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Progressive medicine, exceptional care.

Review of Combined Liver Transplantation in Paediatrics

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Wits Transplant

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Outline

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- Overview
- PH1
- ARPKD
- HUS
- Broad Transplant Issues
- Our experience and lessons

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Overview

- 1st successful CLKT performed by Margreiter in Austria in 1984
- 10 – 30 annually worldwide
- Numbers increasing significantly

- Whilst selection crucial
  - Surgical technique
  - Immunosuppressive regimens
  - Monitoring graft function postoperatively crucial

CLKT

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- Spectrum most commonly congenital diseases affecting both organs
  - Primary hyperoxaluria Type 1
    - Most common indication
  - AR Polycystic Kidney Disease
  - Glycogen Storage Disease Type 1a
  - Heterozygous factor H deficiency with atypical haemolytic uraemic syndrome
    - Transplantation now redundant

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Table 1. Indications for CLKT in children

Indication	Our cohort, *n*	Literature, *n*
PH1	4	49
PKD	3	17*
Factor H deficiency	1†	7
Methylmalonic acidaemia		7
α1-antitrypsin deficiency		4
Cyclosporin toxicity		2
Failed prior liver transplant		2
Cystinosis		1
Drug toxicity		1
Glycogen storage disease 1a		1
Auto-immune hepatitis/hepatorenal syndrome		1
Sclerosing cholangitis/interstitial nephritis		1
Biliary atresia		1
Liver disease secondary to parenteral nutrition		1

CLKT = combined liver-kidney transplantation; PH1 = primary hyperoxaluria type 1; PKD = polycystic kidney disease.
*Polycystic kidney disease/congenital hepatic fibrosis.
†Heterozygous factor H deficiency with atypical haemolytic uraemic syndrome.

PH1

- Deficiency of hepatic peroxisomal enzyme
  - Alanine-glyoxylate aminotransferase (AGT)
  - Metabolise glyoxylate to oxalate and glycolic acid instead of glycine
  - Kidneys burdened eliminating large oxalate load
  - Deposition of calcium-oxalate crystals
    - Kidney
    - Systemically as GFR decreases

PH1

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- More severe when presents in infants
  - ESRD before 2 years of age
- By 15 years of age
  - 50% of patients will have developed ESRD

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PH1

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- Factors affect outcome and improve survival
  - Earlier diagnosis
  - Aggressive and effective pre-transplant dialysis
  - Overall clinical condition at the time of transplantation

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PH1

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- Isolated renal transplant not acceptable
  - 18% graft survival at 3 years
- Early Diagnosis
    - Isolated pre-emptive Liver Transplant in selected subjects to avoid ESRD
    - Timing difficult due to the heterogeneous (unpredictable) nature of the disease
- CLKT addresses
  - Primary metabolic defect
  - End organ damage (ESRD)

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PH1

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- Oxalate burden should not be underestimated
- Of interest
  - Despite a new liver
    - > 50% of renal graft failures following CLKT were due to oxalate deposition in the new kidney
    - Hyperoxaluria detectable up to 45 months post transplantation

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PH1

- European PH1 Transplant Registry
- 127 transplants were performed in 117 patients
  - 99 CLKTs
  - 22 iLTs
  - 6 iLT followed by iKT
- 10-year survival was 69% for all groups

PH2

- Defect of glyoxylate reductase/hydroxypyruvate reductase
- Also significant overproduction of oxalate and thus hyperoxaluria
- Clinical course more benign
- Only 20% experience ESRD
- Procedure of choice iKT

PH3

- Suggestion PH3 second most common form
  - Deficient enzyme is 4-hydroxy-2-oxoglutarate aldolase
  - No patient with ESDR described yet
  - Clinical symptoms
    - Predominantly recurrent urolithiasis
    - Resolve with time in most if not all patients

PH1: Peri-operative

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- High systemic oxalate burden

AND

- ESRD
- High risk prompt recurrence of oxalosis
- Aggressive pre-op haemodialysis
  - Serum oxalate level < 30 micromoles
- Simultaneous transplantation risk of early renal transplant failure
  - Sequential liver followed by kidney transplantation considered

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Organ Allocation

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Recipient defines surgical approach

- Timing
  - Pre-emptive liver
  - Sequential
  - Simultaneous
- Organ
  - Deceased donor
  - Living donor
- Anatomical variations
  - Whole
  - Split

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Organ Allocation

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Diagnosis

Disease severity

Patient weight

- Kidney transplant
  - Extraperitoneal
    - Left or right iliac fossa
- Transperitoneal
  - Anastomotic options
  - Position

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PH1: Peri-operative

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- Post op
  - High fluid intake
  - Crystallanization inhibitors
  - Daily HD to reduce oxalate load
    - Prevent oxalate deposition in new graft
  - Polyuria represent high oxalate burden post TX
  - As does refractory anaemia due to deposition in bone marrow

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Post Operative Concerns

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- Most common cause postoperative death
  - Sepsis in 55%
    - CLKT higher than both iLT or iKT
- Postoperative management high standard
  - Mandatory to avoid over immunosuppression
  - Close infectious surveillance

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Outcomes

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- Comparable outcomes
  - Kids > 15 kg
  - Kids < 15kg
- 5 year survivals
  - Patient 100%
  - Liver 80%
  - Kidney 93%

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ARPKD

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- Most frequently found ciliopathy
  - 1/20 000 live births
  - 6p21 encoding fibrocystin/polyductin
- Variable clinical progression
- Various forms distinguished depending on age at manifestation
  - Congenital
  - Neonatal
  - Infantile
  - Juvenile
- Most severely affected present with ESRD
  - Perinatal period or early infancy

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ARPKD

- Liver involvement
  - Congenital hepatic fibrosis or Caroli disease
  - May progress to portal hypertension, hypersplenism
  - Resultant thrombocytopenia and recurrent ascending cholangitis
    - Caroli syndrome

ARPKD

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- Whilst liver disease always present
  - Not always warrant transplantation
  - iKT is often all that is require
- Liver disease causing progressive and severe complications
  - CLKT

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Heterozygous factor H deficiency

Atypical HUS

- Factor H
  - Produced in the liver
  - Regulates activation of the complement cascade
    - Alternative pathway
- Qualitative or quantitative deficiencies in factor H
  - Uninhibited deposition of complement
  - Destruction of microvasculature and phenotype of HUS (Sort this out….)

HUS

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- Poor prognosis
  - ESRD or death in 50% of patients
- Outcomes following iKT are equally poor
  - Recurrences 50 - 100%
- CLKT addresses both the qualitative and quantitative factor H issues and restores renal function

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HUS

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- Eculizumab registered for the management of aHUS
- Recombinant, humanised monoclonal antibody targeting the complement protein C5
- Protects red blood cells from chronic intravascular haemolysis by preventing generation of the C5b9 complex, thus inhibiting activation of terminal complement, which is responsible for cell lysis
- Current recommendation
  - Kidney transplant combined with lifelong eculizumab therapy
- Lifelong cost prohibitively high

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HUS

- Alternative is CLKT
  - More aggressive
  - Potentially greater morbidity and mortality

- To reduce risk
  - Option one dose of eculizumab peri-operatively in CLKTs to reduce the complications related to uninhibited complement activation
  - Second dose can be held in reserve if necessary

- Where antifactor H antibodies exist a CKLT may need to be combined with lifelong plasma exchange and therapy aimed at reducing antibody levels

The Wits Series: Demographics

- 15 patients
- M:F = 7:8
- Age 29.4 to 212.2 months (mean = 116)
- No re-transplants

- Immunosuppression
  - Induction
    - Daclizumab (Zenapax) and methylprednisolone
  - Maintenance
    - MMF
    - Tacrolimus
    - Prednisone

Aetiology

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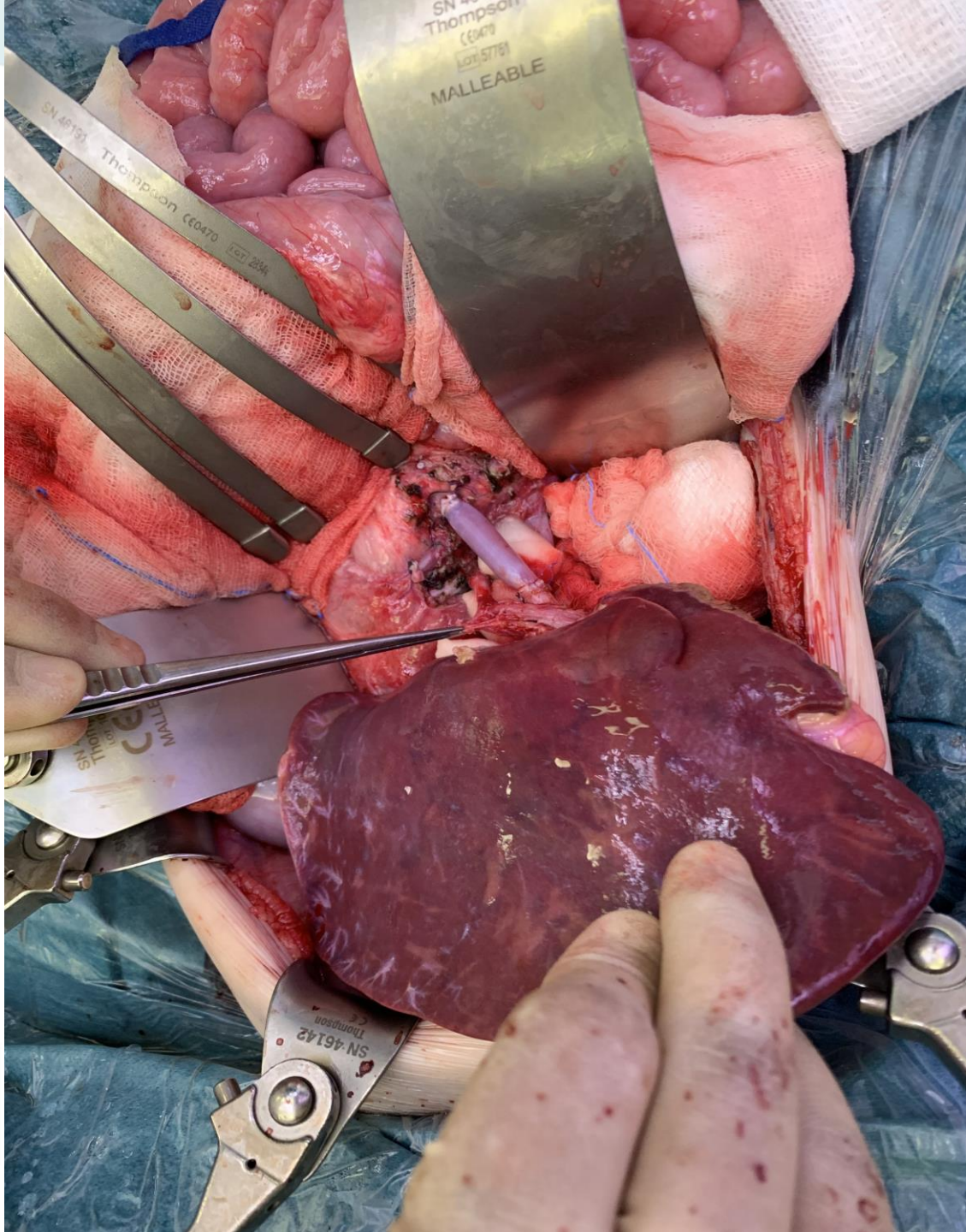
- Oxalosis = 9
- Haemolytic Uraemic Syndrome = 2
- AR Polycystic Disease (1 Caroli's) = 4



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Organ Utilization

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- All Simultaneous deceased donor transplants
- 10 whole liver and 1 Kidney
- 1 whole liver and 2 kidneys en bloc
- 3 Reduced livers 2, 3, (4) and kidney
- 1 Split right liver and kidney

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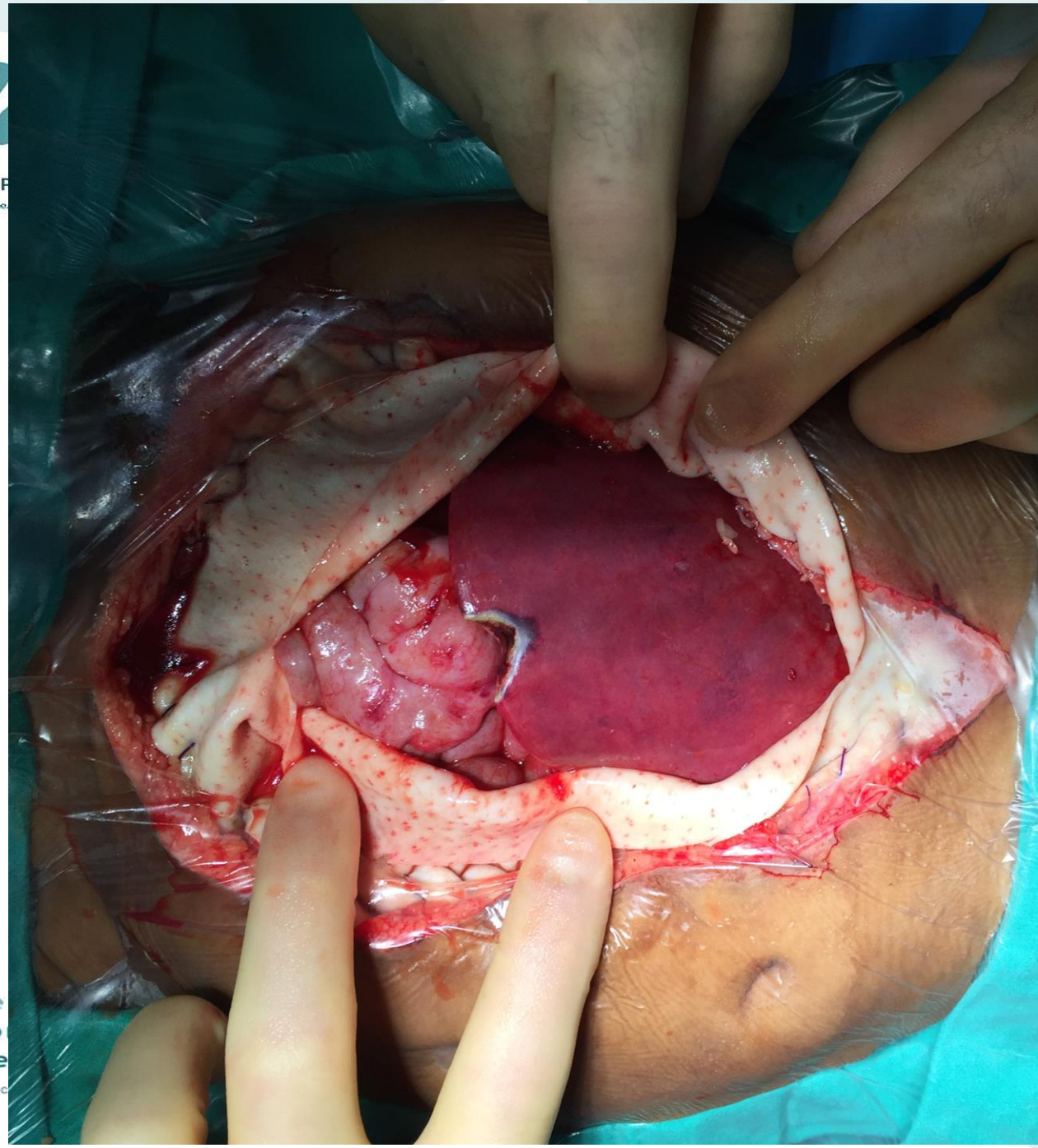
Morbidity

- 7 patients relooked
  - Bleeding
  - ACS secondary to Large for size
    - Decompression and Mesh
  - Wound haematoma
  - En bloc kidney transplant
    - Torsion of one kidney



Morbidities

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- Biliary = 4
    1. Cut surface leak (D12)
        - Drain
    2. Anastomotic leak (D1) then stricture (5 weeks)
        - Revised then PTC
    3. Cut Surface Leak
        - Drain
    4. Anastomotic leak
        - ERCP and stent

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Mortality

1. HAT and PVT
    - FHF
2. 20 days post Tx
    - MOF

- Ongoing follow up of remainder of cohort
    - Both liver and kidney functioning

Immunosuppression

- No specific recommendations
  - Tacrolimus
  - Steroids
  - MMF
- No data on tapering over time
- Immuno-protective effect of the liver
  - Lower incidence graft rejection on kidney
- Biopsy proven rejection 1st 12 months
  - 4 episodes

CLKT Lessons

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- Consideration availability (shortage) deceased donor organs
  - Pressure other patients on the waiting list
- Alternatives
  - Feasibility of RLD kidney as and when DD liver becomes available
  - Consideration simultaneous living donor liver and kidney
- Sizing
- Staging

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CLKT: Oxalosis Lessons

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- Measure serum oxalate
  - Target < 30
- Pre-operative haemodialysis 4 - 5 times per week
- 3 months post transplantation
  - Decrease systemic oxalate load
  - Mitigate any damage to the renal allograft by nephrocalcinosis or urolithiasis

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