Updates to ICD-10-CM Related to Hyperoxaluria

Cristin Kaspar, MD

Objectives

- To review the spectrum of clinical disease that are characterized by ‘Hyperoxaluria’
  - Differences between Primary and Enteric (Secondary) Hyperoxalurias in:
  - Etiology and known genetic mutations
  - Clinical presentation
  - Disease manifestations
  - Treatment

- To review Alnylam recommendation for revised ICD-10 classification

Biography and Affiliation

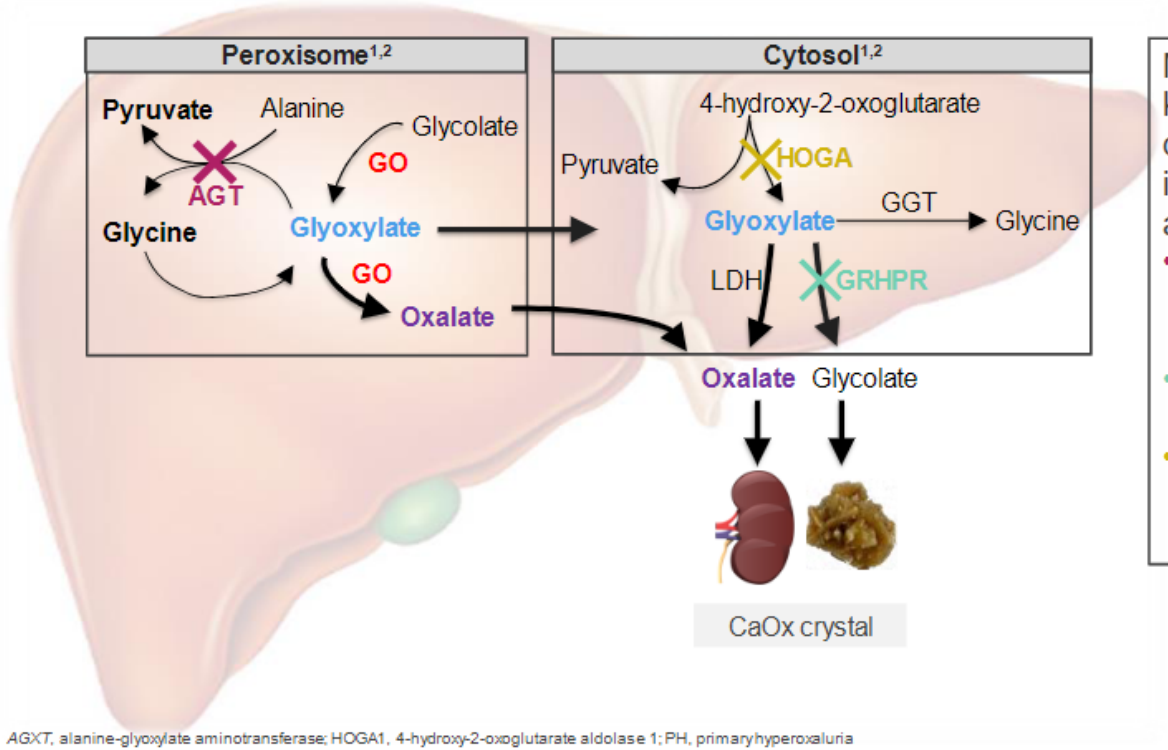
Cristin Kaspar, MD, MS Biostatistics, MS Physiology & Biophysics

- Medical Director Clinical Development at Alnylam Pharmaceuticals
  - Medical Monitor for Phase 3 Lumasiran clinical trials
  - Clinical development lead for Phase 3 pediatric trial
- Pediatric Nephrologist, General Pediatrics Board Certified
  - Children’s Wisconsin Pediatric Nephrology

Sources of Oxalate

Endogenous:

- Glyoxylate detoxification pathway
- Ascorbic Acid metabolism



Mutations in genes coding for key enzymes in the glyoxylate detoxification pathway result in overproduction of oxalate and PHs[2]

- ***AGXT***: PH1 is caused by a deficiency of liver-specific peroxisomal AGT
- ***GRHPR***: PH2 is caused by a lack of GRHPR
- ***HOGA1***: PH3 results from defects in the mitochondrial HOGA

AGXT, alanine-glyoxylate aminotransferase; HOGA1, 4-hydroxy-2-oxoglutarate aldolase 1; PH, primary hyperoxaluria

1. Salido et al. *Biochim Biophys Acta* 2012;1822:1453–64; 2. Cochat & Rumsby. *N Engl J Med* 2013;369:649–58

Exogenous / Enteric:

- Intestinal Absorption of dietary sources of oxalate
  - Spinach
  - Chocolate
  - Almonds
  - Soy products
- May be pathologically increased as a result of a disease

2. Witting C, Lieske JC, et al. Pathophysiology and Treatment of Enteric Hyperoxaluria. Clin J Am Soc Nephrol. 2021 Mar 8;16(3):487-495. doi: 10.2215/CJN.08000520. Epub 2020 Sep 8. PMID: 32900691; PMCID: PMC8011014.

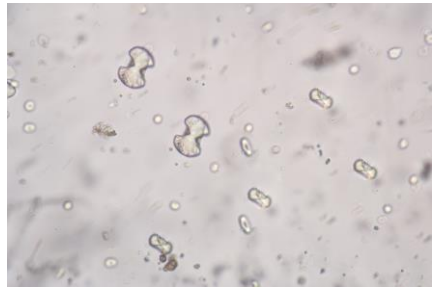
The Accumulation of Oxalate Can Lead to Progressive Kidney Damage

Oxalate cannot be metabolized by the body, and most is transported to the kidneys for excretion through the urine[1,2]

→

Excessive oxalate production leads to increased urinary excretion of oxalate (hyperoxaluria)[3]

→

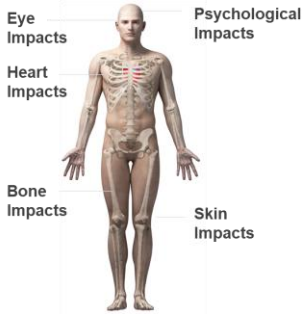


Excess UOx combines with calcium in the kidney parenchyma and urinary tract to form insoluble CaOx crystals[1,4]

→

Accumulation of CaOx crystals in the kidneys can cause direct damage to the kidney, the formation of stones, and nephrocalcinosis[4–6]

→



As eGFR declines, systemic oxalate deposition occurs, resulting in significant morbidity and mortality[7,8]

Oxalate accumulation leads to progressive kidney damage and systemic oxalosis in severe cases[4,9]

CaOx, calcium oxalate; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; UOx, urinary oxalate.

1. Cochat P & Rumsby G. N Engl J Med 2013;369:649–658; 2. Ermer T et al. Curr Opin Nephrol Hypertens 2016;25:363–371; 3. Bhasin B et al. World J Nephrol 2015;4:235–244; 4. Milliner DS et al. GeneReviews® [updated February 10, 2022]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283 (accessed October 2022); 5. Salido E et al. Biochim Biophys Acta 2012;1822:1453–1464;
6. Zhao F et al. Clin J Am Soc Nephrol 2016;11:119–126; 7. Sas DJ et al. Urolithiasis 2019;47:79–89; 8. Lawrence JE & Wattenberg DJ. Clin J Am Soc Nephrol 2020;15:909–911.; 9. Witting C, Lieske JC, et al. Pathophysiology and Treatment of Enteric Hyperoxaluria. Clin J Am Soc Nephrol. 2021 Mar 8;16(3):487-495. doi: 10.2215/CJN.08000520. Epub 2020 Sep 8. PMID: 32900691; PMCID: PMC8011014.

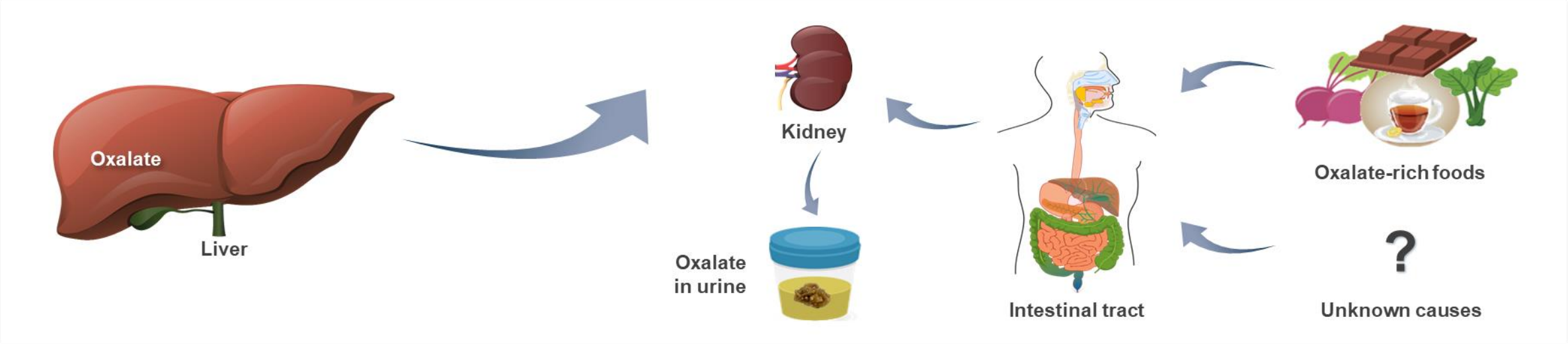
Hyperoxaluria Is an Excessive Urinary Excretion of Oxalate

Primary hyperoxaluria

- Caused by rare autosomal recessive genetic mutations that result in overproduction of oxalate by the liver[1]
- Three main types classified by enzyme deficiency[2,3]:
  - **Type 1** is the **most severe** and accounts for 70−80% of all cases
  - **Type 2** accounts for 10% of all cases
  - **Type 3** accounts for ~10% of all cases

Enteric (previously Secondary) hyperoxaluria

- Caused by increased dietary and intestinal absorption of oxalate, excessive intake of oxalate precursors, or alteration in intestinal microflora[4]
- Three types:
  - The **enteric** form is caused by intestinal disorders[6]
  - The **dietary** form is caused by excessive intake of oxalate[5]
  - The **idiopathic** form is due to unknown causes[5,6]



1. Cochat & Rumsby. N Engl J Med 2013;369:649–58; 2. Rare Clinical Diseases Research Network. Available from: https://www.rarediseasesnetwork.org/cms/rksc/PH-Registry (accessed December 10, 2019); 3. Hoppe et al. Kidney Int 2009;75:1264–71; 4. Bhasin et al. World J Nephrol 2015;4:235–44; 5. Glew et al. World J Nephrol 2014;3:122–42; 6. Nazzal et al. Nephrol Dial Transplant 2016;31:375–82

Inheritance and Genetics

The genetic prevalence of **PH1** is estimated to be **~6.6 per million**[2]

The prevalence of **diagnosed PH1** in North America and Europe is estimated to be **1–3 patients per million people**[1]

The prevalence of diagnosed PH2 and **PH3** is **lower than PH1**, likely because of underdiagnosis due to milder phenotypes or incomplete penetrance[2]

PH1 is likely underdiagnosed due to heterogeneous clinical presentation[2]

PH1	PH2	PH3
• *AGXT* gene mutations[1] **Enzyme defect: AGT**	• *GRHPR* gene mutations[1] **Enzyme defect: GRHPR**	• *HOGA1* gene mutations[1] **Enzyme defect: HOGA**
• >150 genetic mutations identified[1]	• ~30 genetic mutations identified[1]	• ~19 genetic mutations identified[1]
• Variable age of onset (infancy to 54 years old)[3]	• Typical onset in childhood[4]	• Onset in childhood or adolescence[5]

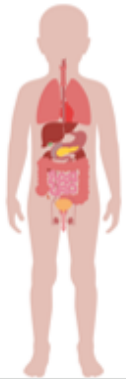
Most severe → **Least severe**

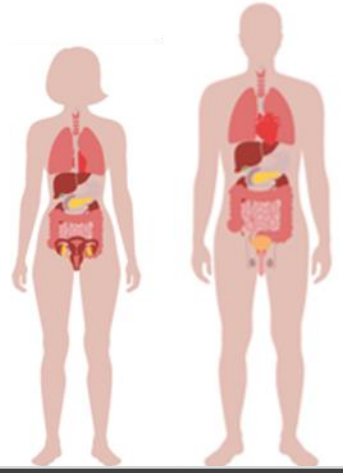
PH1 is the most common and severe form of PH, caused by mutations in the *AGXT* gene[1,2]

AGXT, alanine-glyoxylate aminotransferase; GRHPR, glyoxylate reductase/hydroxypyruvate reductase; HOGA1, 4-hydroxy-2-oxoglutarate aldolase 1; PH, primary hyperoxaluria; PH1, PH type 1; PH2, PH type 2; PH3, PH type 3.

1. Cochat P & Rumsby G. N Engl J Med 2013;369:649–658; 2. Hopp K et al. J Am Soc Nephrol 2015;26:2559–2570; 3. Lieske JC et al. Am J Nephrol 2005;25:290–296;
4. Rumsby G & Hulton S. GeneReviews®. Available at: https://www.ncbi.nlm.nih.gov/books/NBK2692/ (accessed March 2021); 5. Milliner DS et al. GeneReviews®.
Available at: https://www.ncbi.nlm.nih.gov/books/NBK316514/ (accessed May 2023).

PH1 Symptom Profiles in Adults Differ from those in Children and are Harder to Diagnose





Relative incidence[1]	Infancy (~10%)	Childhood (~60%)	Adulthood (<10%)
Typical features of PH1 phenotype at initial presentation[1–3,*]	• One or a combination of the following symptoms: • Kidney stones • Nephrocalcinosis • Recurrent UTI • Hematuria • Elevated serum creatinine • Failure to thrive • May have a family history of PH	• ≥1 of the following symptoms: • Unexplained abdominal pain • Dysuria • Kidney colic • Hematuria • Elevated serum creatinine • UTI • Recurrent urolithiasis • Nephrocalcinosis • Bilateral obstruction with acute kidney failure • Kidney failure	• One or a combination of the following symptoms: • Mild-to-moderate reduction in kidney function • Acute kidney failure • CKD • Recurrent kidney stones • Nephrocalcinosis

PH1 may be perceived as a childhood condition and may be underrecognized in adults[4]

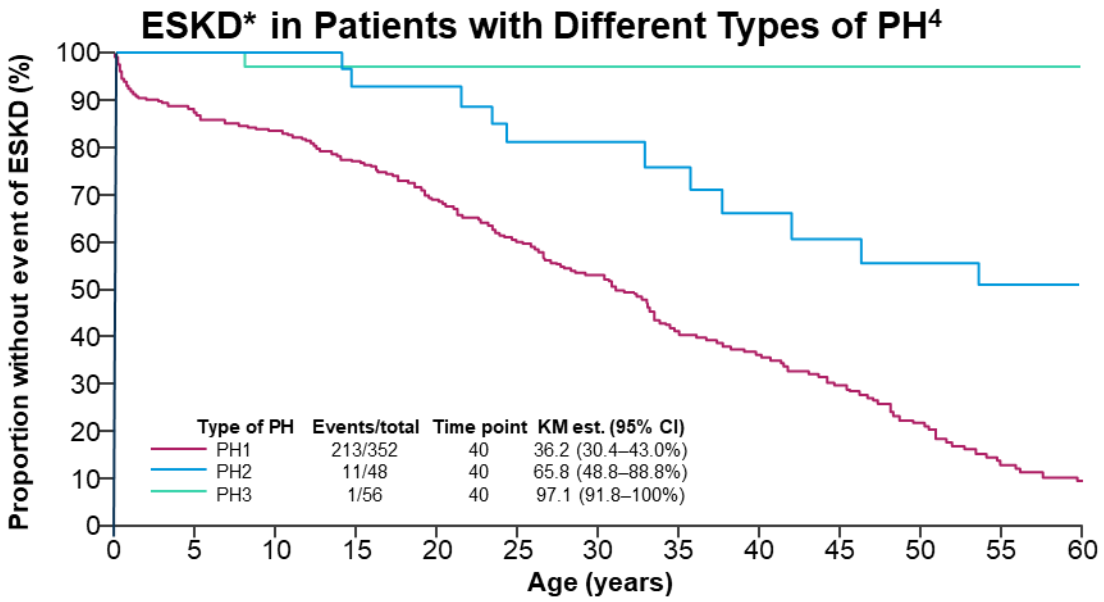
* The remainder of cases are accounted for by disease recurrence post-kidney transplant (~10%) and diagnosis as a result of positive family history (<10%).1

CKD, chronic kidney disease; PH, primary hyperoxaluria; PH1, PH type 1; UTI, urinary tract infection.

1. Milliner et al. GeneReviews® [updated February 10, 2022]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283 (accessed October 2022);
2. Hoppe B & Langman C. Pediatr Nephrol 2003;18:986–991; 3. Cochat P et al. J Pediatr 1999;135:746–750; 4. Poyah P et al. Can J Kid Health Dis 2021;8:1-7.

Kidney Disease Progression of Primary Hyperoxalurias

The risk of ESKD is greater in PH1 than in PH2 or PH3



- Most patients with PH1 progress to kidney failure, with >50% of adult patients presenting with kidney failure at diagnosis[1,2]
  - Based on data from a single study, almost all patients with PH1 (88%) experience kidney failure by the age of 60 years[3]
- Patients with PH1 typically have worse kidney function relative to PH2 and PH3; however, the rate of progression to ESKD is variable. Acute decline in kidney function may occur suddenly even in previously stable disease[4–7]

Most patients with PH1 progress to kidney failure, with significant implications on morbidity and mortality; however, the rate of progression is variable[1–6]

Figure adapted from Singh P et al. 2022.4 *ESKD: eGFR <15 mL/min/1.73 m2, initiation of dialysis or kidney transplant.4

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KM, Kaplan–Meier; PH, primary hyperoxaluria; PH1, PH type 1; UTI, urinary tract infection.

1. Cochat P et al. Nephrol Dial Transplant 2012;27:1729–1736; 2. Devresse A et al. Kidney Int. Rep. 2020;5:2136–2145; 3 Hopp K et al. J Am Soc Nephrol 2015;26:2559–2570; 4. Singh P et al. Nephrol Dial Transplant 2022;37:869–875; 5. Hoppe B et al. Kidney Int 2009;75:1264–1271; 6. El-Reshaid K et al. Saudi J Kidney Dis Transpl 2016;27:606–609; 7. Milliner DS et al. GeneReviews® [updated February 10, 2022]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283 (accessed October 2022).

Differentiating between Primary and Enteric or Dietary Hyperoxaluria

	Primary hyperoxaluria	Enteric or Dietary hyperoxaluria
Etiology	• Inborn error of metabolism with specific enzymatic defects	• Increased dietary intake of oxalate or precursors • Increased intestinal absorption • Altered intestinal microflora
Clinical presentation	• Recurrent stones, nephrocalcinosis, CKD, ESKD, and hypercalciuria • Clinical heterogeneity: variety in severity and presentation between early and late onset, and between different types	• Recurrent kidney stones, nephrocalcinosis, CKD, and ESKD
Systemic oxalosis	• Common	• Less common • It may appear in severe cases of IBD or SBS
Diagnosis	• Family history, genetics	• Dietary history (Dietary hyperoxaluria) • Medical & surgical history (Enteric hyperoxaluria)
Urinary excretion of oxalate	• >1.0 mmol/1.73 m^2 body surface area[1]	• <1.0 mmol/1.73 m^2 body surface area • Some cases of enteric hyperoxaluria may extend into the primary range
Composition of kidney stones	• 95% CaOx monohydrate (whewellite)	• Mixed stones (whewellite and CaOx Dihydrate weddellite)
Other diagnostic points	• POx levels are >60–80 µmol/L in ESKD	• ^{14}C test to assess for increased intestinal absorption • Polymerase chain reaction in stool samples to identify *Oxalobacter formigenes*

[1]Majority of cases

^{14}C, carbon-14; CaOx, calcium oxalate; CKD, chronic kidney disease; ESKD, end-stage kidney disease; IBD, inflammatory bowel disease; Pox, plasma oxalate; SBS, short bowel syndrome

Bhasin et al. World J Nephrol 2015;4:235–44

Treatment of Primary vs Enteric or Dietary Hyperoxalurias

	Primary hyperoxaluria	Enteric or Dietary hyperoxaluria
Medical Treatments	• Treatment is directed at preventing urinary CaOx supersaturation, which decreases risk of stone formation in the kidney: Urinary alkalinization, Hyperhydration • Dietary interventions have limited impact on oxalate levels, but still dietary changes are encouraged • In PH1: Pyridoxine may decrease hepatic oxalate production in patients with certain AGXT genetic variants ('pyridoxine responsive patients') while normalizing it in a small subset of these patients	• Treatment is directed at preventing urinary CaOx supersaturation, which decreases risk of stone formation in the kidney: Urinary alkalinization, Hyperhydration • Reduce dietary oxalate, increase dietary calcium, increase dietary citrate • No role for pyridoxine
Dialysis	Dialysis may be required in patients with ESRD and/or those with systemic oxalosis who require increased oxalate removal. In PH1, frequent, intensive dialysis > 5 days per week may be required	Renal replacement therapy when ESRD occurs
Transplant[1]	• In PH1: Liver transplant replaces the defective AGXT gene in the liver, corrects the metabolic defect and normalizes oxalate production. Liver-kidney transplant may be needed in patients with CKD/ESRD. Isolated kidney transplant may be chosen if fully responsive to pyridoxine; isolated kidney transplant has also been reported among patients taking OXLUMO and nedosiran. • In PH2: isolated kidney transplant is preferred in ESRD as the defective enzyme is not limited to the liver • In PH3: not typically required	Limited data available for transplant as a treatment for ESRD in enteric / dietary hyperoxalurias
siRNA	• In PH1: - OXLUMO is a HAO1-directed small interfering ribonucleic acid (siRNA) indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients. - Nedosiran was submitted for FDA review in Q3, 2022. • In PH2 and PH3: - There are no FDA approved therapies for PH2 and PH3	No approved siRNA treatments for secondary hyperoxalurias

ESRD: end stage renal disease; PH: primary hyperoxaluria; CaOx: calcium oxalate. 1. Bhasin B, Ürekli HM, Atta MG. Primary and secondary hyperoxaluria: Understanding the enigma. World J Nephrol. 2015 May 6;4(2):235-44.

Recommendation

Due to distinct differences in etiology and clinical presentation, different code sets are recommended for primary, enteric, and dietary hyperoxalurias

- In recent years, better understanding of the Primary, Enteric, Dietary hyperoxalurias has revealed they are distinct in their *cause, diagnosis, disease mechanism, clinical presentation, severity of outcome, and treatment*
- Unfortunately, these differences are not reflected in the current ICD-10-CM code set. To better reflect the clinical distinction of these diseases, we recommend additional granularity in the coding set to further differentiate the various types of hyperoxaluria
  - New code for Primary Hyperoxaluria Type 1 (PH1)
  - New code with inclusion terms for Primary Hyperoxaluria Type 2 (PH2) and Primary Hyperoxaluria Type 3 (PH3)
  - New code for Primary Hyperoxaluria Type Unspecified
  - New inclusion terms for Enteric Hyperoxaluria and Dietary Hyperoxaluria