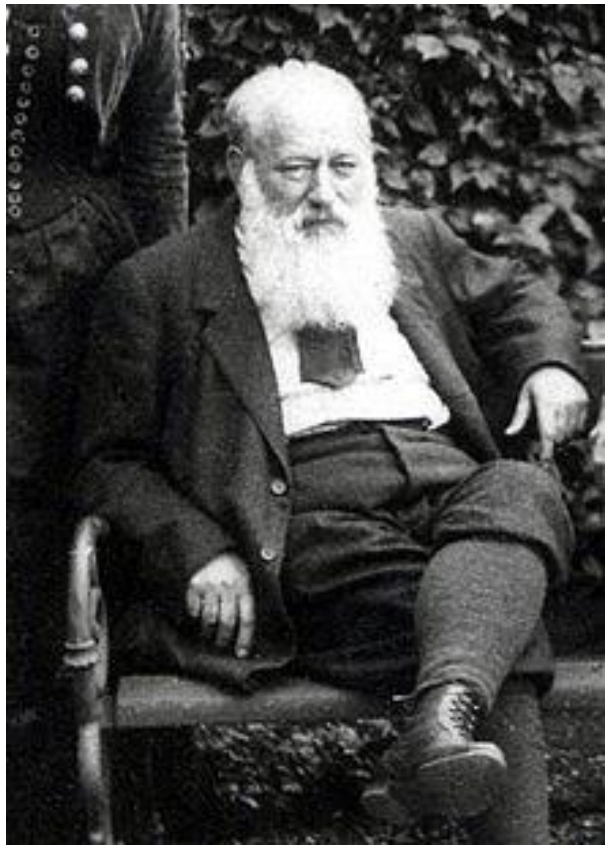
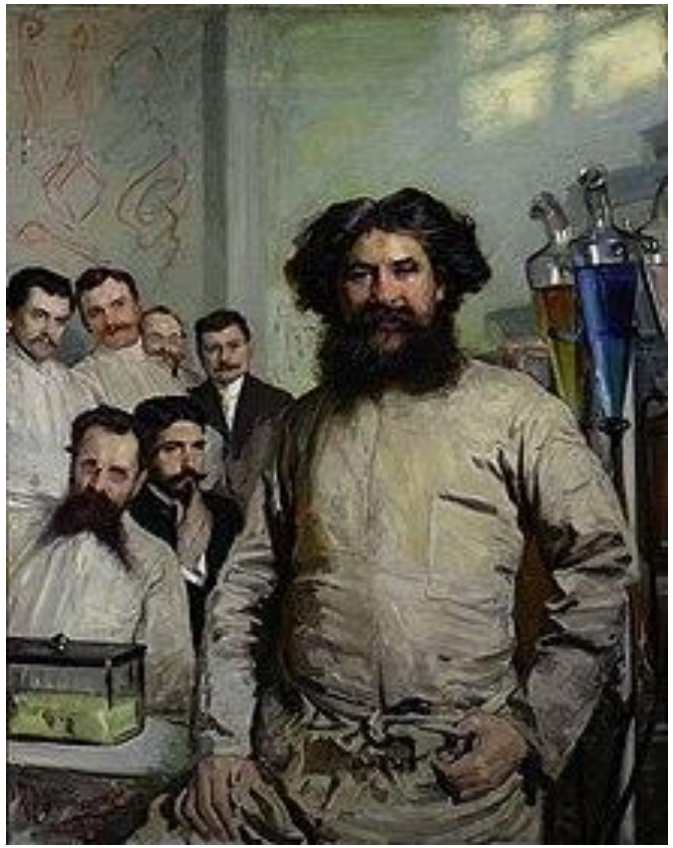
Crystal Balls of Theodor Billroth

16.05.2022

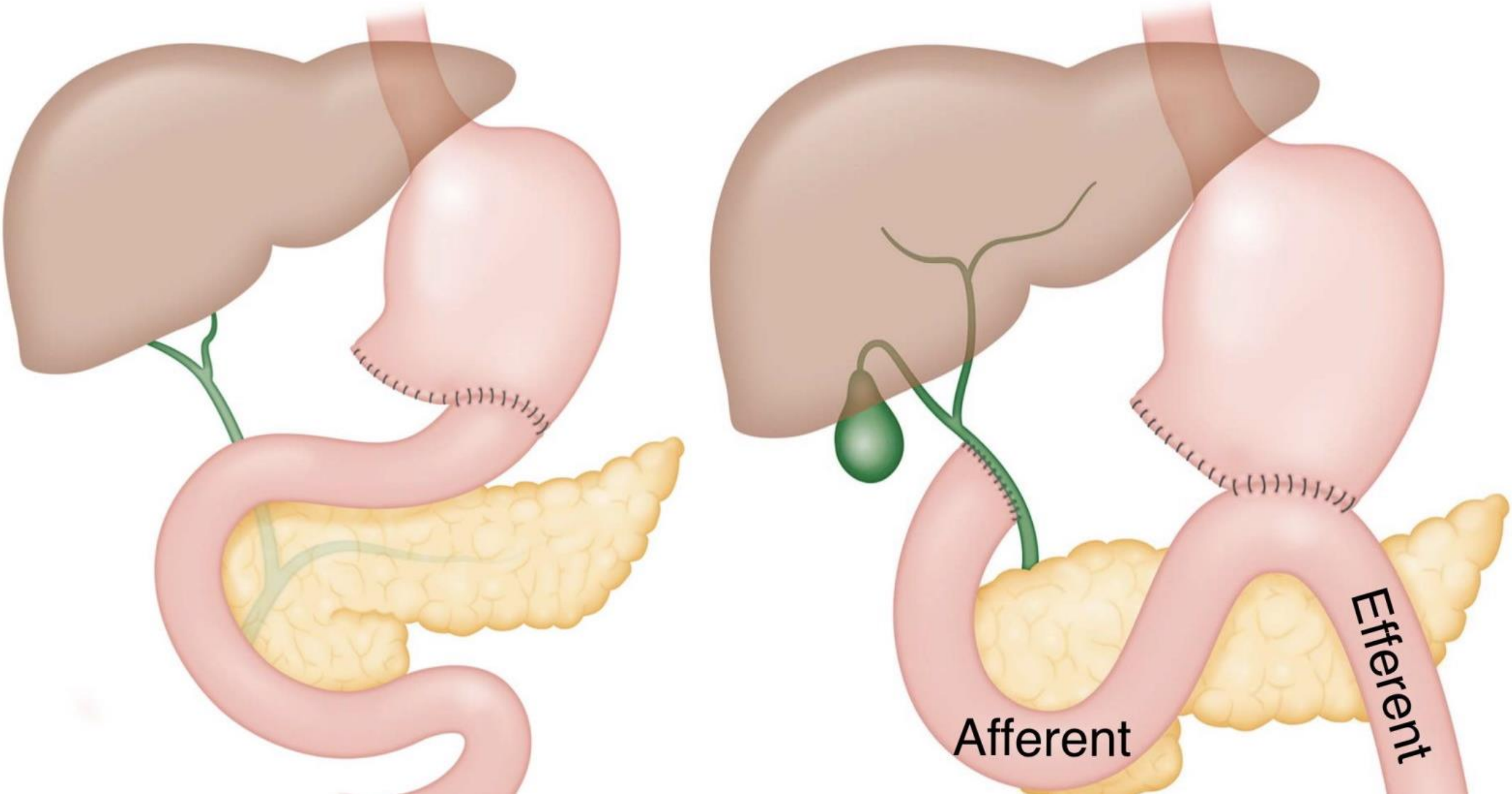
Theodor Billroth and Ludwik Rydygier





Billroth I = 1 Limb

Billroth II = 2 Limbs



- 80 year old gentleman had a normal renal function in 11.2018. His eGFR began to decline at an average rate of 9 ml/min per year. His creatinine was 123 (eGFR 48) in May 2019, creatinine 180 (eGFR 30) in May 2021 and then it peaked at 360 (eGFR 16) in August 2021. Bland urine, urine PCR 87 and ACR 12.

- No history of UTI, kidney stones, skin rash, rheumatism, discoloured urine or prostatism.

- Weight loss of 13 – 14g with dysphagia over the last 3 months. No other relevant systemic symptoms. Independent and active, exercises daily on treadmill, cycling and weights for years.

- Background
  - Type 2 diabetes diagnosed in 2007 with minimal diabetic retinopathy
  - Ischaemic heart disease / CABG in 2009
  - Hypertension diagnosed decades ago / unsure of control
  - Osteopenia
  - Previous partial gastrectomy for peptic ulcer disease in 1985
  - Constipation with longstanding iron deficiency anaemia / normal colonoscopy 2015

- Medications
  - Metformin 500mg TDS
  - Empagliflozin 25mg OD (began in 4.2021)
  - Aspirin EC 100mg OD
  - Simvastatin 40mg NOCTE
  - Cholecalciferol 1.25mg MONTHLY
  - Amitriptyline 100mg NOCTE
  - Folic acid 800mcg OD
  - Ferrograd 2 tablets OD
  - Hydroxocobalamin MONTHLY

- Blood pressure 110/62 mmHg, height 177cm and weight 65kg. Euvolumeic. Examination was unremarkable.

What is the likely cause of his kidney injury?

- ❑ Drug-induced tubulointerstitial nephritis
- ❑ Oxalate-induced acute kidney injury
- ❑ Diabetic kidney disease
- ❑ Hypertensive nephropathy
- ❑ Obstructive uropathy
- ❑ Glomerulonephritis
- ❑ Volume depletion

Investigations

- Secondary GN screen normal

- Renal ultrasound (2.2021): 3mm calculus in right kidney with mid-kidney scarring and 4mm calculus in the left kidney

- Kidney biopsy (3.2021)
  - H&E: 2 sclerosed glomeruli, 10 normal glomeruli, 15% interstitial scarring, moderate intimal fibrosis of arteries, negative IF
  - EM: mild scarring and hypertensive vascular changes

But, cortex sample was very small

Next…..

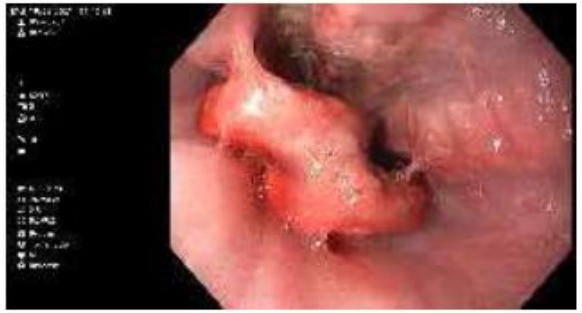
- Repeat kidney biopsy (7.2021)
  - 7 sclerosed gloms, 28 normal, 30 – 40% interstitial scarring, several tubules containing **oxalate crystals** and tubules containing necrotic cellular debris indicative tubular injury; and negative IF
  - EM: moderate interstitial scarring, mild features of ATN, **intratubular oxalate crystals** and glomerular basement membrane changes in keeping with diabetic nephropathy
- *Why…..?*

Laboratory results

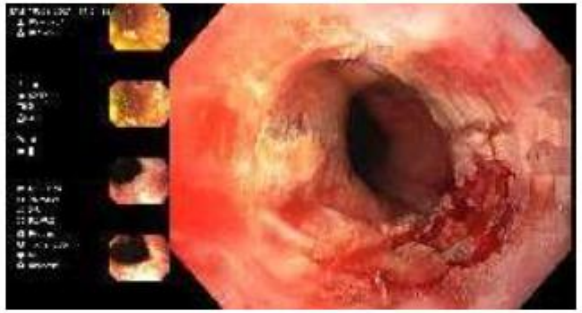
- 24 hour urine collections *(already commenced on potassium citrate)*
  - Urine volumes 1.46L to 1.84L
  - Sodium 244 mmol (100 – 250)
  - Potassium > 150 mmol (ref 35 – 90)
  - Calcium 1.4 mmol (ref 2.5 – 7.5)
  - Citrate 3.78 mmol (ref > 1.9)
  - **Oxalate 2937 micromol (ref < 450)**
  - pH 7.93
  - Glycerate and glycolate levels normal

- Bloods: K, Mg, Ca, PO4, HCO3-, urate and TSH were normal, PTH 15

Gastroscopy (8.2021)



1 Tablets stuck at GO junction



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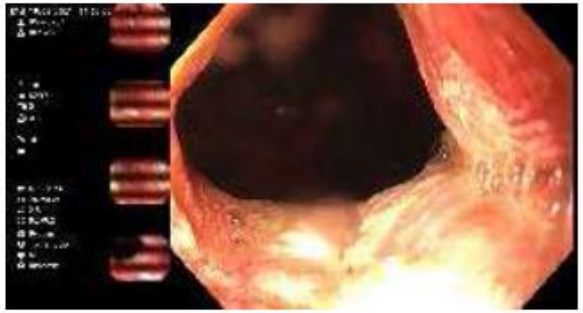

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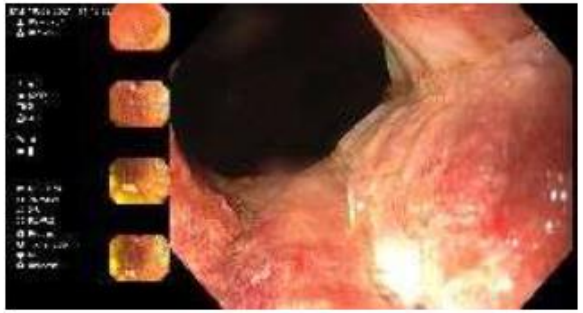

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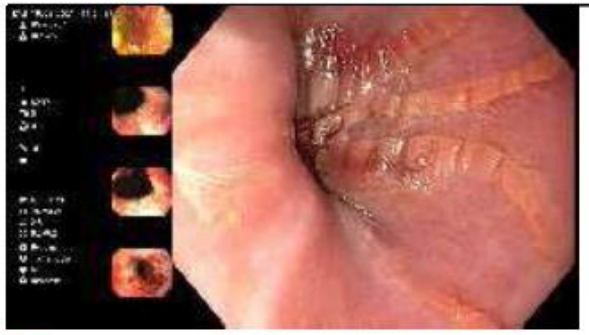

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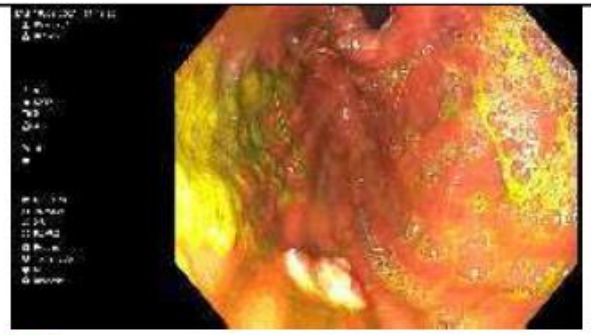

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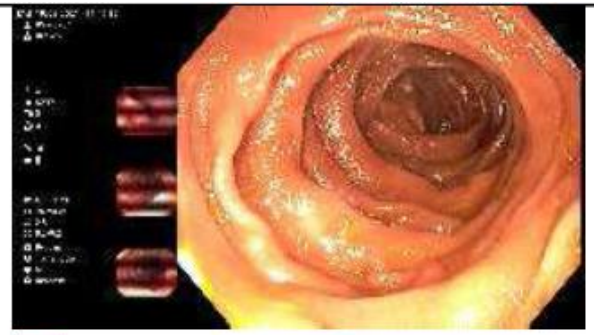

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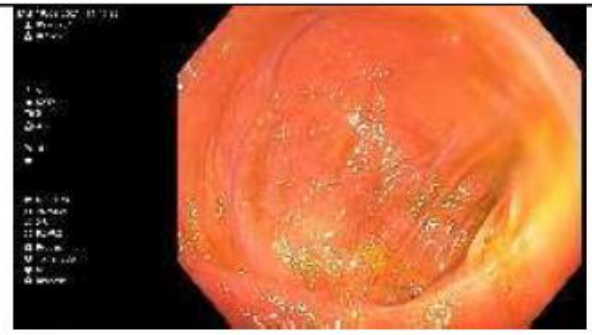


8 Anastomosis

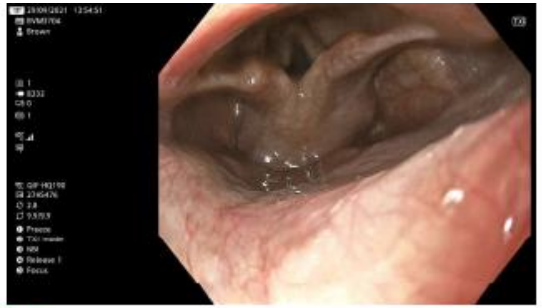
Diagnosis

Oxalate crystal induced acute kidney injury or oxalate nephropathy

Enteric hyperoxaluria

Treatment

- Increase fluid intake
  - Aim to produce urine output > 2L/day
- Calci-tab 1 tab BD
- Potassium citrate 5ml BD
- Famotidine 20mg BD
- Low salt diet
- Low oxalate diet
- High citrate diet
- Dietitian referral



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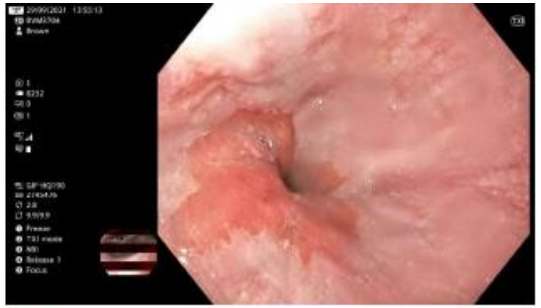
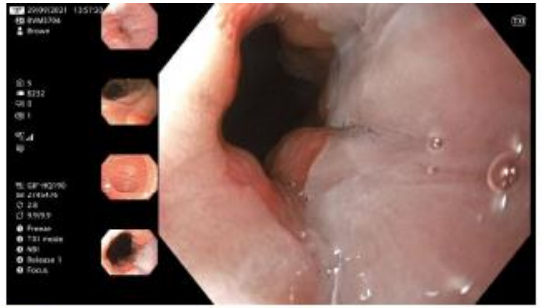
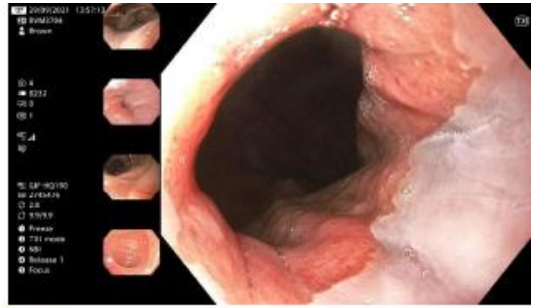


2 Oesophagus



3 Oesophagus



4 Gastric Cardia

Outcome

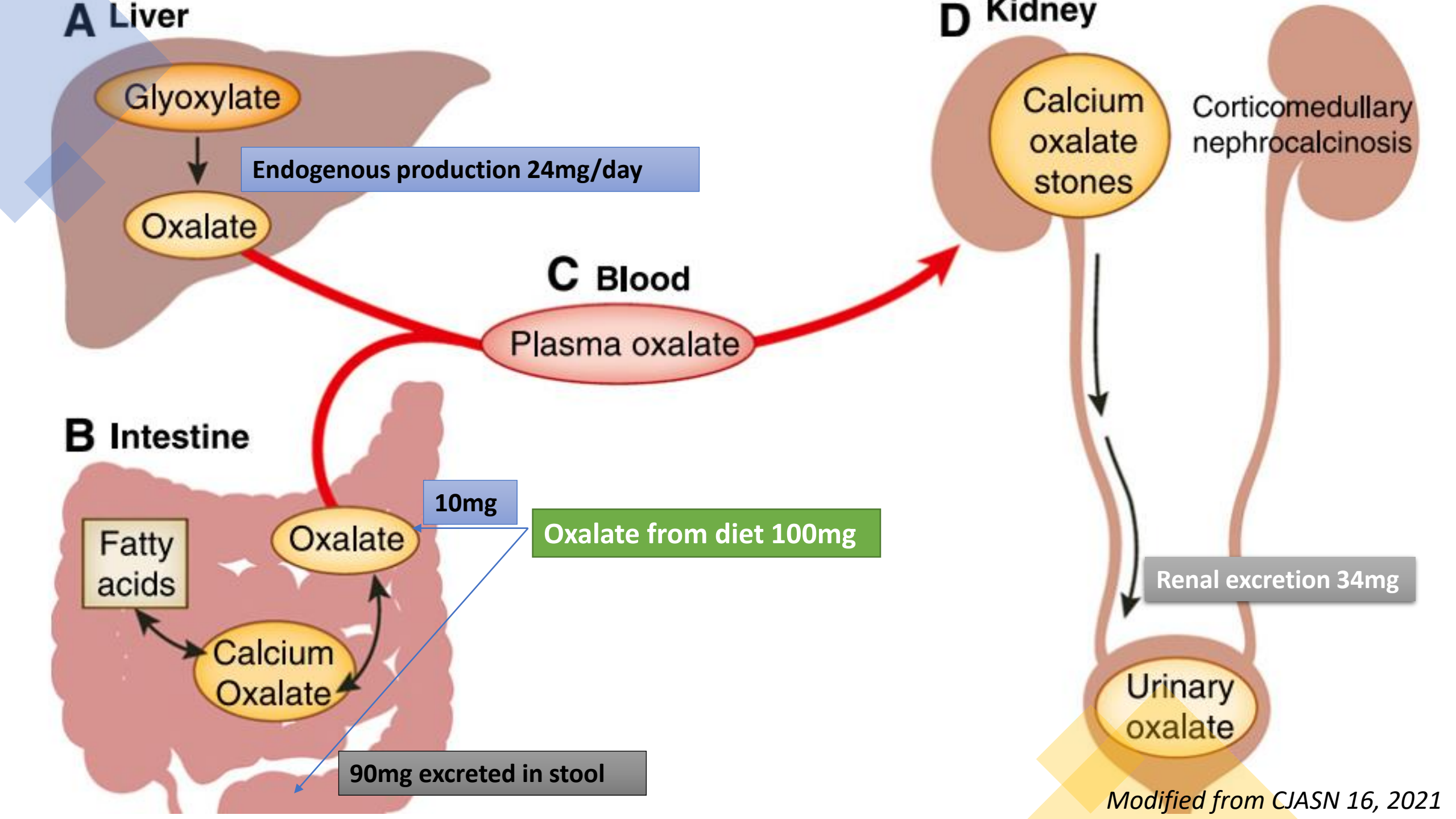
Repeat 24 hour urine collections:

- Urine volumes: 1.8 – 2.5L
- Oxalate 2937 -> 684

Creatinine 168, eGFR 33

Oxalate production and function

- Organic salt, C_2O_4
- Calcium oxalate is insoluble
- Oxalate transporter is SLC26A6
- Absorbed primarily from the colon, but can be anywhere in the GI tract
- Produced in the liver as part of glycolate metabolism.
- Secreted in the proximal tubule



Modified from CJASN 16, 2021

Definition of hyperoxaluria

- The normal upper level of urinary oxalate excretion is 40mg (440 micromol)/day
- Men – 43mg/day (larger body habitus and large average meal size)
- Women – 32mg/day

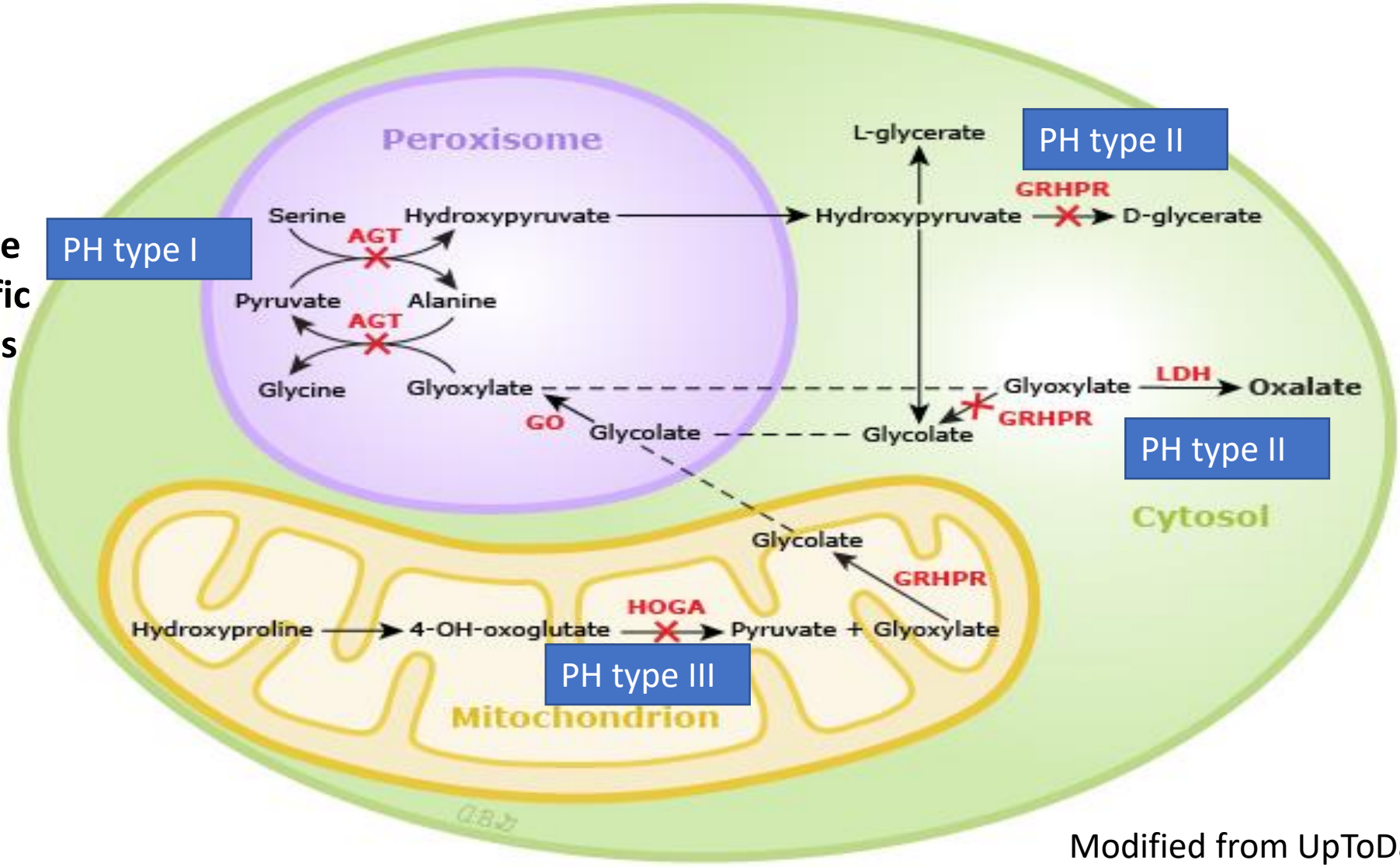
4 main types of hyperoxaluria

- Primary hyperoxaluria type I to III
- Enteric hyperoxaluria
- Dietary Hyperoxaluria
- Idiopathic or mild hyperoxaluria

Primary Hyperoxaluria

A rare disorder of glyoxylate metabolism in which specific hepatic enzyme deficiencies result in overproduction of oxalate

Urinary oxalate excretion > 1000mcg / day



Modified from UpToDate

	Age of onset (years)	Genetics	Enzyme/factor	Prevalence	Severity	Treatment if ESKD
PH type 1 (80%)	5.5 (1 – 50)	Autosomal recessive AGT-gene defect on chromosome 2	Dysfunction of ALA-glyoxylate aminotransferase (Pyridoxine (Vit B6) is a co-factor)	1-3 per million 1% of ESRD in paediatric population is due to PH1 in European and Japanese studies	More likely to develop ESKD. 50% by age 15 without treatment	Kidney and liver transplant
PH type 2 (10%)	3.2 – 7.4 (0.1 – 41)	Autosomal recessive GRHPR gene on chromosome 10	Dysfunction of the enzyme glyoxalate/hydroxypyruvate reductase (GRHPR) (Increased L-glyceric acid in urine)		Less likely than type 1 25- 30% reach ESKD (median age 40 years) 30% normal renal function	Kidney transplant
PH type 3 (10%)	2	Mutations in HOGA1 (DHDPSL) gene On chromosome 9	Reduced mitochondrial 4-OH-2-oxoglytarate aldolase activity (Also has increased hypercalciuria. Increased urinary hydroxy-oxo-glutarate can be used for diagnosis)		No risk of ESKD	

WJN 2015, KI 2009 and UpToDate

Secondary hyperoxaluria

- Dietary Hyperoxaluria
  - Consumption with foods rich in oxalate such as chocolate, cocoa, leafy green vegetables (rhubarb and spinach), black teas, nuts, peanut butter and starfish fruit
  - Ethylene glycol

- Enteric hyperoxaluria
  - Increased intestinal oxalate absorption associated with fat malabsorption due to malabsorptive bariatric surgery, small bowel disease, or cystic fibrosis
  - Absence of intestinal oxalate degrading bacteria (*Oxalobacter formigenes*)

Enteric hyperoxaluria and calcium oxalate stones

- Underdiagnosed
- Stone incidence 3 - 7% higher postoperatively compared with preoperatively
- Calcium binds to unabsorbed fatty acids leading to increased free oxalate
- Increased colonic permeability to oxalate induced by non-absorbed bile acids
- A reduction in bacterial breakdown of oxalate due to decreased *oxalobacter formigenes*
- Volume depletion, metabolic acidosis, a low urine pH and a marked decrease in urinary citrate excretion

Prevention and Management

- Treat the cause
- Urine output > 2L/day - fluid intake is dependent on urine output (add the deficit to the daily intake)
- Low salt diet
- Low oxalate diet
- Reduce non-dairy animal protein intake
- Reduce sugar intake
- Normal calcium diet
- High citrate / phytate diet

- Potassium citrate to correct metabolic acidosis +/- reduced urinary citrate excretion if present
- Oral calcium carbonate (1 to 4g/day) to bind oxalate in the intestinal lumen *(generally not recommended; timing is NB if taken)*
- Thiazide diuretic to reduce calcium excretion in urine if needed

- Metabolic surveillance at 2 months, 6 months and then yearly