Oxalate nephropathy

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CKJ Review

CKJ REVIEW

Oxalate nephropathy: a review

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CLINICAL RESEARCH

Etiologies, Clinical Features, and Outcome of Oxalate Nephropathy

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Outlines:

- ✓Intruduction
- ✓Prevalence
- ✓Causes of ON
- ✓Clinical Presentation and Features
- ✓Treatment

INTRODUCTION

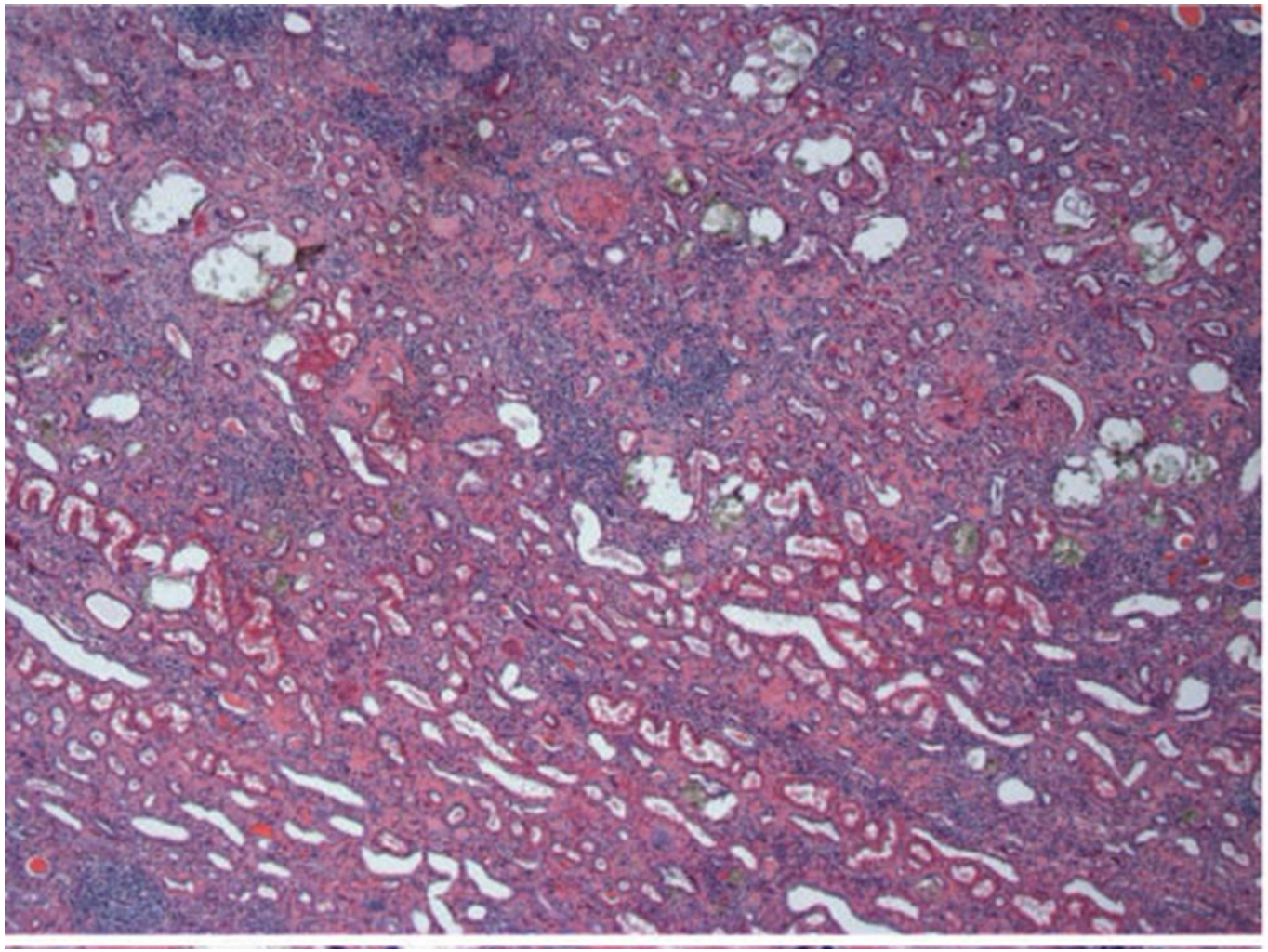
- ✓**Oxalate nephropathy (ON)** is a potentially **underestimated cause of kidney failure** characterized by **an acute and/or chronic decrease** in kidney function associated with the **massive deposition of calcium oxalate crystals**, in **kidney tubules** and **renal parenchyma**.

- ✓**Term ON** implies a **pathological diagnosis** that include typically **acute tubular injury** and an associated **acute/chronic interstitial nephritis** or **fibrosis**.

- ✓**Nephrocalcinosis** is also often used as a term to **describe calcification of the renal parenchyma** as seen on **radiological imaging**.

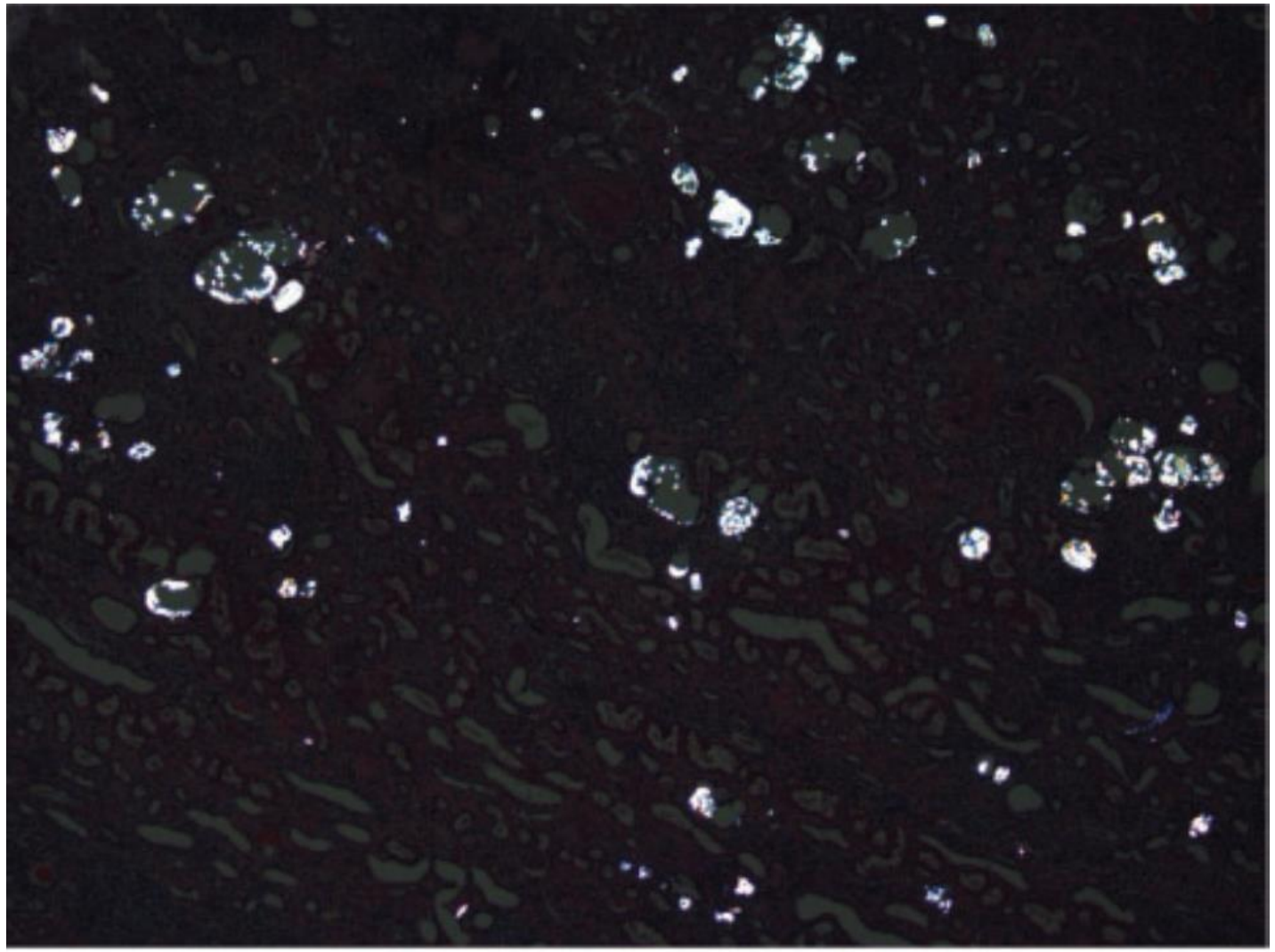
Renal oxalosis

Massive deposition of oxalate crystals is noted in tubules with associated **advanced chronic tubulointerstitial disease** with **atrophy** and **dropout** **of tubules** and **prominent interstitial fibrosis** and **nonspecific inflammation** (H&E, bright field, 40X).



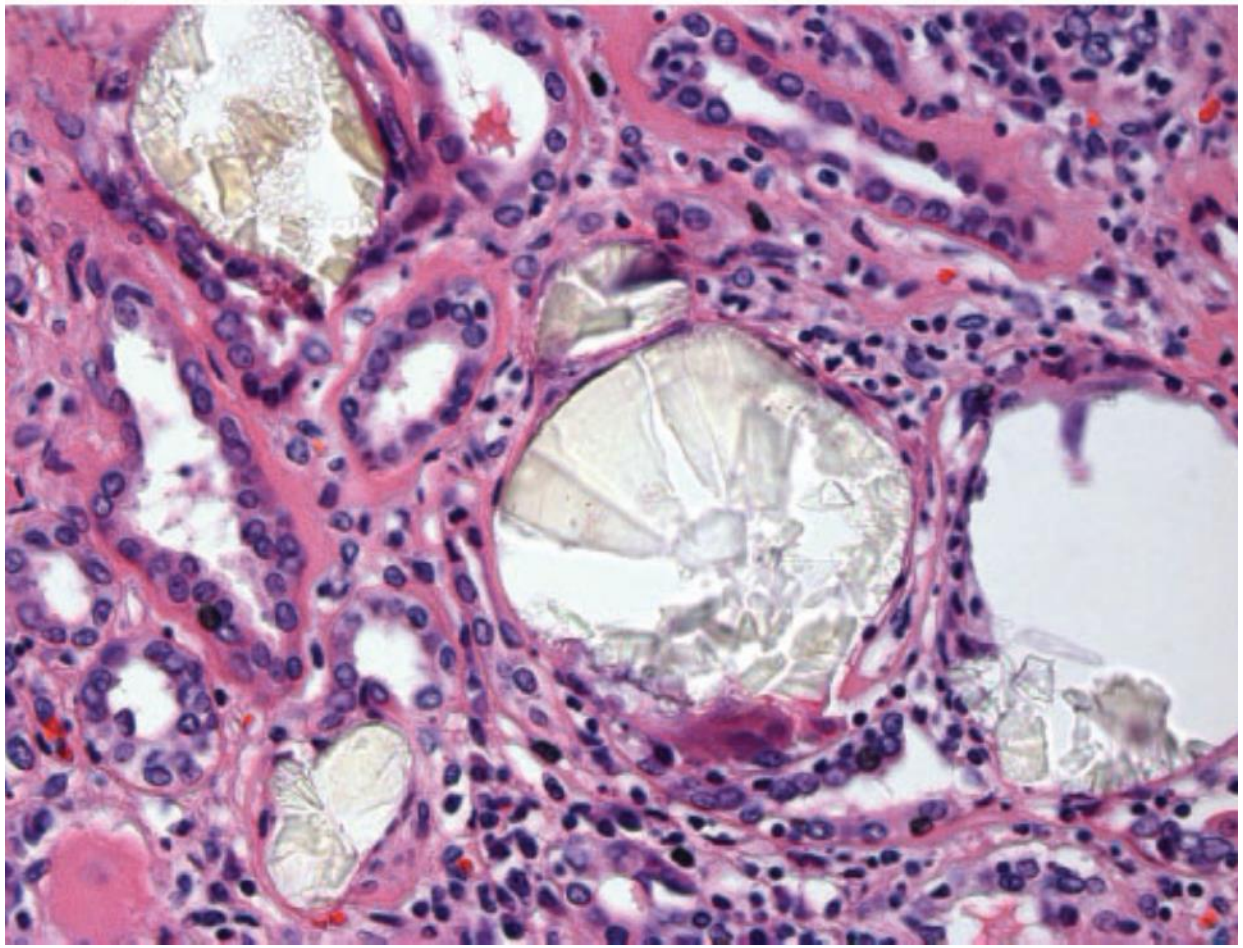
Renal oxalosis

Same area visualized under polarized light reveals **numerous intratubular crystals** (H&E, polarized light, 40X).

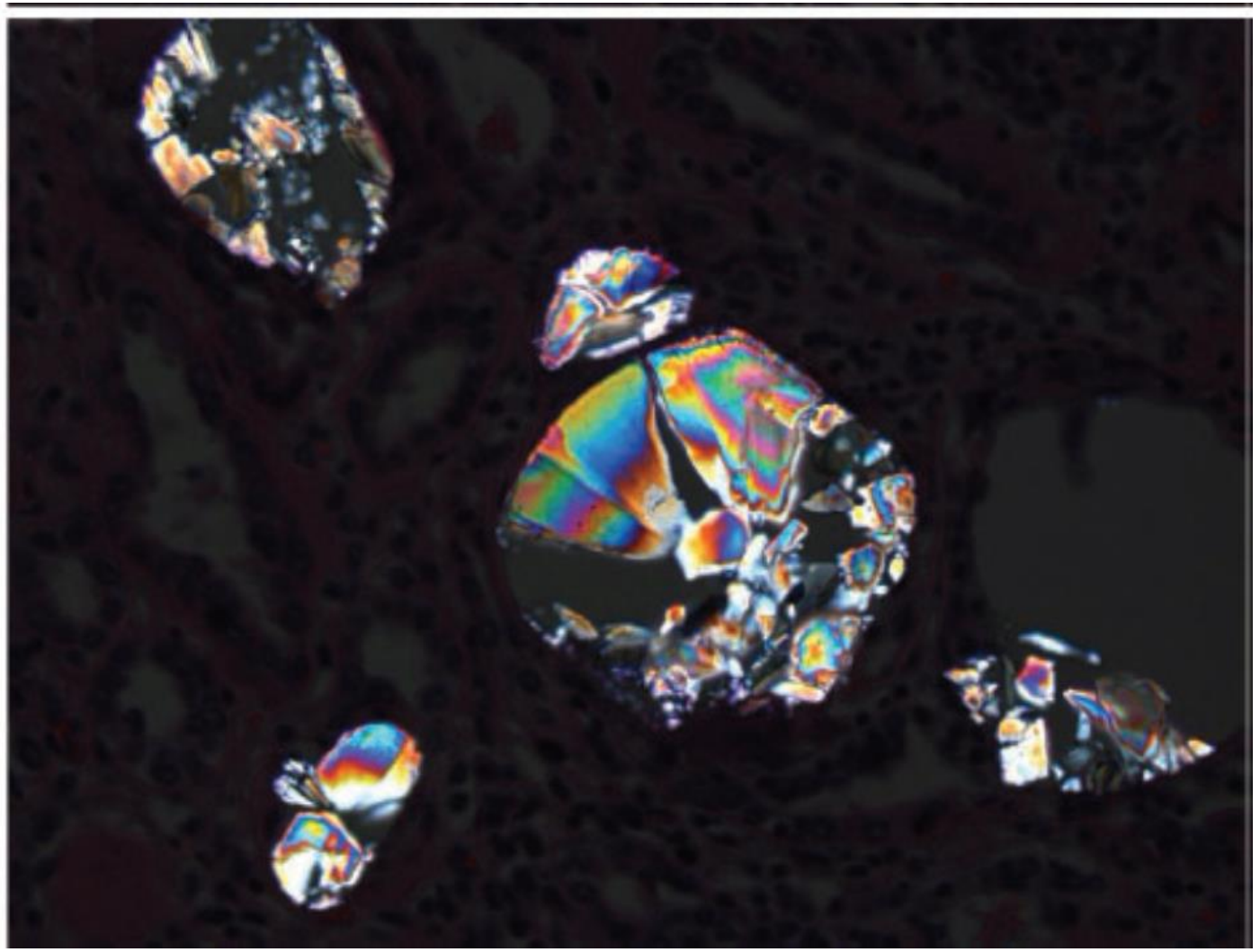


Renal oxalosis

Intratubular oxalate crystals are often **transparent** or reveal **yellow or gray color**, with **needle** or **other shapes** of crystals (H&E, bright field, 600X).



Same area visualized **under polarized light** reveals **colorful crystals** (H&E, polarized light, 600X)



- ✓**Oxalate nephropathy** may occasionally result in adults from **primary oxalosis**, an **inborn error of glyoxylate metabolism leading to overproduction of oxalate.**

- ✓However, it results **more frequently** from **secondary**, **enteric hyperoxaluria**.

PREVALENCE

- ✓**The overall prevalence of ON has <u>not been clear</u>** as a significant amount of the literature has been based on case reports.
- ✓Two recent reviews have addressed found that **ON made up 1% of native kidney biopsies**.

CAUSES OF ON

1. Primary hyperoxaluria
2. Enteric hyperoxaluria
3. Ingestions

CAUSES OF ON

Primary hyperoxaluria

Primary hyperoxaluria

- ✓**Primary hyperoxaluria (PH)** is a group of **autosomal recessive disorders** causing primarily hepatic **overproduction of oxalate**, due to **accumulation of the oxalate precursor glyoxylate.**

- ✓This leads to **calcium oxalate nephrolithiasis** and **multisystem deposits of calcium oxalate,** including **in the kidneys**, and accounts for **1–2% of pediatric ESKD.**

- ✓While **the median age of onset is 5.5years**, it can **sometimes present in adulthood with kidney stones or kidney failure**, and **should be considered in cases of hyperoxaluria and ON** without another obvious cause.

PH Type 1 (PH1)

- PH Type 1 (PH1), which accounts for **80% of PH cases**, is also the **most severe subtype**.
- It is due to a **deficiency of hepatic alanine glyoxylate aminotransferase (AGT)**,which **normally catalyzes the metabolism of glyoxylate to glycine.**

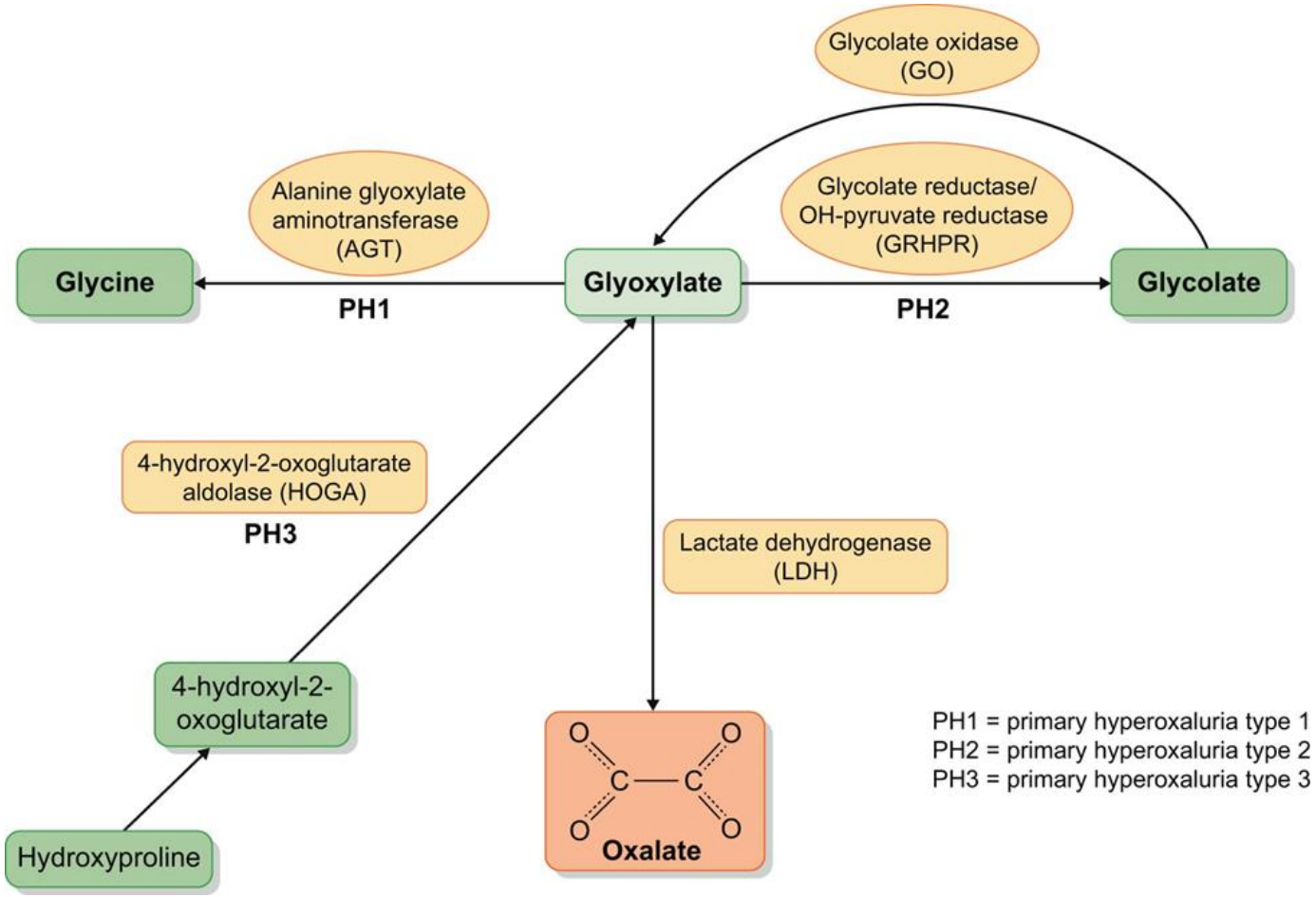
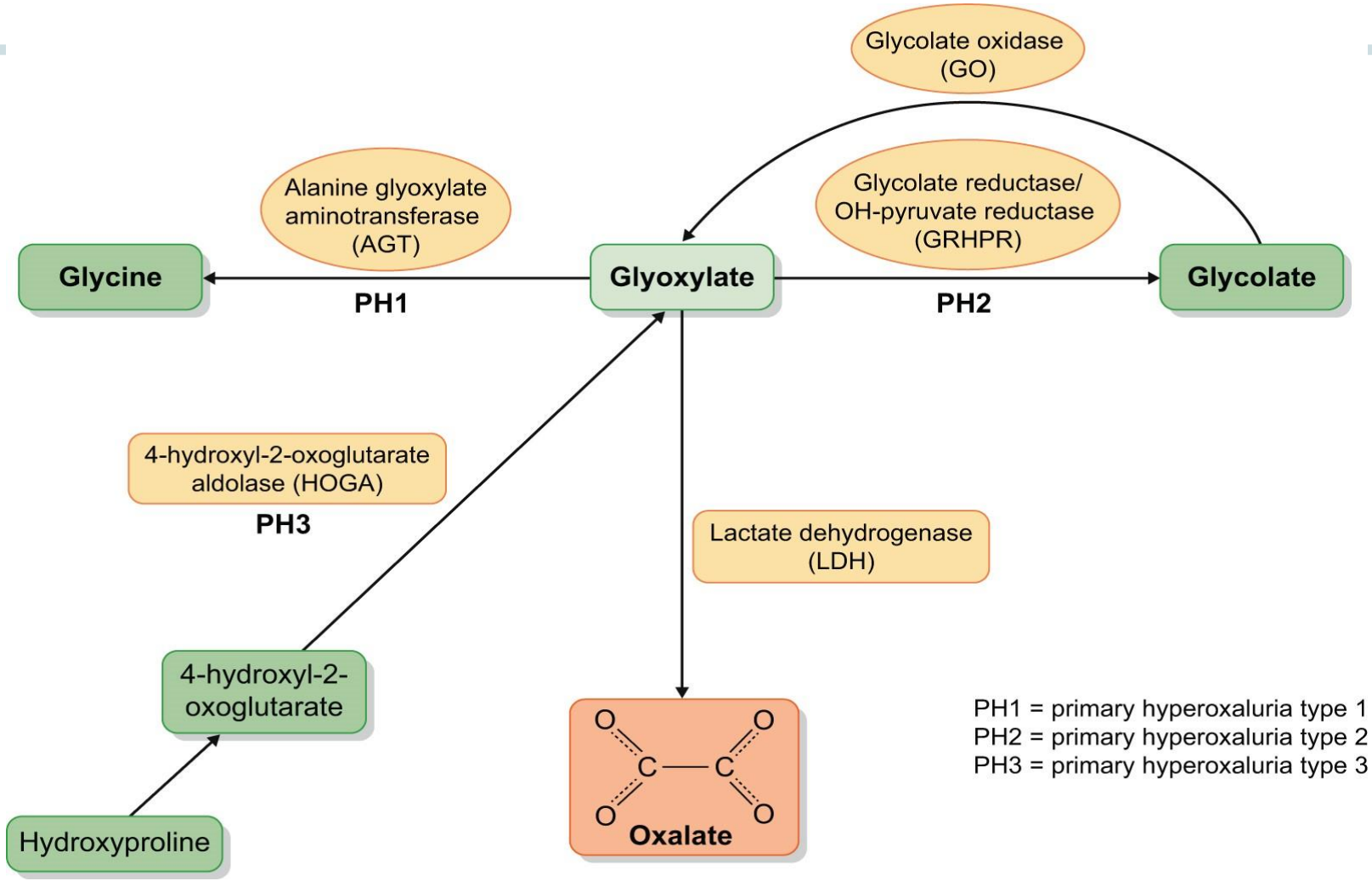


FIGURE 2: Simplified hepatic pathways of glyoxylate metabolism



Primary hyperoxaluria

- ✓A definitive diagnosis of PH requires **genetic testing**, such as for a **mutation in AGXT**, which encodes AGT, in PH1.

- ✓It is notable that the **urinary oxalate excretion** tends to be higher in **PH (>88mg/day)** as opposed to **44–70mg/day in enteric hyperoxaluria(EH).**
- ✓However, **there is enough overlap** that a definitive distinction between PH and enteric hyperoxaluria **cannot generally be made based on urinary oxalate excretion alone.**

Primary hyperoxaluria

- ✓**Systemic oxalosis**, due to **very high plasma oxalate levels**, is **common in PH** as renal failure progresses, but this is seen only **very rarely in other forms of hyperoxaluria**.

- ✓In patients with **renal insufficiency**, **very high plasma oxalate levels** might be **useful in distinguishing PH** from other forms of kidney disease, including **secondary hyperoxaluria**

CAUSES OF ON

Enteric hyperoxaluria

Enteric hyperoxaluria (EH)

- ✓**Enteric hyperoxaluria (EH)** is defined by hyperoxaluria occurring in the setting of **fat malabsorption** or **steatorrhea**.
- ✓Normally, **calcium binds oxalate** in the bowel to form **insoluble calcium oxalate** that is excreted in the feces.
- ✓In a state of fat malabsorption, **calcium is bound by free fatty acids and becomes unavailable for oxalate binding**.
- ✓There is then **increased soluble oxalate** available to be absorbed by the bowel.

- ✓Free fatty acids and bile salts may also directly **increase colonic permeability to oxalate.**
- ✓An **intact colon** appears likely to **be important for oxalate absorption.** and hyperoxaluria in EH has generally not been observed in patients with **ileostomies after colectomy**
- ✓**Oxalate absorption also occurs in the proximal gut** as evidenced by an **increase in urinary oxalate in response to an oral oxalate load** in patients with **ileostomies** in one study

- ✓**Solute-linked carrier 26 (SCL26) anion exchangers**, which are a family of transporters that mediate **transcellular oxalate transport**, are differentially expressed along the gut.
- ✓Although it is felt that **most oxalate absorption** likely occurs **paracellularly.**
- ✓The risk of **calcium oxalate precipitation** is likely worsened by **volume depletion from diarrhea** as well as **bicarbonate loss**, which can lead to **metabolic acidosis** and **hypocitraturia**.

❑Causes of enteric hyperoxaluria:

- **Fat malabsorption** from various causes:

✓**Chronic pancreatitis**

✓**Pancreatectomy**

✓**Roux-en-Y gastric bypass surgery** (recent procedure of choice for malabsorptive bariatric surgery)

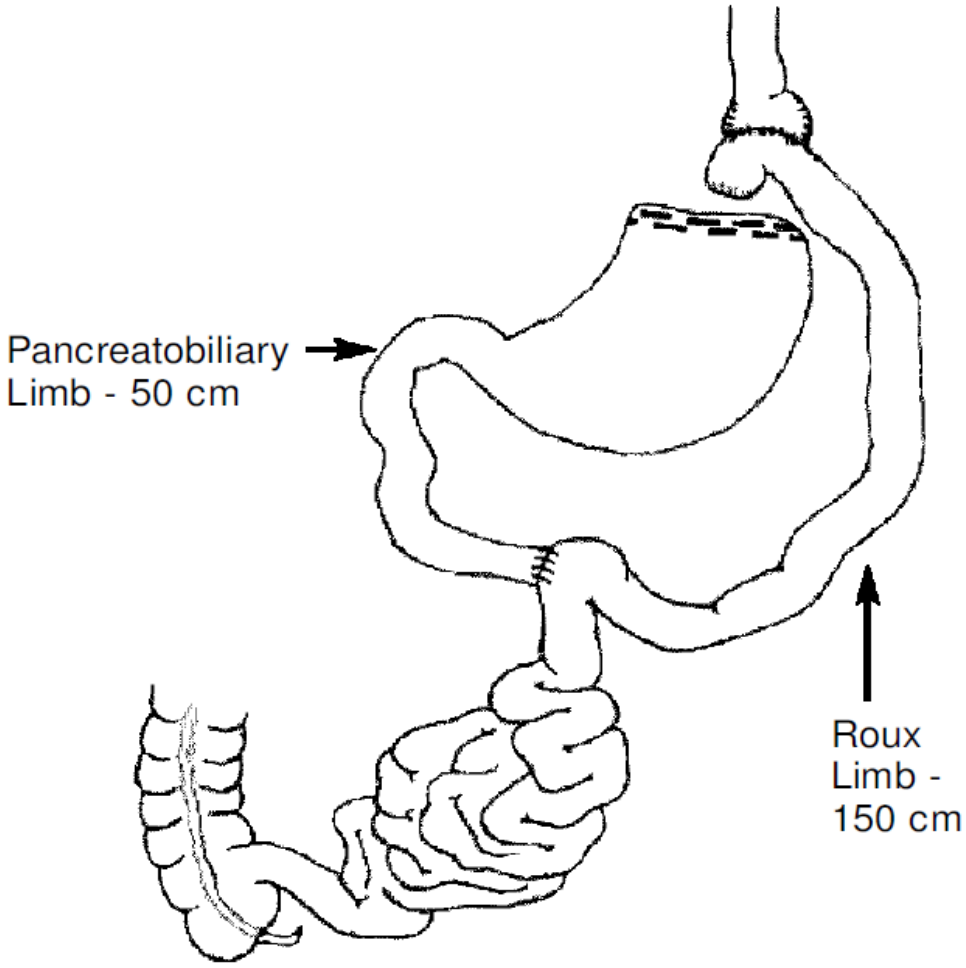
✓**Short bowel syndrome**(jejunoileal bypass, the first surgical treatments for obesity; bowel resections for inflammatory bowel disease (IBD))

✓**Crohn's disease**

✓**Use of Orlistat**

Roux-en-Y Gastric Bypass Surgery

- The **surgical technique** involved creation of a **15-ml proximal gastric pouch** and creation of a **150-cm Roux-limb**.
- The **pancreatobiliary limb** was approximately **50 cm**.
- Surgery was performed using both the open (midline incision) and laparoscopic approaches.



- **Decreased intestinal oxalate degradation** secondary to reduced intestinal colonization with **Oxalobacter formigenes.**

Fat malabsorption

enteric hyperoxaluria

jejunoileal bypass

- ✓**One of the first surgical treatments for obesity.**
- ✓This procedure involved **bypassing much of the small bowel**, causing **significant malabsorption**.
- ✓This procedure was largely **abandoned** by 1979 due to **high morbidity**, including the development of **renal failure in as many as 35% of patients.**
- ✓Both **nephrolithiasis** and **ON** were frequent complications.

- ✓**Malabsorptive bariatric surgery**, such as **jejunoileal bypass** and **Roux-en-Y surgery**, **is strongly associated with ON**, **this has not been seen with restrictive weight loss surgeries** such as **sleeve gastrectomy**, where the **small bowel is not bypassed**.

Orlistat

- ✓**Orlistat**, a **weight loss agent** **that also causes** **fat malabsorption**, has similarly been recognized to **cause hyperoxaluria and ON.**
- ✓Brand and Other Names:**Alli**, **Xenical**
- ✓Mechanism of Action: **Inhibits gastric and pancreatic lipases**, **prevents triglyceride hydrolysis** resulting in **decreased absorption of dietary fats.**

CAUSES OF ON

Ingestions

- ✓**Ingestions** include the **direct consumption of oxalate in foods with high oxalate** content, and also the **ingestion of oxalate precursors**.

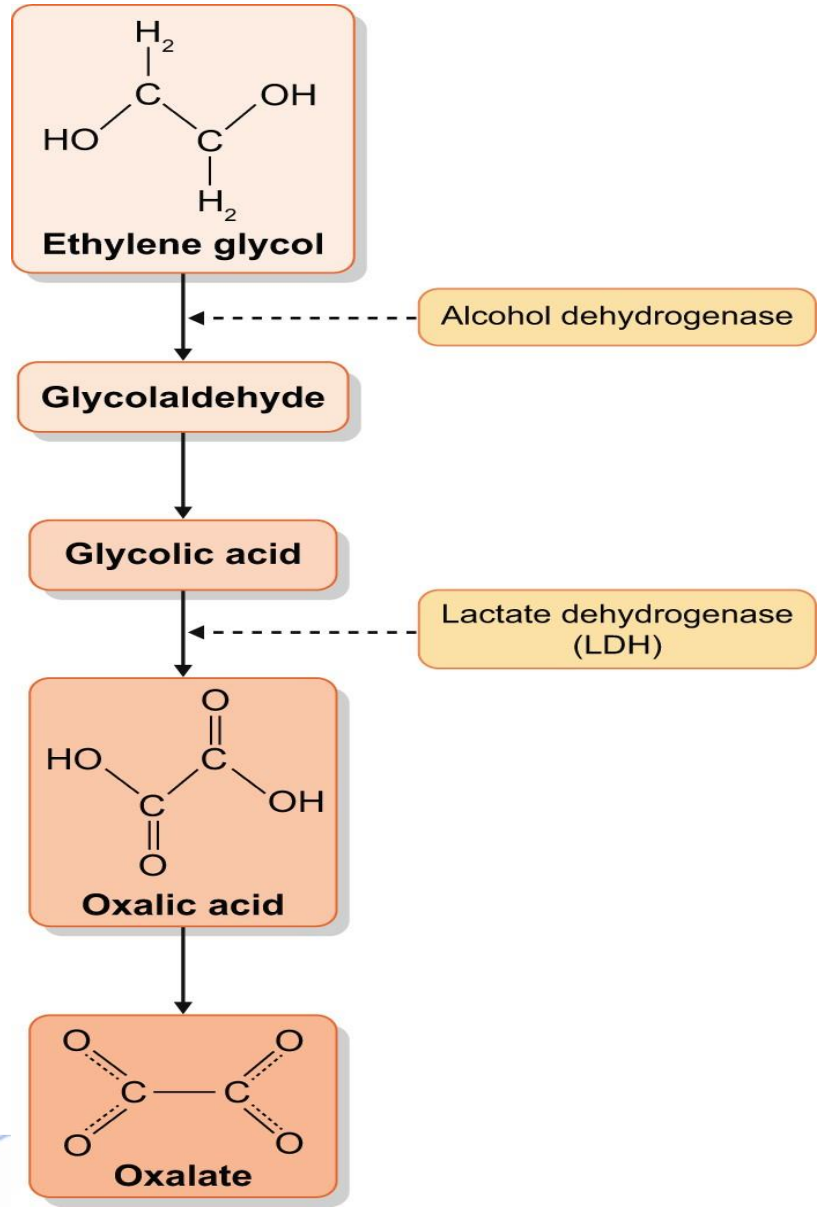
ethylene glycol (EG)

- ✓A classic and dramatic cause of **ingestion-related ON** is **ethylene glycol (EG)**.

- ✓**EG** is the active ingredient in **antifreeze**, but is also present in **a number of solvents**, **paints** and other **industrial and commercial products.**

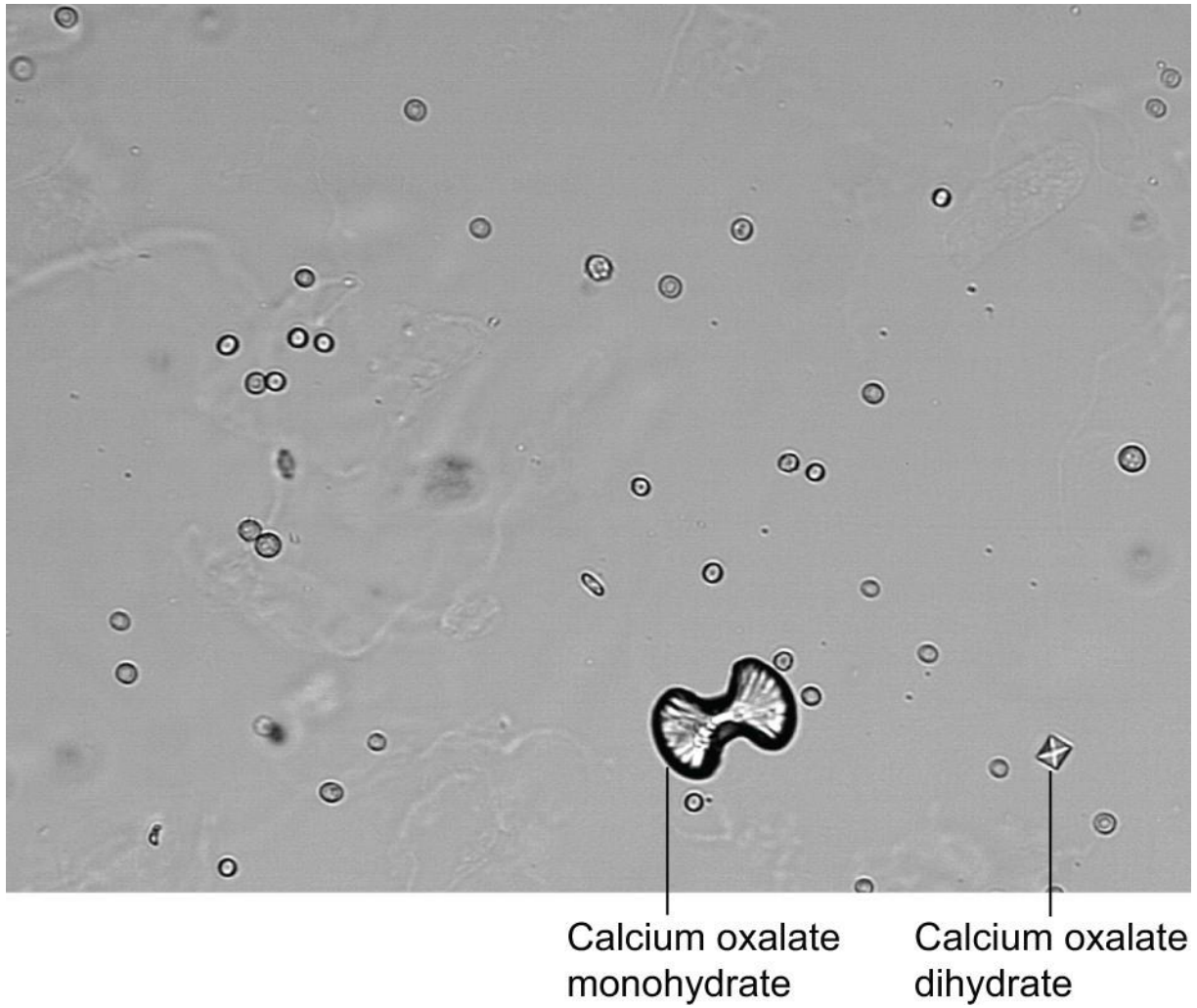
Ingested EG is metabolized in the **liver** to **oxalic acid** and causes **acute ON** with **acute tubular injury** and **oxalate crystal deposition in tubules**.

Metabolism of ethylene glycol to oxalate



ethylene glycol (EG)

There are frequently numerous **urine calcium oxalate crystals** present in the urine that can be a sign of the diagnosis.



- Multiple case reports of ON associated **high dietary oxalate intake** from a number of sources:
  - Due to ingestions of the **oxalate precursor vitamin C** (ascorbic acid).
  - These reports have generally involved **excessive intake of high oxalate foods** or **megadoses of vitamin C**, though some cases have been reported involving **more moderate amounts**, especially with **chronic intake**.

- ✓There have been reports of ON from **juicing of vegetables**, such as **spinach smoothies** in one report and an assortment of **high oxalate vegetables** (together with vitamin C) in another.

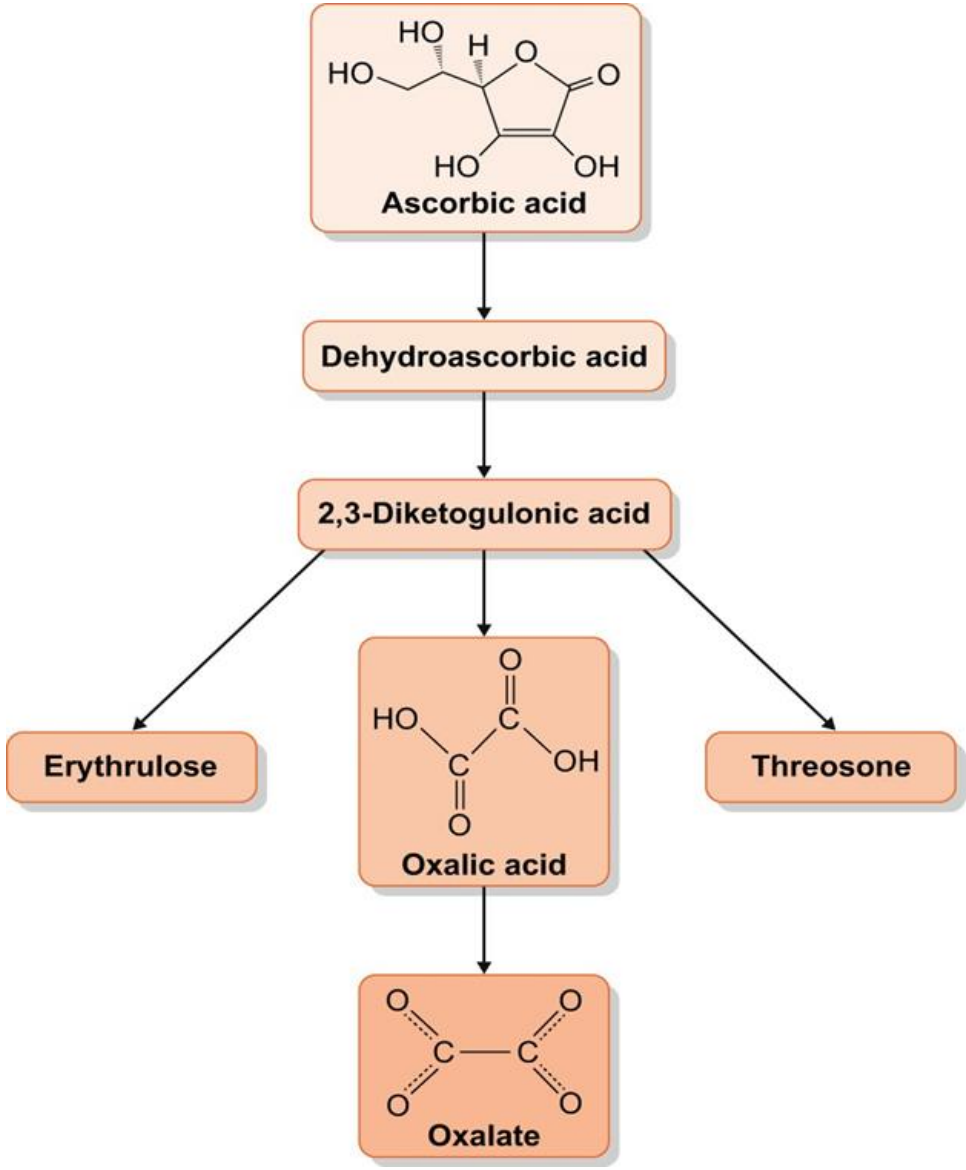
- ✓It has been speculated that **juiced oxalate foods may be more effectively absorbed** in the intestine via **the paracellular pathway** via **solvent drag** and because of **dilution of calcium by water**.

- ✓Recently, the most frequent case reports have seemed to involve **star fruit (carambola)** and **vitamin C supplements**.

Vitamin C

- ✓**Vitamin C** is likely a **more bioavailable source of oxalate** than **food**.
- ✓This is because oxalate in food is complexed with calcium(and to a lesser degree magnesium), limiting absorption.
- ✓**vitamin C** is taken by a large segment of the population, sometimes at very high doses.
- ✓ It has recently also used at **high intravenous doses** as a **treatment for sepsis**, including in patients **with COVID-19 infection.**
- ✓It should also be noted that there is **a significant amount of vitamin C in common beverages** such as **apple juice** or **orange juice** **(800 mg/L)**.

Metabolism of ascorbic acid (vitamin C) to oxalate



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Star fruit

- ✓**Carambola**, also known as **star fruit**, is the fruit of *Averrhoa carambola*, a species of tree native to tropical Southeast Asia/
- ✓It is a fruit-bearing tree of the genus *Averrhoa*, family Oxalidaceae.

- ✓**Star fruit** may be a **frequent culprit**, even though it is estimated **to contain less oxalate** than **spinach** or **rhubarb** by weight, possibly because **it can be consumed as a concentrated juice** or can be eaten easily in **large quantities**.
- ✓Star fruit may contain a **neurotoxin**(**caramboxin**) as well, and there have been reports of **acute neurological symptoms** from star fruit.

Table 1. Reported ingestions causing ON

Substance ingested	Quantity of typical reported ingestion causing biopsy confirmed ON	Notes
Star fruit (*Averrhoa carambola*)	200–3000 mL of pure juice 6–12 fruit in 1 setting [28–32]	One case reported ingestion of only 200 mL as remedy for diabetes. One case only reported chronic intake of 5–6 fruit over 1 month and then four fruit over 4 days [29]
Vitamin C [23–27, 46, 49–54, 57]		
Oral	2–6.5 g daily	One case reported ingestion as low as 480–960 mg vitamin C daily for 4 months [26]
IV	4–5 g daily	Two cases reported in COVID+ patients receiving 50 mg/kg 4×/day vitamin C for sepsis [23]
Irumban puli (*Averrhoa bilimbi*)	150–400 mL juice/day [43]	Irumban puli (*A. bilimbi*) is a local fruit in South India which has relatively high oxalic acid content and is drunk as a beverage Oxalate content of the fruit was 25.1 mg/100 g of the fruit [42]
Peanuts	100–243 g peanuts daily for 2–3 months [39–40]	–
Cashews	1 kg of cashews/week for 4 months [38]	–
Almonds and almond-containing marzipan	150–200 g of almonds and 50–100 g of almond-containing marzipan daily [41]	–
Rhubarb	500 g fresh weight/day for >4 weeks [44]	–
Chaga mushroom powder	4–5 teaspoons/day of Chaga mushroom powder for 6 months [48]	11.2 g of oxalate in 100 g of the powder; it was used as a remedy for liver cancer [48]
Black iced tea	Sixteen 8 oz glasses daily [45]	Daily consumption of oxalate >1500 mg in one case report [45]
Juicing	Celery, carrots, parsley beets with greens and spinach taken with Vitamin C in one [47] and two cups spinach/day in the other [55]	The oxalate content was estimated at ~1300 mg/day in each report
Nafronyl oxalate	7 g over 2 days [36]	19 mg oxalate/100 mg Nafril capsule Was given to patient for toothache and otalgia Used to treat peripheral and cerebrovascular disease [36]

Table 2. Foods with high oxalate content and estimated amounts

Substance	Oxalate content in mg/100 g
Purslane	910–1679
Spinach varieties	320–1260
Garden orach	300–1500
Rhubarb	260–1235
Sorrel	270–730
Cocoa	170–623
Beet leaves	121–920
Beet root	76–675
Almonds	431–490
Cashews	231–262
Hazelnuts	167–223
Peanuts	96–705
Carambola/star fruit	80–730
Buckwheat	269–271
Soy	179–187
Coffee	50–150
Black tea (100 mL brewed)[a]	48–92

[a]Tea 100 g fresh weight content estimated much higher (300–2000), green tea (6–26) and herbal tea (0–8) much lower estimates/100 mL.

Clinical Presentation and Features

- ✓There have been four published series of patients with biopsy-proven ON, comprising more than a few cases, published relatively recently.
- ✓The key clinical data are for these series.

Patients who had Roux-en-Y gastric bypass

- ✓**Most of the patients** had underlying **diabetes** and **all** had **hypertension**.
- ✓**All patients** presented with **acute renal failure (ARF), often superimposed on chronic kidney disease (CKD)**, with a mean serum creatinine at presentation of **5.0 mg/dL.**
- ✓**Mean** and **median** times from **surgery to ARF** were **33** and
- ✓**12** months, respectively.
- ✓**urine or serum oxalate levels** done and they were reported as **‘elevated’.**

- ✓**Biopsies** were notable for abundant **tubular calcium oxalate deposits** in **intraluminal** and **intracellular** areas, and also focally in the **interstitium and** accompanied **by diffuse tubular injury**, **tubular atrophy** and **interstitial fibrosis (IF).**

Series of 12 patients with chronic pancreatitis

- ✓**Hypertension** was present in **67%**, **diabetes** in **75%**.
- ✓Many of the patients had a **recent history of diarrhea**, **diuretic use** and/or **use of angiotensin-converting enzyme inhibitors** or **angiotensin receptor blockers**.
- ✓**One-third of patients** had been given **antibiotics** shortly before presentation.
- ✓On presentation with ON, mean serum creatinine was 587 mmol/L or **6.6 mg/dL**.

✓**<u>On biopsy</u>**,there were:

- **Oxalate deposition**
- **Acute tubular injury in 64%**
- **Chronic interstitial nephritis in 32%**
- **Acute interstitial nephritis in 12%**

In summary

- ✓**ON is likely not rare**, especially among those with risk factors such as **bowel disease**.
- ✓Most cases have other **underlying risk factors** for worsening kidney disease such as **older age**, **diabetes** and/or **hypertension**, and **underlying CKD**.
- ✓Aside from **oxalate deposits**, **tubular injury** is the **most common pathologic finding.**
- ✓**Renal imaging** was generally **unremarkable** when done, without evidence of **nephrocalcinosis**, though some cases had renal stones present.

- ✓**Low estimated glomerular filtration rate (eGFR)**, **hypovolemia**, **use of renin-angiotensin system inhibitors** and **diuretics**, and **older age** all have been anecdotally associated with the **development of oxalate nephropathy** in patients with hyperoxaluria.

- ✓**In the Rare Kidney Stone Consortium registry**, **kidney stones** were found in **61%** and **nephrocalcinosis** in **37%** on **imaging** (**primarily ultrasound**) of **PH patients.**
- ✓The **prognosis of ON was poor** in these series, with a **high percentage of progression to ESKD** or **persistent advanced CKD**.

Table 3. Key clinical data in four largest case series

Clinical data	Nasr *et al.* [4] (2018) ($n = 11$)	Cartery *et al.* [5] (2011) (n = 12)	Buysschaert *et al.* [2] (2020) ($n = 21$)	Yang *et al.* [3] (2020) ($n = 25$)
Age, years (range)	61.3 (45–79)	67 (41–91)	61 ± 20	63.6 ± 9.1
Gender, male	5 (45)	9 (75)	14 (67)	13 (52)
White race	8 (72.7)		21 (100)	
Diabetes	9 (81.8)	9 (75)	12 (57)	16 (64)
Hypertension	11 (100)	8 (66.7)	16 (76)	19 (76)
Baseline CKD		7 (58.3)	13 (62)	
Urinary stones		3 (25)	3 (14)	1 (4)
RAAS inhibitor use	3 (27.3)	8 (66.7)	8 (38)	
Diuretic use	3 (27.3)	5 (41.6)	9 (43)	
Baseline creatinine, mg/dL (range)	1.5 (0.9–2.5)	1.1 (0.79–2.02)		
GFR baseline, mL/min/1.73 m^2 (range)		57 (36–89)	36 ± 7	
Serum creatinine at time of presentation, mg/dL (range)	5.0 (2.4–9.2)	6.6 (3.3–9.6)	8.0 ± 4.5	6.3 ± 3.2
EH	11 (100)	12 (100)	10 (48)	10 (40)
Ingestion related	–	1 (8.3)	2 (10)	4 (16)
Recent antibiotic use	–	4 (33.3)	3 (14)	13 (52)
Uncertain cause	–		3 (14)	11 (44)
Presence of hypocalcemia	–	9 (75)		6 (24)
Microscopic hematuria	3 (27.3)	3 (25)	5 (24)	
Leukocyturia	6 (54.5)	10 (83.3)	5 (24)	
Urine protein (range)	24 h, 1.4 g/day (0.37–6.00)	0.34 g/day (0.05–1.01)	1.4 g/g ± 2.0	52.04 mg/g ± 71.38
Diabetic glomerulopathy	7 (63.6)	3 (25)	6 (28.6)	8 (29.6)
Acute tubular injury	11 (100)	12 (100)	21 (100)	17 (63)
Acute/chronic tubulointerstitial nephritis	11 (100)	9 (75)	(Acute) 18 (85.7)	(Acute) 9 (33.3) (Chronic) 8 (32)

ANTIBIOTIC USE

- ✓A significant percentage of cases in the previous two series did not have a clear cause of ON.
- ✓It has been suggested that **antibiotic use**, especially antibiotics that **deplete intestinal Oxalobacter formigenes**, which metabolizes oxalate, could lead to **hyperoxaluria.**
- ✓Studies have shown that **depletion of gut Oxalobacter** was associated with **increased urinary oxalate**, especially in kidney stone-forming patients with a **risk of kidney stones > 3months after exposure**.

DIABETES

- ✓**Diabetes** has also been associated with **increased oxalate excretion**, perhaps via an **increase in oxalate precursors** such as **glyoxylate** and **glyoxal** that has been observed in diabetes
- ✓**Diabetes** is associated **gastroparesis** and **diabetes-related enteropathy**, which would make these patients **prone to volume depletion** and an increase in urine **supersaturation of calcium oxalate.**

- ✓Not all patients with **hyperoxaluria** develop ON and a **concomitant insult such as volume depletion** is likely **one key factor** in precipitating it.

TREATMENT

- ✓The **main intervention** used in most patients in case series and case reports is, as expected, **intravenous** or **oral hydration**, which would serve to **lower the concentration of urinary oxalate.**
- ✓**Oral citrate** has been used **to inhibit crystallization** in both **primary** and **secondary hyperoxaluria**.

Treatment of PH

- ✓**The treatment of PH depends on the mutation.**

- ✓**Pyridoxine** may be useful for some with **Type 1 mutation** as well as **liver transplantation**.

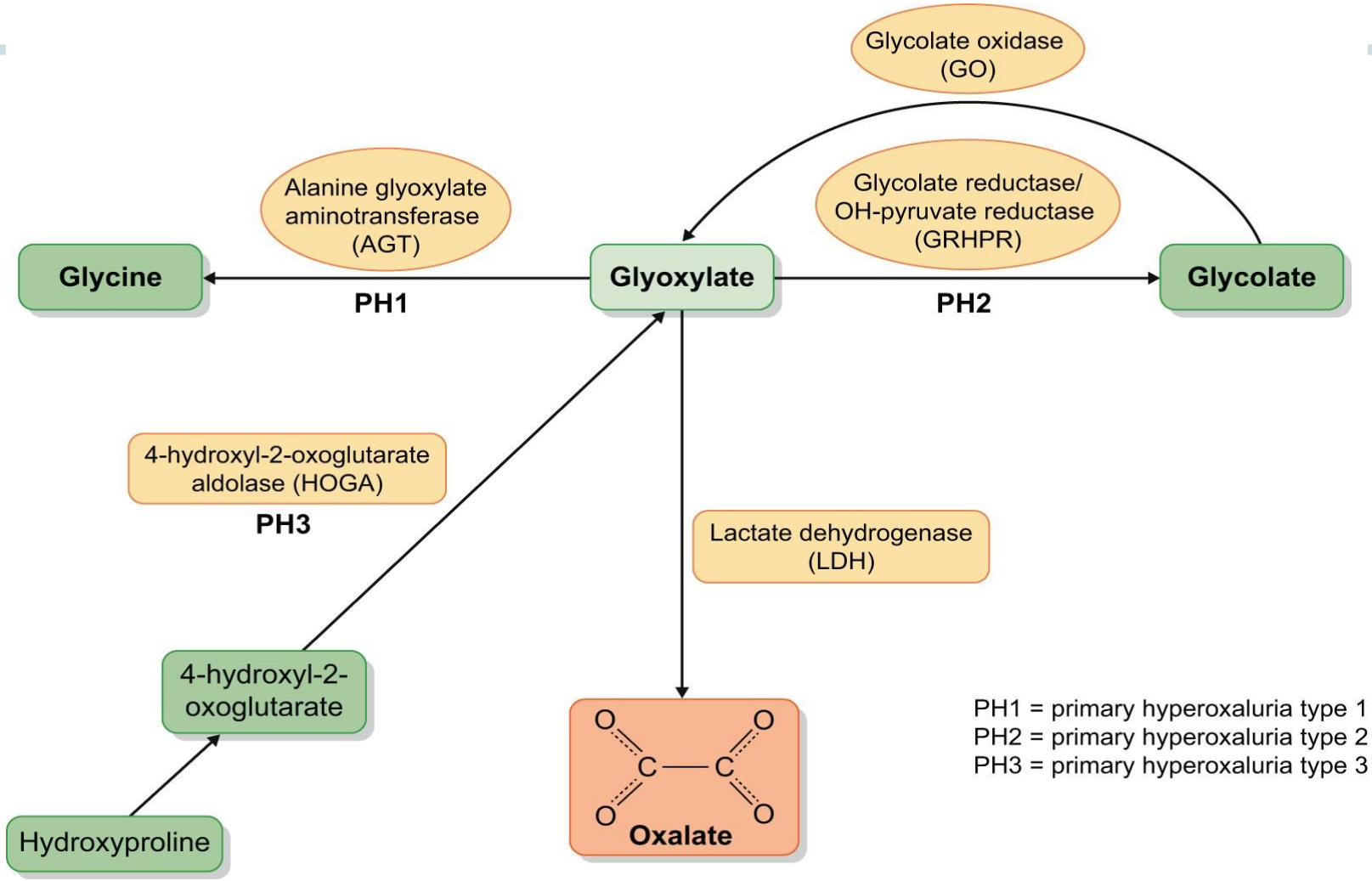
- ✓**In November 2020**, the US Food and Drug Administration approved **lumasiran as the first drug treatment for PH1.**

- ✓**Lumasiran** is an **RNA interference (RNAi)** agent that **degrades the messenger RNA** for the hepatic enzyme **glycolate oxidase**.

- ✓**Lumasiran**, a **HAO1-directed double-stranded** small interfering **ribonucleic acid**, **reduces levels of glycolate oxidase (GO) enzyme** by **targeting the hydroxyacid oxidase 1 mRNA** in hepatocytes through **RNA interference**

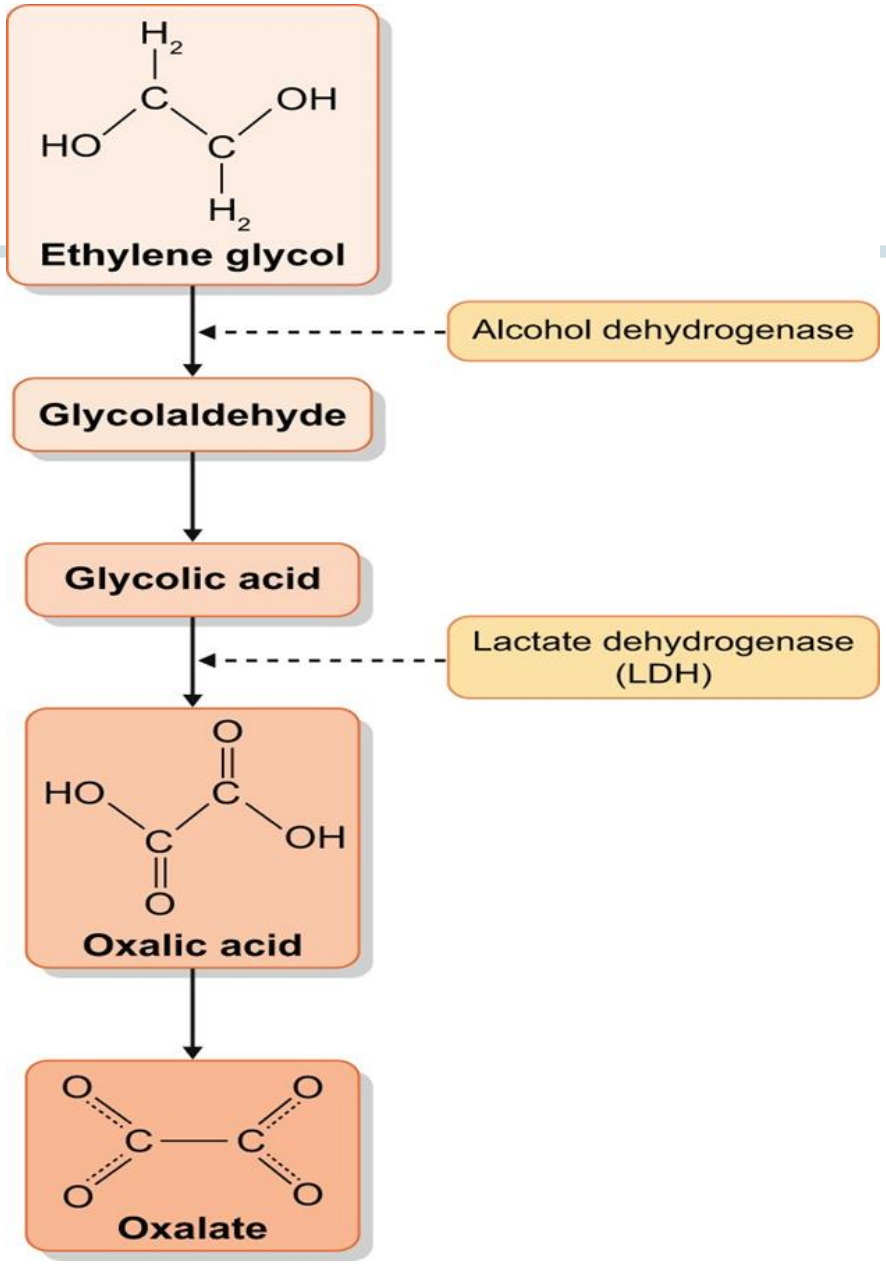
- ✓By **preventing the conversion of glycolate to glyoxylate** this agent **decreases the amount of glyoxylate** available to be converted to **oxalate**.

- ✓The **anti-epileptic agent stiripentol** has been found to **inhibit the lactate dehydrogenase (LDH) isoenzyme 5** that converts **glyoxylate to oxalate**.
- ✓**An RNAi of LDH** was developed **(Nedosiran**) and was used in a single patient with ESKD with significant decrease in blood oxalate levels


Glycolate oxidase
(GO)
Alanine glyoxylate
aminotransferase
(AGT)
Glycolate reductase/
OH-pyruvate reductase
(GRHPR)
Glycine
PH1
Glyoxylate
PH2
Glycolate
4-hydroxyl-2-oxoglutarate
aldolase (HOGA)
PH3
Lactate dehydrogenase
(LDH)
4-hydroxyl-2-
oxoglutarate
Hydroxyproline
Oxalate
PH1 = primary hyperoxaluria type 1
PH2 = primary hyperoxaluria type 2
PH3 = primary hyperoxaluria type 3

Treatment of ingestions

- ✓For **acute ingestions**, it is crucial **to identify the source of oxalate or precursor** and **remove it from the patient's diet**.
- ✓**EG ingestion** is treated with **ethanol** or **fomepizole** to **competitively inhibit the metabolism of EG by alcohol dehydrogenase.**


Ethylene glycol
Alcohol dehydrogenase
Glycolaldehyde
Glycolic acid
Lactate dehydrogenase (LDH)
Oxalic acid
Oxalate

Treatment of EH, or if the cause of the ON is not clear

❑Non-specific treatments:

- **lowering oxalate intake**
- **increasing oral calcium intake** via **diet** or **calcium supplements** as a means of binding oxalate in the bowel.
- **Lowering fat intake**
- **Sevelamer hydrochloride**, a phosphate binder that also **binds fatty acids**.
- **Cholestyramine**, a **bile acid binder**, has been studied with the understanding that it may **decrease bile acid effect on colon permeabilityand** also may **directly bind oxalate**.

- **Manipulating the microbiome** with **probiotics** or specifically with **oral O. formigenes** has been studied.
- **Reloxaliase** (formerly known as ALLN-177) is a **recombinant oxalate decarboxylase**. It lowered urine oxalate.
- **Chronic pancreatitis** is treated with **pancreatic enzymes**.
- **Reversal of Jejunoileal bypass & Roux-en-Y** have been successfully in number of cases of hyperoxaluria

- There is downstream **inflammation(Pro-inflammatory molecules are released from tubular cells damaged** by crystals) in hyperoxaluric patients that perpetuates **chronic interstitial damage** and progressive kidney disease.
- **Suppressing mediators of inflammation** including **cytokines** like **tumor necrosis factor**, as well as components of **cytokine activators in macrophages and dendritic cells** called **inflammasomes**, can be beneficial in limiting progressive damage.

Table 4. Treatments discussed in this review

Clinical data	Mechanism	Notes	Current trials
PH			
High fluid intake	Lowers urinary calcium oxalate supersaturation	Prompt initiation of high fluid intake with urinary alkalinization may slow progression [82]	–
Pyridoxine	Increase function of AGT	Useful in some PH1 [9]	–
Citrate	Inhibit calcium oxalate crystallization	May stabilize or improve renal function in some cases [69]	–
Liver transplant	Restore oxalate metabolism primarily in PH1 [9]	PH2 may not necessarily respond and no data in PH3 [9]	–
Lumasiran	RNAi of glycolate oxidase enzyme [70]	FDA approved—no long-term data on outcomes.	Single-arm study in advanced kidney disease ongoing—NCT04152200
Nedosiran	RNAi of LDH enzyme [72]	Trial ongoing in PH1 and PH2	NCT03847909

Secondary hyperoxalurias			–
High fluid intake	Lowers urinary calcium oxalate supersaturation [10]		–
EH			–
Increased calcium and low fat intake	Use calcium to bind oxalate in gut	Generally can lower urine oxalate in short term studies [10, 12]	–
Lower oxalate intake	decrease gut oxalate	Variable results [10, 12]	–
Citrate	Inhibit calcium oxalate crystallization	Only data is in stone patients with low urine citrate [10, 12]	–
Sevelamer	Fatty acid binding	Non-significant decrease in urine oxalate in single trial [76]	–
Cholestyramine	Decrease bile acids	Conflicting results [10, 12]	–
Microbiome manipulation	Increase oxalate degradation in gut	Have generally not been effective [64]	–
Reversal of bariatric surgery	Reverse malabsorption	Single case report with Roux-en-Y [79]	
Reloxilase (ALLN-177)	Recombinant oxalate decarboxylase	Limited data—clinical trial ongoing [77]	NCT03847090
Cytokine/inflammasome inhibition	Block downstream inflammation leading to fibrosis	Animal studies only so far [80, 81] Potentially also could be useful in PH and ingestions	–

Ingestions		
Identify and remove offending agent from diet		
EG		
Ethanol	Competitively inhibits metabolism with alcohol dehydrogenase	Reduces formation of toxic metabolites [22]
Fomepizole	Competitively inhibits metabolism with alcohol dehydrogenase	Reduces formation of toxic metabolites [22]