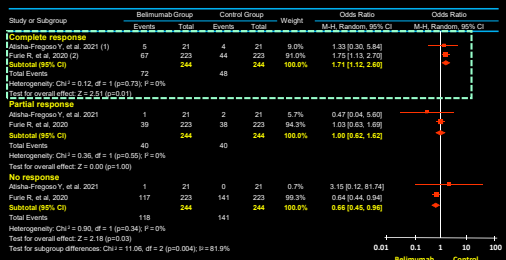
Belimumab in Lupus Nephritis: A Systematic Review and Meta-Analysis

Sanjeev Shrestha [1], Pravash Budhathoki [2], Yuvraj Adhikari [3], Anupama Marasini [3], Shakar Bhandari [3], Wasey Ali Yadullahi Mir [4], Dhan B. Shrestha [4]

DOI: 10.7759/cureus.20440

- Aim of systematic review: Role of belimumab in the maintenance phase of treatment for lupus nephritis
- PubMed, PubMed Central (PMC), Cochrane Library and Embase were searched using appropriate keywords
- Screening of title and abstract was done in Covidence and review manager (RevMan 5.4) was used for data analysis with random or rixed effects model based on heterogeneities
- 2 randomized controlled trials were included in the quantitative analysis (n=488)

There were 1.71 x higher odds of complete renal response in the belimumab group with no significant differences between the groups for the occurrence of treatment-related adverse events



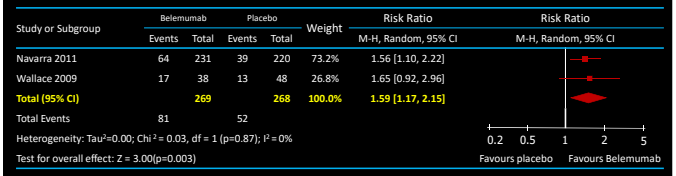
(1) At week 96 (2) At week 104

(Shrestha et al; Cureus 2021; 13:12)

Efficacy and safety of belimumab therapy in systemic lupus erythematosus: A systematic review and meta-analysis

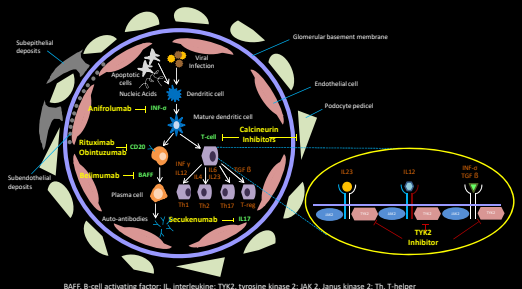
Hsin-Yu Chiang, Zi-An Guo, Ta-Wei Wu, and Tzu-Rong Peng

Lupus
Volume 31, Issue 6, May 2022, Pages 666-673



- 7 RCTs with 3009 participants
- Belimumab significantly reduced the prednisone dose by 50% or more than placebo at 52 weeks

Pathogenetic targets of new therapeutic strategies



BAFF, B-cell activating factor; IL, interleukine; TYK2, tyrosine kinase 2; JAK 2, Janus kinase 2; Th, T-helper

(Michela Gasparotto et al, Rheumatology 2020)

Recently completed clinical trials of new therapies for lupus nephritis

Trial (patient no)	Drug	Therapeutic target	Primary outcome / Results
NOBILITY (phase II) (n=125) *Furie RA; Clin Sci 2021*	Obinutuzumab	CD20	**CRR greater with obinutuzumab at week 104 (41% vs 23%, difference 19%, 95%CI 2.7-35)**
TULIP-LN1 (phase II) (n=145) *Jayne D; Clin Sci 2021*	Anifrolumab	IFN-1R	CRR higher with anifrolumab at week 52 (45.5% v s31.1%, p=ns)
AURA-LV (phase IIb) (n=265) *Rovin BH; Kidney Int 2019*	Voclosporin	Novel CNI	**CRR higher with low dose voclosporin at week 24 (32.6% vs 19.3%, OR 2.03, 95%CI 1.01-4.05)**
AURORA 1 (phase III) (n=357) *Rovin BH; Lancet 2021*	Voclosporin	Novel CNI	**CRR higher with voclosporin at week 52 (41% vs 23%, OR 2.65, 95%CI 1.64-4.27)**

Will use of these newer agents allow further lowering or discontinuation of the steroid dose in those who achieve complete remission?

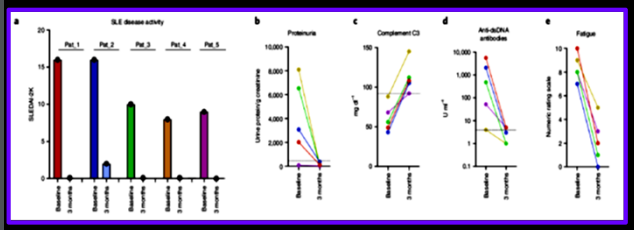
Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[2,4], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[2,7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8]

NATURE MEDICINE | VOL 28 | OCTOBER 2022 | 2124–2132

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics					
Age (years)	22	23	22	24	18
Sex (female/male)	F	M	F	F	F
Disease duration (years)	4	1	6	9	3
Disease activity SLEDAI-2K (score)	16	16	10	8	9
Organ involvement					
Skin (presence/absence)	+	+	+	+	+
Kidney (presence/absence)	+ (stage III)	+ (stage III)	+ (stage IV)	+ (stage III/V)	+ (stage III/V)
Joints (presence/absence)	–	+	+	+	+
Lungs (presence/absence)	+	–	+	+/–	–
Heart (presence/absence)	+	–	–	+	–
Other (presence/absence)	HEM	–	SER	MYO	HEM
Treatments					
Glucocorticoid pulses (yes/no)	+	+	+	+	+
Hydroxychloroquine (yes/no)	+	+	+	+	+
MMF (yes/no)	+	+	+	+	+
Azathioprine (yes/no)	–	–	–	+	+
Cyclophosphamide (yes/no)	+	+	+	–	–
Rituximab (yes/no)	+	–	–	–	–
Belimumab (yes/no)	+	+	+	+	+
Other (yes/no)	TAC	–	–	MTX, LEF	–

Drug-free remission of SLE disease activity was achieved following CAR-T cell treatment



Conclusion

THE TAKE-HOME MESSAGE

- SLE in children has a higher rate of major organ involvement especially lupus nephritis
- Patients with proliferative lupus nephritis have poorer long-term outcomes in terms of renal survival if they do not achieve complete renal remission
- Steroid-based treatment protocols together with immunosuppressive agents which are the mainstay of treatment in children with severe lupus nephritis are associated with significant steroid side effects in particular growth retardation

THE TAKE-HOME MESSAGE

- Protocols involving stabilization of disease with mycophenolate and calcineurin inhibitors and minimization of steroid dose tapering to alternate day or discontinuation result in improvement in height velocity
- Use of biologics such as rituximab and belimumab and other novel therapies may allow steroid-minimization or steroid-free management of lupus nephritis
- Drug-free remissions are potentially possible with the new CAR-T therapies

Management of lupus nephritis

Individualize therapy:

Neonatal AKI: Considerations in Management

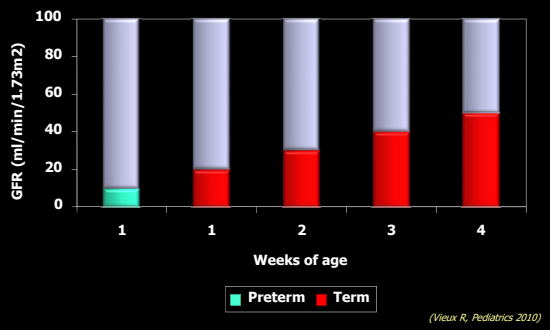
Hui-Kim Yap
Shaw-NKF-NUH Children's Kidney Centre
KTP-National University Children's Medical Institute
Department of Pediatrics
National University of Singapore

Key Questions

- What is the burden of AKI in neonates?
- Can we recognize neonatal AKI earlier?
- How can we improve early outcomes in neonatal AKI?
- What is the risk of chronic kidney disease following neonatal AKI?

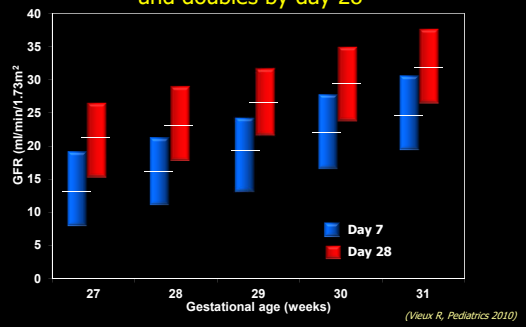
What is the burden of AKI in neonates?

GFR is lower in neonates especially premature infants



(Vieux R, Pediatrics 2010)

Median GFR increases with gestational age in preterms and doubles by day 28



(Vieux R, Pediatrics 2010)

Newborns especially premature infants are more susceptible to kidney injury than older infants and children

- Functional and developmental immaturity of the neonatal kidney which limits urine concentrating ability and GFR
- Hemodynamic changes that occur at delivery
- Risk of hypovolemia due to large insensible water losses

Incidence of neonatal AKI

Study	N (# sites)	Population	AKI definition	AKI incidence (%)	Need for KRT (%)
Jetton 2017 AWAKEN	2022 (24)	All gestational age (GA)	KDIGO S Cr and UO	29.9	1.2 (CRRT>PD)
Sethi 2022 TINKER	1600 (11)	All GA	KDIGO S Cr and UO	30.7	2.8 (All PD)
Askenezi 2020 PENUT	900 (19)	ELGAN GA<28 wks	KDIGO S Cr	38	0
Grossman 2021	66 (4)	HIE Term GA	KDIGO S Cr and UO	44.6	0
Garg 2021	202 (1)	NEC	KDIGO S Cr and UO	44.5	0

AKI is associated with similar mortality as older children

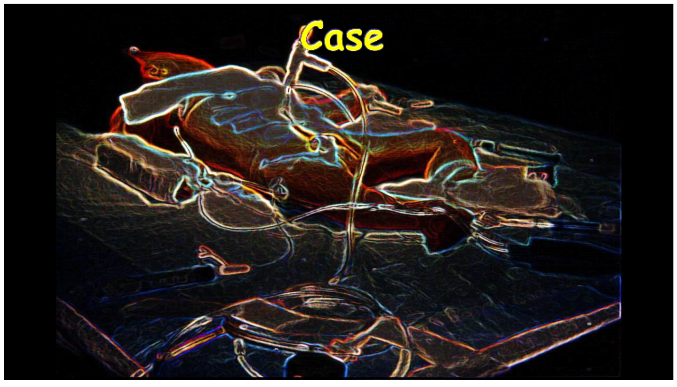
	AWARE (Kaddourah A et al NEJM 2017)	AWAKEN (Jetton JG et al Lancet Child Adolesc Health 2017)
Population	4683 children	2162 infants
Pooled Incidence of AKI	26.9% (95% CI 25.6-28.2)	30 % By *gestational age group:* 48% :22 weeks to <29 weeks 18% :29 weeks to <36 weeks 37% :36 weeks or older
Mortality	11.0% (adjusted OR, 1.77; 95% CI, 1.17 to 2.68)	10%

Acute Kidney Injury in Neonates: A Meta-Analysis

Meena J, Kumar J, Kocharlakota JP, Gupta H, Mittal P, Kumar A, Sinha A, Hari P, Bagga A
Pediatrics. 2024 Jul 1;154(1):e2023065182

- Databases (Embase, PubMed, Web of Sciences) from Jan 2004 to Dec 2022 searched
- Eligible studies with at least 10 participants fulfilling standard criteria for AKI (AKIN, pRIFLE, KDIGO)
- 201 studies (98228 participants) from 45 countries
- Incidence of neonatal AKI was 30% (95% CI 28-32) and severe AKI was 15% (95% CI 14-16)
- Associated mortality was 30% (95% CI 27-33) with odds of mortality higher in neonates with AKI (OR 3.4, 95% CI 2.9-3.0)

How do we recognize neonatal AKI earlier?



A male infant was born at 32+2 weeks gestation by emergency Caeserean for poor CTG with reduced variability. FCC scan showed increased liquor and thick placenta with hydropic fetus. Apgar was 2 (1'), 4 (5') and 8 (10'). Estimated weight was 1.8 kg (measured birth weight 2.7 kg). He was intubated at birth and required HFOV. Examination: BP 55/42, with anarsaca, cardiomegaly, hepatosplenomegaly.

Initial investigations 18 h after birth showed Hb 10.9 g/dL, platelets 123x10^9/L, pH 7.12, pCO2 70.9 mmHg, pO_2 28 mmHg, bicarbonate 28 mmol/L, base excess -6 mmol/L, Na 141 mmol/L, K 3.5 mmol/L, Cl 107 mmol/L, urea 2.9 mmol/L, Ca 2.08 mmol/L, iP 1.92 mmol/L, creatinine 63 umol/L.

Urine output was 26 ml (0.6 ml/kg/h) on day 0.

MCQ 1

Does this neonate have acute kidney injury?

A. Yes
B. No
C. Maybe

How do we define AKI in the neonate?

Serum creatinine in the first 2-3 days of life reflects maternal levels making it an unreliable marker of renal dysfunction

Definition of oliguria:
Minimum volume of urine required to excrete a solute load of 15 mOsm/kg

	Urine Osm max	Urine volume (ml/kg/day)	**Urine volume (ml/kg/hr)**
Preterm	360	41.6	**1.7**
Term infant	525	28.0	**1.2**
Child	1200	12.5	**0.5**

Suspect AKI in the newborn if:

- Presence of oliguria:
  - Newborn with no urine output noted by 48 hours of age
  - Urine output ≤1 ml/kg/hour
- Increase in serum creatinine:
  - By at least 26.5 umol/L (0.3 mg/dL) within 48 hours
  - 1.5-1.9 times from baseline within 1st 7 days of life

Modified KDIGO (Kidney Disease Improving Global Outcomes) criteria for neonatal AKI

Stage	Serum creatinine (SCr)	Urine output (d2-7 post birth)
1	Increase to 1.5-1.9x reference SCr* within 7d OR Increase of SCr ≥0.3 mg/dL (≥26.5 umol/L) within 48h	>0.5 and ≤1 ml/kg/h
2	Increase to 2-2.9x reference SCr*	>0.3 and ≤0.5 ml/kg/h
3	Increase >3x reference SCr* OR SCr ≥2.5 mg/dL (≥227.2 umol/L) OR Initiation of KRT	<0.3 ml/kg/h

*Reference SCr is lowest previous value

(Jetton JG, Ashkenei DJ, Clin Perinatol 2014)

Absolute serum creatinine rise outperformed a 50% change in serum creatinine for prediction of mortality in first week of life (AWAKEN study):

- ≤29 weeks GA: 54.5 umol/L (0.6 mg/dL)
- >29 weeks GA: 26.5 umol/L (0.3 mg/dL)

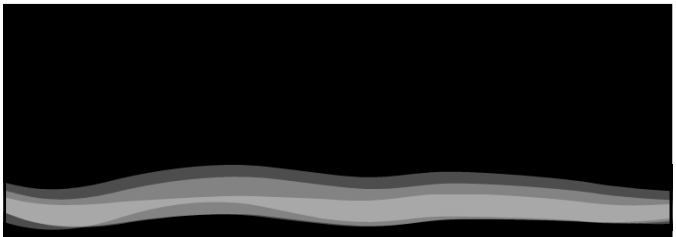
(Askenazi DJ et al, Pediatr Res 2019)

What should the urine output criteria be for premature or low birth weight infants?

Stage (nRIFLE)	**Modified KDIGO for neonatal AKI (D2-7 post birth)**	**KDIGO (infants >7 days)**	**nRIFLE**
1 (Risk)	**>0.5 and ≤1 ml/kg/h**	<0.5 ml/kg/h for 6-12h	**UO <1.5 mL/kg/h x 24h**
2 (Injury)	**>0.3 and ≤0.5 ml/kg/h**	<0.5 ml/kg/h for ≥12h	**UO <1.0 mL/kg/h x 24h**
3 (Failure)	**<0.3 ml/kg/h**	<0.3 ml/kg/h for 24h or anuria for 12h	**UO <0.7 mL/kg/h x 24h or anuric for 12h**

Does this neonate have acute kidney injury?

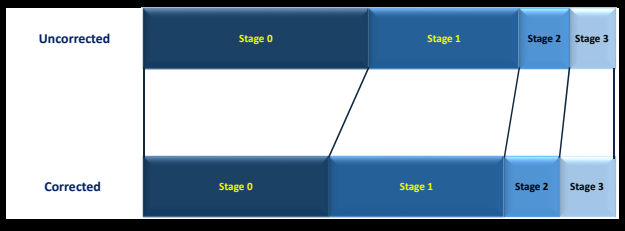
A. Yes
B. No
C. Maybe



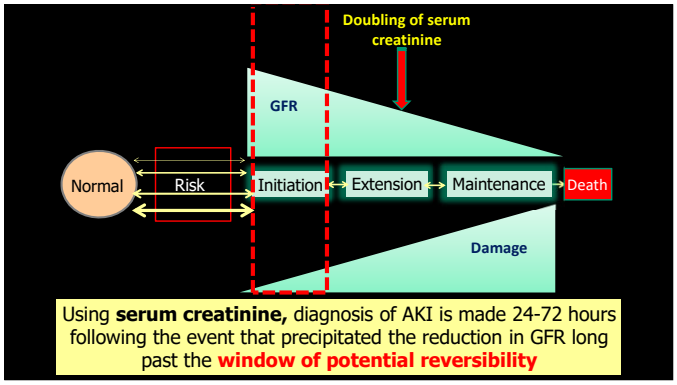
Effect of fluid overload on creatinine levels

Corrected creatinine = Serum creatinine x [1+(Cumulative fluid balance/total body water)]

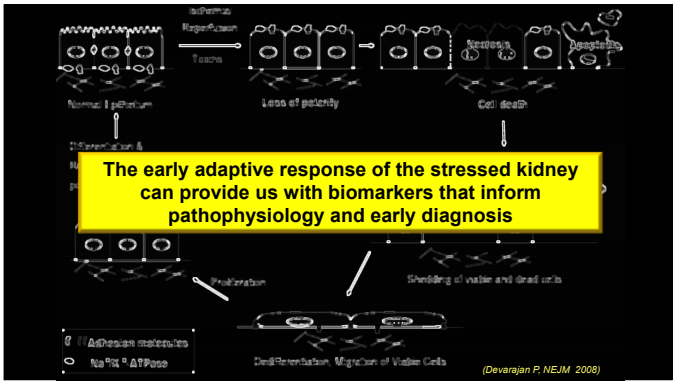
Fluid corrected creatinine results in re-classification of AKI based on creatinine

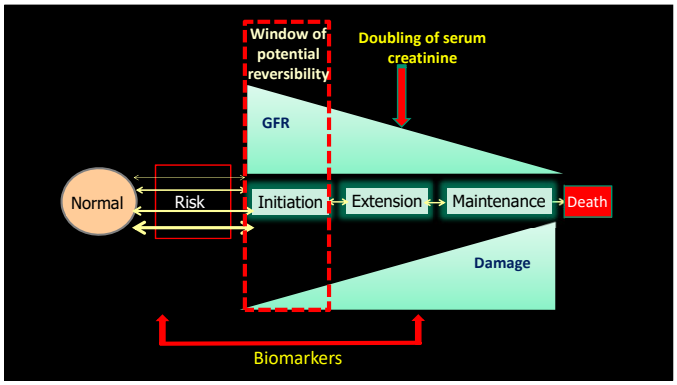


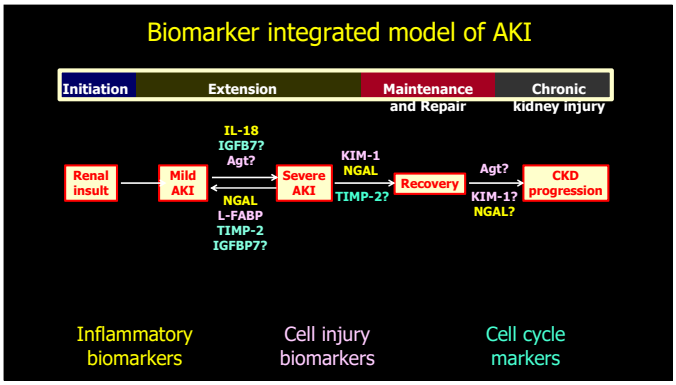
(Gorga SM et al, Pediatr Nephrol 2024)



Using **serum creatinine,** diagnosis of AKI is made 24-72 hours following the event that precipitated the reduction in GFR long past the **window of potential reversibility**







High-performing biomarkers for predicting AKI in neonates

Etiology	Studies	Biomarkers predictive of AKI
Hypoxia-ischemia (HI)	Li (2012), Askenazi (2012), Sarafadis (2012), Raggal (2013), Hadzimuratovic (2014), Treiber (2014), Essajee (2015), Cao (2016)	**Urine, serum (D3) and umbilical cystatin C Serum and urine NGAL Urine KIM-1 Urine netrin-1**
Prematurity	Askenazi (2011), Elmas (2013), Pejovic (2015)	**Urine NGAL (VLBW) Serum NGAL at 4h (HI preterms) Serum cystatin C (RDS preterms)**
Cardiopulmonary by-pass (CBP)	Catherine (2011), Sermiak (2015), Herbert (2015)	**Umbilical NGAL (HLHS) Serum cystatin C (post cardiac surgery)**

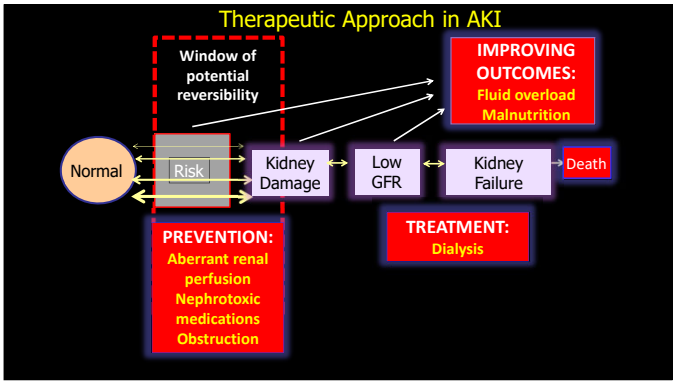
*Sensitivity or Specificity of test (>0.75) orAUC (>0.75) *(Sweetman DU, Early Hum Deve 2017)*

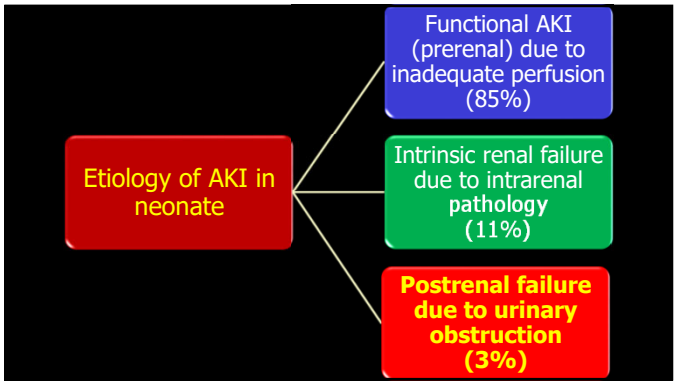
Urine acute kidney injury biomarkers in extremely low gestational age neonates: a nested case control study of 21 candidate urine biomarkers

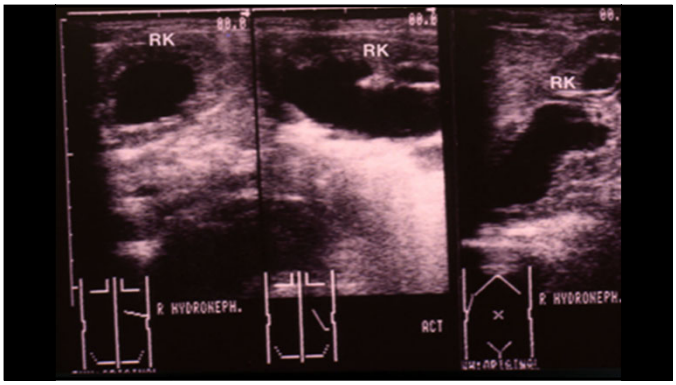
David J. Askenazi[1] · Brian A. Halloran[1] · Patrick J. Heagerty[2] · Robert H. Schmicker[2] · Sandra E. Juul[3] · Sangeeta Hingorani[3] · Stuart L. Goldstein[4] on behalf of the PENUT Trial Consortium

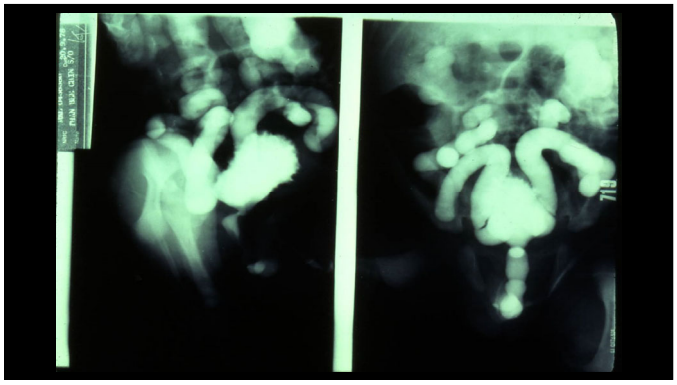
Higher in early severe AKI	Lower in early severe AKI
• Cystatin C • Creatinine, • ghrelin • fibroblast growth factor-23 (FGF23) • tissue metalloproteinase 2 (TIMP2) • vascular endothelial growth factor A (VEGFa)	• Urine epidermal growth factor (EGF) • Uromodulin (UMOD)

How can we improve early outcomes in neonatal AKI?









MCQ 2

What is the cause of the hydronephrosis in this neonate?

A. Anterior urethral stricture
B. Bilateral vesicoureteric junction obstruction
C. Neurogenic bladder
D. Posterior urethral valve
E. Primary bilateral vesicoureteral reflux

What is the cause of the hydronephrosis in this neonate?

A. Anterior urethral stricture
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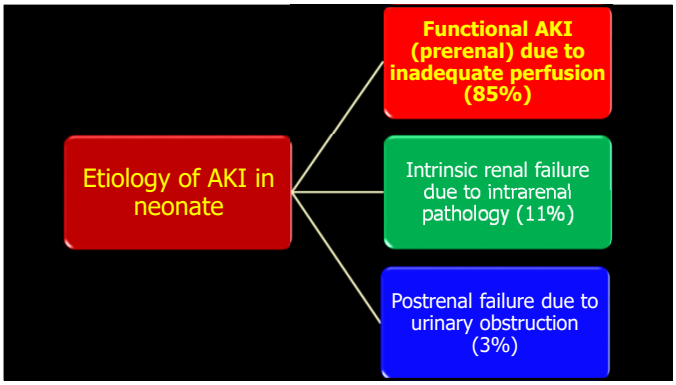
D. Posterior urethral valve
E. Primary bilateral vesicoureteral reflux

Postrenal: Obstructive uropathy

- Urethral obstruction:
  - **Posterior urethral valves**
  - Urethral stricture
- Neurogenic bladder
- Bilateral or solitary kidney with
  - Vesicoureteric junction obstruction
  - Pelviureteric junction obstruction



Types of neonatal AKI	Potential causes	Associations
Developmental (prematurity, LBW)	Hypoperfusion Renal under-development	Decreased gestational age and birth weight associated with high risk of AKI AKI increased mortality and increased length of hospital day
Cardiac (CHD)	Hypoxia Reduced cardiac output Fluid overload	AKI after cardiac surgery most likely on D1 AKI severity associated with increased mortality
Asphyxia (HIE)	Hypoxia	HIE associated AKI associated with increased length of hospital stay

(Hu J et al, J Neonatal Pernatal Med 2023)

Types of neonatal AKI	Potential causes	Associations
Gastrointestinal (NEC)	Sepsis Inflammation	AKI associated with higher risk of death and increased length of hospital stay
Medication-induced (aminoglycoside)	Nephrotoxicity	87% of VLBW infants received at least 1 nephrotoxic medication
Supportive therapy related factors (ECMO)	Inflammation Hormonal changes	AKI during ECMO associated with longer duration of treatment and increased adjusted odds for mortality
Hematologic	Hypoxia	Lower Hb and albumin associated with increased risk of AKI in neonates

(Hu J et al, J Neonatal Pernatal Med 2023)

What are the strategies to improve renal perfusion?

MCQ 3

Which of the following have been shown in randomized controlled trials to be effective in preventing AKI in neonates? (Multiple answers)

A. Caffeine
B. Dopamine
C. Erythropoietin
D. Fenoldopam
E. Theophylline

Which of the following have been shown in randomized controlled trials to be effective in preventing AKI in neonates? (Multiple answers)

A. Caffeine
B. Dopamine
C. Erythropoietin
D. Fenoldopam
E. Theophylline

INTERVENTION		SUBJECT	STUDIES	OUTCOMES
RENAL PERFUSION PRESSURE: Renal vasodilators	DOPAMINE	Adults (low-dose, or "renal dose")	Meta-analysis 24 Studies	MORTALITY: RR 0.90 [0.44-1.83] ONSET OF AKI: RR 0.81 [0.55-1.19] NEED FOR DIALYSIS: RR 0.83 [0.55-1.24]
	FENOLDOPAM	Children (0.07±0.08 µg/kg/min)	Retros-pective	Increased urine output in critically ill children with progressive oliguria Did not affect overall outcome
		Neonates undergoing CPB (0.1 µg/kg/min)	RCT	Did not improve urine output, fluid balance or AKI
		Neonates undergoing CPB (1 µg/kg/min)	RCT subgroup analysis	Urinary NGAL and CysC values were significantly reduced at the end of surgery

Low-dose dopamine and fenoldopam have not been tested in a large prospective neonatal cohort study and cannot be recommended for prevention or management of AKI outside the context of a clinical trial

(Basu RJ , Recent Pat Biomark 2011; Ricci Z, Interact Cardiovasc Thorac Surg 2008; Ricci Z, Crit Care 2011)

JAMA Pediatrics | Original Investigation

Association Between Early Caffeine Citrate Administration and Risk of Acute Kidney Injury in Preterm Neonates Results From the AWAKEN Study

Matthew W. Harer, MD; David J. Askenazi, MD, MSPH; Louis J. Boohaker, MPH; J. Bryan Carmody, MD, MPH; Russell L. Griffin, PhD; Ronnie Guillet, MD, PhD; David T. Selewski, MD; Jonathan R. Swanson, MD, MSc; Jennifer R. Charlton, MD, MSc; for the Neonatal Kidney Collaborative (NKC)

- AWAKEN Study: Involving 24 centers in 4 countries designed to evaluate the incidence, risk factors, and outcomes associated with neonatal AKI
- Secondary analysis of the role of caffeine administered in the first 7 days after birth on the development of AKI (n=675 preterm neonates)
- AKI occurred in 122 preterm neonates (18.1%)

Early caffeine citrate administration is associated with reduced incidence or severity of AKI in preterm neonates

Primary AKI Outcomes Stratified by Caffeine Citrate Administration

Variable	No./Total No. (%)		OR (95% CI)		NNE
	Caffeine	No Caffeine	Unadjusted	Adjusted	
Early AKI ≤ 7d					
Overall	50/447 (11.2)	72/228 (31.6)	0.28 (0.18-0.44)	0.20 (0.11-0.34)	4.3
Extremely preterm, <27wk	30/149 (20.1)	38/55 (69.1)	0.07 (0.03-0.16)	0.13 (0.06-0.31)	2.2
Very preterm, 28-32wk	20/298 (10.1)	34/173 (19.7)	0.31 (0.16-0.61)	0.27 (0.13-0.56)	8.1
Any AKI ≤ 120d					
Overall	103/447 (23)	83/228 (36.4)	0.56 (0.38-0.84)	0.27 (0.16-0.47)	4.4
Extremely preterm, <27wk	69/149 (29.5)	44/55 (80)	0.12 (0.05-0.30)	0.24 (0.10-0.58)	3.1
Very preterm, 28-32wk	34/293 (11.6)	39/170 (22.9)	0.52 (0.29-0.94)	0.32 (0.16-0.62)	8.0

(Harer MW et al JAMA Pediatrics 2018)

Neonates who developed early AKI but were given caffeine had an 80% decrease in the odds of stage 2 or 3 AKI

Secondary AKI Outcomes Stratified by Caffeine Citrate Administration

Variable	No. (%)		Adjusted OR (95% CI)
	Caffeine (n=447)	No Caffeine (n=228)	
Early AKI ≤ 7d			
AKI, sCr plus UOP	50 (11.2)	72 (31.6)	0.20 (0.11-0.34)
AKI, sCr	47 (10.5)	60 (26.3)	0.20 (0.11-0.37)
AKI, UOP	8 (1.8)	17 (7.5)	0.40 (0.15-1.06)
Stage 1	27 (6.0)	32 (14.0)	
Stage 2	17 (3.8)	16 (7.0)	0.20 (0.12-0.34)
Stage 3	6 (1.3)	24 (10.5)	
Any AKI ≤ 120d			
AKI, sCr	100 (22.4)	71 (31.1)	0.28 (0.16-0.49)
Stage 1	54 (12.1)	40 (17.5)	
Stage 2	34 (7.6)	17 (7.5)	0.30 (0.19-0.48)
Stage 3	15 (3.4)	26 (11.4)	

(Harer MW et al JAMA Pediatrics 2018)

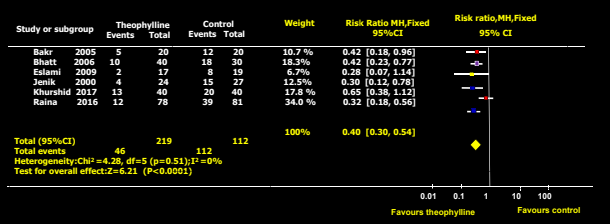
Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: a systematic review

Girish Chandra Bhatt,[1] Priya Gogia,[1] Martin Bitzan,[2] Rashmi Ranjan Das[3]

Arch Dis Child 2019;**0**:1–10

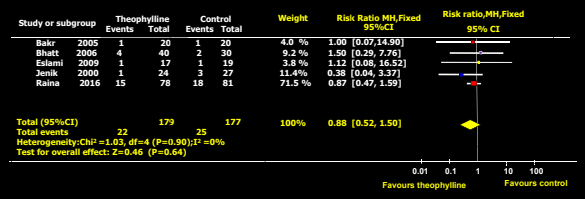
- Database searching for randomized clinical trials and quasi-randomized trials in PubMed/MEDLINE, Embase, Google Scholar and Cochrane renal group from 1970 to May 2018
- 6 trials involving 436 term neonates with birth asphyxia who received a single dose of theophylline
- Primary outcomes were incidence of AKI, serum creatinine levels and all-cause mortality

Pooled estimate showed 60% reduction in incidence of AKI in neonates with severe birth asphyxia after single dose of prophylactic theophylline



(Bhatt GC et al, Arch Dis Child 2019)

12% reduction of mortality in neonates who received prophylactic theophylline



(Bhatt GC et al, Arch Dis Child 2019)

The Impact of Erythropoietin on Short and Long-term Kidney-Related Outcomes in Extremely Low Gestational Age Neonates. Results of a Multi-center Double-Blind Placebo-Controlled Randomized Clinical Trial

David J. Askenazi, MD, MSPH[1], Patrick J. Heagerty, PhD[2], Robert H. Schmicker, MS[2], Patrick Brophy, MD[3], Sandra E. Juul, MD, PhD[4], Stuart L. Goldstein, MD[5], Sangeeta Hingorani, MD, MPH[4,*] on behalf of the PENUT Trial Consortium

J Pediatr. 2021 May ; 232: 65–72.

- Ancillary study to an RCT aiming at evaluating whether ELGANs (n=923) randomized to erythropoietin (n=469) have better or worse kidney-related outcomes during hospitalization and at 22–26 months cGA compared with those randomized to placebo (n=454).
- Prevalence of severe (stage 2 or 3) AKI was 18.2%.
- Recombinant erythropoietin appeared to protect ELGANs against long-term elevated SBP, but does not appear to protect from AKI, low eGFR, albuminuria or elevated DBP at 22–26 months cGA

What are the strategies to avoid nephrotoxic medications?

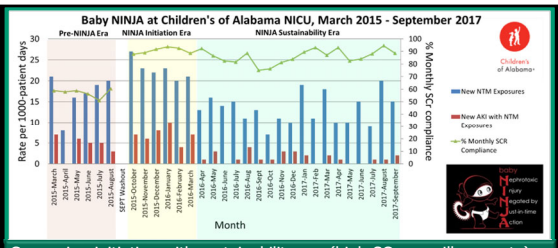
Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): Reduction in Nephrotoxic Medication-Associated Acute Kidney Injury in the Neonatal Intensive Care Unit

Christine Stoops, DO, MPH[1,2], Sadie Stone, PharmD[2], Emily Evans, PharmD[2], Lynn Dill, RN[1,3], Traci Henderson, RPh[2], Russell Griffin, PhD[4], Stuart L. Goldstein, MD[5,6], Carl Coghill, MD[1,2], David J. Askenazi, MD, MsPH[1,2,3]

J Pediatr 2019 December ; 215: 223–228.

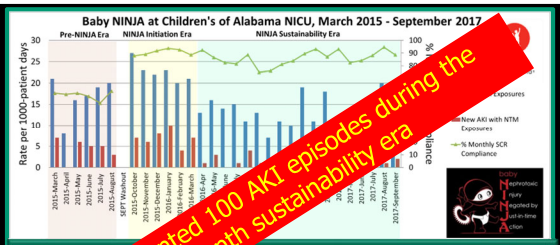
- Quality improvement project between March 2015 and September 2017 in a single center, level IV NICU
- Screened for high-risk nephrotoxic medication exposure
  - ≥3 nephrotoxic medication within 24 hours or
  - ≥4 calendar days of an IV aminoglycoside
- Daily serum creatinine obtained until 2 days after end of exposure or end of AKI

- Study divided into 3 eras:
  - Pre-Nephrotoxic Injury Negated by Just-in-time Action (NINJA)
  - Initiation
  - Sustainability
- Differences for 5 metrics across 3 eras were compared
  - SCr surveillance
  - High nephrotoxic medication exposure rate (per 1000 patient-days)
  - AKI rate (per 1000 patient-days)
  - Nephrotoxin-AKI percentage
  - AKI intensity (number of AKI days per 100 susceptible patient-days)



Comparing initiation with sustainability era (high SCr surveillance rate), there was a **reduction** in:

- High nephrotoxic medication exposures: 16.4 to 9.6 per 1000 patient-days (P=0.03)
- Percent nephrotoxic medication-AKI: 30.9% to 11.0% (P<0.001)
- AKI intensity: 9.1 to 2.9 per 100 susceptible patient-days (P<0.001)



Comparing initiation with sustainability era (high SCr surveillance rate) resulted in

- High nephrotoxic medication exposures: 16.4 to 9.6 per 1000 patient-
- Percent nephrotoxic medication-AKI: 30.9% to 11.0% (P<0.001)
- AKI intensity: 9.1 to 2.9 per 100 susceptible patient-days (P<0.001)

What are the strategies to decrease fluid overload?

JAMA Pediatrics | Original Investigation

Association Between Fluid Balance and Outcomes in Critically Ill Children
A Systematic Review and Meta-analysis

Rashid Alobaidi, MD; Catherine Morgan, MD, MSc; Rajit K. Basu, MD; Erin Stenson, MD; Robin Featherstone, MLIS;

JAMA Pediatr. 2018;172(3):257-268. doi:10.1001/jamapediatrics.2017.4540
Published online January 22, 2018.

- 44 studies involving 7505 children were included

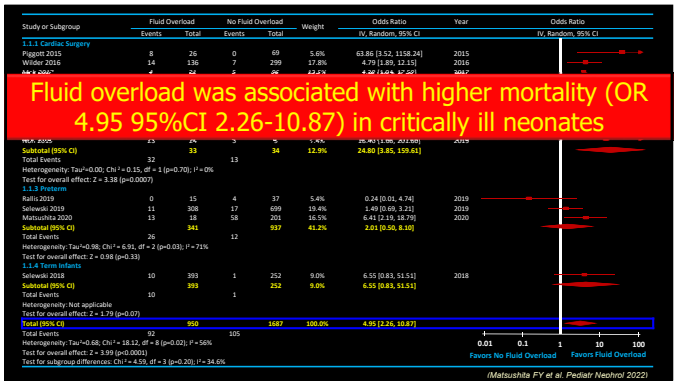
Fluid overload associated with increased risk of:	No of studies (no of children)	RR(95%CI)
In-hospital mortality	17 (2853)	**4.34 [3.01, 6.26]**
Mechanical ventilation >48 hrs	3 (631)	**2.14 [1.25, 3.66]**
AKI	7 (1833)	**2.36 [1.27, 4.38]**

Association between fluid overload and mortality in newborns: a systematic review and meta-analysis

Felipe Yu Matsushita[1] · Vera Lúcia Jornada Krebs[1] · Werther Brunow de Carvalho[1]

Pediatric Nephrology (2022) 37:983–992

- 17 studies involving 4772 neonates were included
- 3 (17%) studies involved neonates after cardiac surgery, 3 (17%) in neonates receiving CKRT, 1 (6%) after open laparotomy, 6 (35%) in preterm neonates, and 2 (11%) in term infants
- Primary outcome: all-cause mortality
- Secondary outcomes: AKI, intraventricular hemorrhage, mechanical ventilation, bronchopulmonary dysplasia



Fluid overload was associated with higher mortality (OR 4.95 95%CI 2.26-10.87) in critically ill neonates

(Matsushita FY et al. Pediatr Neohrol 2022)

MCQ 4

Is frusemide associated with improved survival in neonates?

A. Yes
B. No

Is frusemide associated with improved survival in neonates?

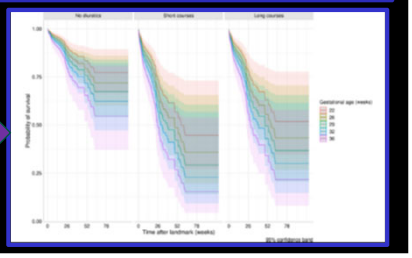
A. Yes
B. No

Diuretic therapy and acute kidney injury in preterm neonates and infants

Tahagod H. Mohamed[1,2,3] · Brett Klamer[1,4,5] · John D. Mahan[1,2,3] · John D. Spencer[1,2,3,4] · Jonathan L. Slaughter[3,6,7]

Pediatric Nephrology (2021) 36:3981–3991

- Multicenter retrospective study: 2121 preterms GA <37 wks with AKI
- Infants receiving short or long courses of frusemide associated with worse survival



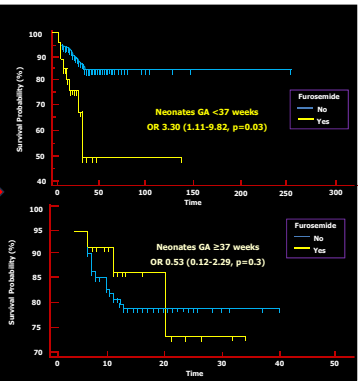
Use of furosemide in preterm neonates with acute kidney injury is associated with increased mortality: results from the TINKER registry

Rupesh Raina[1] · Sidharth Kumar Sethi[2] · Gopal Agrawal[3] · Sanjay Wazir[4] · Naveen Bajaj[5] · Naveen Parkash Gupta[6] · Abhishek Tibrewal[1] · Ananya Vadhera[7] · Shishir Mirgunde[8] · Binesh Balachandran[9] · Jagdish Sahoo[10] · Kamran Afzal[11] · Anubha Shrivastava[12] · Jyoti Bagla[13] · Sushma Krishnegowda[14] · Ananth Konapur[15] · Kritika Soni[2] · Khalid Alhasan[16,17] · Mignon McCulloch[18] · Timothy Bunchman[19]

Pediatric Nephrology (2024) 39:857–865

- Prospective online database involving 14 centers with 1852 neonates of which 32.4% (n=600) had AKI
- Frusemide used in 8.8% (53/600)

Frusemide use associated with increased mortality in neonates <37 weeks GA



Pediatric Nephrology (2021) 36:3807–3811
https://doi.org/10.1007/s00467-021-05201-w

EDITORIAL COMMENTARY

Diuretic use, acute kidney injury, and premature infants: the call for evidence-based guidelines

Jeffrey Segar[1] · Jennifer G. Jetton[2]

- Review of records from over 70,000 infants <37 weeks gestation and admitted within the first week of life identified 2379 infants with AKI
- 76% of infants with AKI received at least 1 dose of diuretics
- In neonates with AKI, treatment with diuretics was significantly associated with increased mortality, need for mechanical ventilation, and length of stay

(Mohamad TH et al, Pediatr Nephrol 2021)

MCQ 5

Does early institution of dialysis improve outcomes in AKI?

A. Yes
B. No
C. Maybe

Does early institution of dialysis improve outcomes in AKI?

A. Yes
B. No
C. Maybe

Updated American College of Critical Care Medicine Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock (2007)

$$\% \text{ Fluid overload} = \frac{[\text{total fluid (L)} - \text{fluid out (L)}]}{\text{admission weight (kg)}} \times 100$$

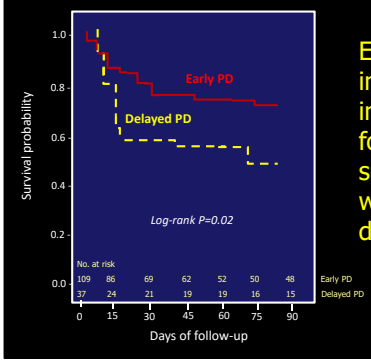
AKRT should be considered when fluid overload >10% in a critically ill child

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

Stéphane Gaudry*, David Hajage*, Nicolas Benichou†, Khalil Chaibi†, Saber Barbar, Alexander Zarbock, Nuttha Lumlertgul, Ron Wald, Sean M Bagshaw, Nattachai Srisawat, Alain Combes, Guillaume Geri, Tukaram Jamale, Agnès Dechartres, Jean-Pierre Quenot‡, Didier Dreyfuss‡

Lancet 2020; 395: 1506–15

- Systematic review of RCTs in MEDLINE, Embase, Cochrane Central Register of Controlled Trials from 1/4/2008 to Dec 20 2019
- 9 studies where 1879/2083 patients had severe AKI and were randomly allocated to delayed KRT 946 (50%) and early KRT 933 (50%) groups
- No significant difference in mortality at 28 days between delayed KRT (44%) and early KRT (43%) groups with risk ratio of 1.02 (95% CI 0.92-2.24)



Early initiation of PD in neonates and infants with AKI following cardiac surgery is associated with significant decrease in mortality

(Bojan M et al Kidney Int 2012)

What is the risk of CKD following neonatal AKI?

MCQ 6

Following recovery of AKI with normalization of serum creatinine, the neonate requires the which of the following parameters to be monitored annually: (Multiple answers)

A. No follow-up
B. Blood pressure measurement
C. Serum creatinine
D. Urine protein:creatinine ratio
E. Kidney ultrasound

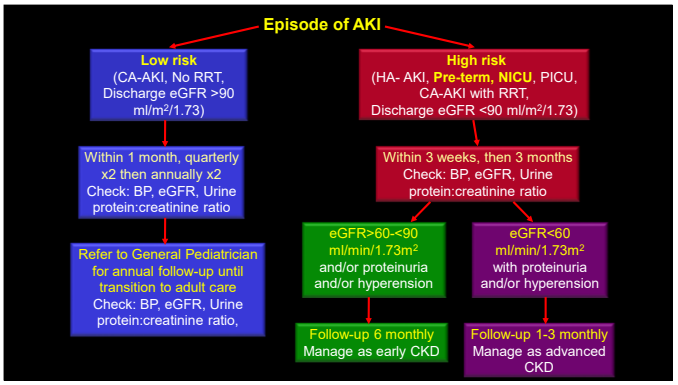
Following recovery of AKI with normalization of serum creatinine, the neonate requires the which of the following parameters to be monitored annually: (Multiple answers)

A. No follow-up
B. Blood pressure measurement
C. Serum creatinine
D. Urine protein:creatinine ratio
E. Kidney ultrasound

Long-term outcomes in neonates with AKI

Abitbol et al 2003: Infants <1000g FU: 7.5 yrs AKI (20)	ARF (peak sCr > 2.0 mg/dL for 48h Urine output < 0.5 ml/kg/h for 24h	**55% with low GFR (sCr) 25% with ESKD**
Bruel et al, 2016: Infants <33 wks FU 6.5 yrs AKI (25), non (49)	AKI: sCr (mg/dL) >1.6 (24-27 wks) >1.1 (28-29 wks) >1.0 (30-32 wks)	**No difference in microalbuminuria, eGFR (sCr) ELBW lower eGFR**
Masqood et al, 2017: FU 3.0 yrs AKI 2/3 (23), AKI 1 (87), non (112)	Modified KDIGO	**No difference in CKD (eGFR w/sCr) ELBW: higher DBP on discharge**
Harer et al, 2017: FU 5.0 yrs AKI (20), non (14)	Modified KDIGO (sCr only)	**AKI grp with more renal dysfunction (low eGFR, HPT, proteinuria)**

(Harer et al, J Perinatol 2020)



THE TAKE-HOME MESSAGE

- Pooled incidence of AKI in neonates was 30% with a mortality rate of 10% in large studies
- Higher incidence of AKI in babies <29 weeks GA
- Identifying neonates at risk of AKI may be useful in instituting early measures of prevention
- Early caffeine citrate administration associated with reduced incidence or severity of AKI in preterms
- Single dose of theophylline associated with reduction in AKI incidence in neonates with severe birth asphyxia

THE TAKE-HOME MESSAGE

- Fluid overload is an important cause of morbidity and mortality in AKI
- Early dialysis in neonates with AKI may be necessary to create fluid space for nutrition and drug delivery
- Infants with previous AKI are at risk of progressive chronic kidney disease in later life
- Follow-up of infants post-AKI is important with monitoring of blood pressure, proteinuria and eGFR


Do you have any Questions?