Understanding the Burden of Primary Hyperoxaluria Type 1 (PH1): A Survey of Physician Experiences with PH1

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Background and Objective:

Objective:

To better characterize PH1 natural history in terms of clinical manifestations, interventions, and resource use events that contribute to disease burden throughout the patient journey

Primary Hyperoxaluria Type 1 (PH1):

Background[1]:

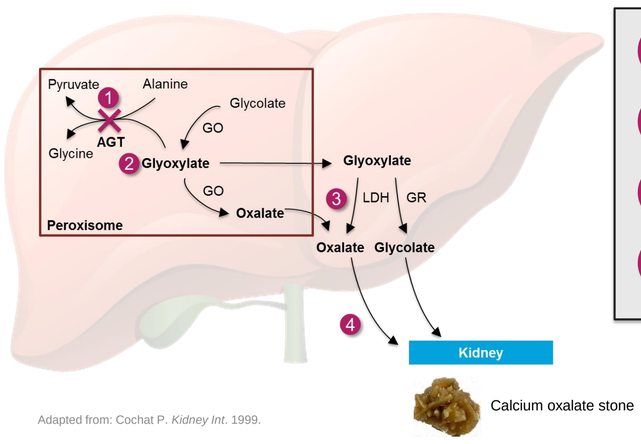
- Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~ 32/1,000,000 in Middle East[2]
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Disease course ultimately leads to multi-organ damage from systemic oxalosis
- Phenotype varies significantly across patients; may present at any age, but typically in children

Clinical Presentation

- Overproduction of oxalate results in formation of insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure; declining ability to renally clear oxalate also leads to systemic oxalosis
- Wide spectrum of clinical manifestations and potentially frequent need for medical intervention
- Detailed natural history data on PH1 manifestations and required interventions / resource use is limited

No therapies are approved for treatment of PH1

Oxalate Synthesis in PH1:



Adapted from: Cochat P. *Kidney Int*. 1999.

1. AGT in liver peroxisome metabolizes glyoxylate to glycine
2. When AGT is deficient, glyoxylate cannot be metabolized to glycine
3. Glyoxylate is instead converted to oxalate
4. Oxalate initially deposits and accumulates in the kidneys, followed by systemic deposition as kidney function declines

Methods

Physician Research Interviews

A series of case-based physician interviews

- Key inclusion criteria: physicians in practice for >2 years; active role in diagnosing, treating, or managing ≥1 PH1 patients within last 5 years; spend ≥50% of time in direct patient care; see 100+ total patients per year; able to review PH1 patient medical records
- Case history forms served as basis for further probing of details in 60-minute interviews conducted with open-ended questions from a semi-structured interview guide

Physicians screened via telephone for key qualifications → Physicians completed written detail on patient cases → Physicians participated in 60-minute telephone interview → Data from patient case history forms and interviews analyzed

Results

Physician and Patient Characteristics

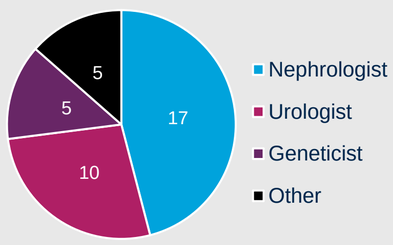
Physician Characteristics

- 37 physician interviews were conducted between November 2018 and March 2019
- Physicians were from the United States (N=17), Europe (N=13), and Middle East / South Asia (N=7)

Patient Characteristics

- A combined total of 54 patient cases were reported by the physicians interviewed
- Age at diagnosis ranged from 1 month – 48 years (median 7.5 years)
  - By the time of interviews, patients were a median of 9.5 years (range: 0.5 – 25 years) post-diagnosis

Physician Specialties

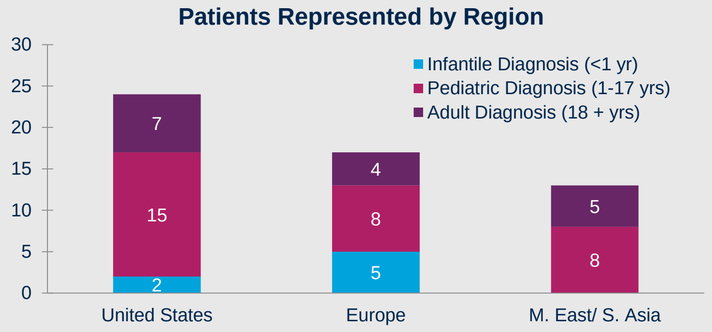


Number of patients seen by HCP type

Nephrologists
Mean: 9 patients
Median: 5 patients
Range: 1 to 40 patients

Urologists
Mean: 4 patients
Median: 3 patients
Range: 1 to 8 patients

Patients Represented by Region



54% of patients progressed to advanced kidney disease* before obtaining a diagnosis

*Physician explicitly stated that patient had advanced renal disease (known eGFR ≤29 mL / min / 1.73m²) or ESRD prior to diagnosis

Burden of Disease Throughout the Patient Journey

Stone Burden

76% of patients had stones

- Those who did not have stones mainly presented with highly diminished renal function, signs of nephrolcalcinosis, or failure to thrive (FTT)

2.7 stone events (lifetime average, among those who had at least 1 stone event)

- Stones caused high levels of pain, especially when obstructive, and often required acute removal
- Obstructive ureteral stones can cause acute kidney injury or acute renal failure

Average of 5 years under urology care pre-diagnosis

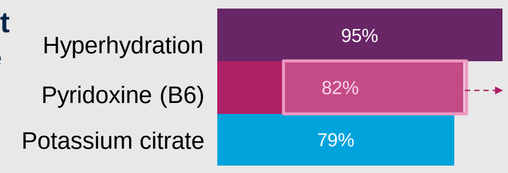
- Urological care addressed immediate concern for stones, but often delayed metabolic workup and ultimately PH1 diagnosis

Treatment Burden

48% of patients required dialysis at some point in the disease course

- Progression to advanced kidney disease resulted in patients requiring dialysis, potentially awaiting eventual transplant

Treatments Non-ESRD Patients* Received During Their Journey



2/3 of patients were completely B6 **unresponsive**

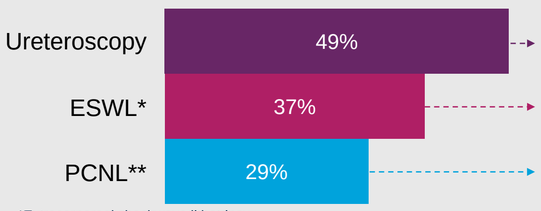
- Hyperhydration often proved difficult for patients, especially for children tasked with drinking multiple liters of water per day

*Defined as patients who were not at ESRD at initial presentation

Patient Burden

Intervention Burden

Percentage of Patients Ever Requiring Stone Intervention, by Intervention Type



	Range
Ureteroscopy	1-9 interventions
ESWL*	1-8 interventions
PCNL**	1-8 interventions

*Extracorporeal shockwave lithotripsy
**Percutaneous nephrolithotomy

- Invasive stone-removal procedures (ureteroscopy, PCNL) posed a great burden to patients, including potential adverse effects such as bleeding, scarring, infections, and internal organ damage, as well as days in inpatient care

Hospitalization Burden

65% of patients were ever hospitalized for PH1

- Many patients incurred financial and physical burden, as well as lost time at work (for adults or caregivers) or school (for children) as a result of hospitalization

Among patients who were **hospitalized**:

3.6 hospitalizations (lifetime average)

- Younger patients were often hospitalized for symptoms such as renal colic, UTI, or vomiting
- Older patients were often hospitalized for acute pain from ureteral stones or pyelonephritis

12.8 hospital days (lifetime average)

- Over multiple hospital visits, patients spent almost two weeks total in the hospital (range: 1-60 days)
- Hospital stay for stones could be extended due to recovery time for stone-removal procedures

Burden Prior to Advanced Disease†

59% of stone patients had **multiple stone events**

***27%** had **4+** stone events*

***Average time between stone events** (among patients who had recurrent stones)*

<1 yr.	1-5 yrs.	5+ yrs.
38%	54%	8%

78% of stone patients required **intervention** for their stones

	Average #
Ureteroscopy	2.4
ESWL	2.7
PCNL	1.4

40% of PH1 patients without ESRD **hospitalized** for symptoms

	Average #
Hospitalizations	1.9
Days spent in hospital	7.7
Range of days spent in hospital	1-28

†(known eGFR ≤29 mL / min / 1.73m²)

Burden of Advanced Disease†

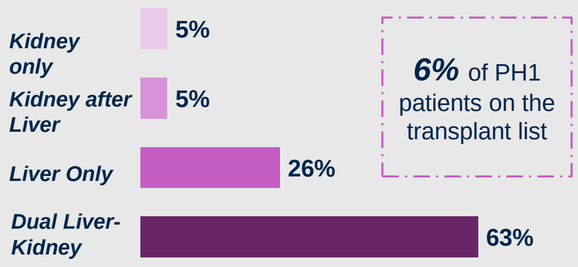
48% of patients required dialysis treatment at some point in their journey

Dialysis Regimen

# of times per week:	*3*	*4*	*5*	*6*
Dialysis Patients	54%	8%	4%	35%

34% of patients required organ transplant at some point in their journey

Transplant Type, among Transplant Recipients



6% of PH1 patients on the transplant list

- 1 patient received a kidney transplant before diagnosis, which ultimately failed due to oxalate overload

†(known eGFR ≤29 mL / min / 1.73m²)

Discussion & Summary

- **PH1 manifestations were burdensome even prior to advanced renal compromise, as demonstrated by the occurrence of substantial numbers of kidney stone events (often recurrent, and often requiring surgery) and hospitalizations**
  - **Most patients underwent at least one PCNL or ureteroscopy procedure as a result of stones associated with PH1 – these are invasive procedures which can result in bleeding, infection[4] and internal injury[5]**
  - **Many patients underwent an ESWL procedure as a result of stones associated with PH1: this non-invasive procedure may be less effective for patients with PH1 due to the potential resistance of calcium oxalate monohydrate stones,[6] and concerns exist about the risk of renal injury in patients undergoing multiple ESWL procedures – particularly children and individuals with existing kidney damage[7]**
- **This progressive disease commonly leads to ESRD if left untreated, further increasing disease burden as patients require intensive dialysis and eventual solid organ transplant (mainly dual kidney/liver)**
  - **Nearly half of patients ultimately required dialysis, which carries a significant financial and emotional burden given the intensive nature of treatment and time required (usually around 4 hours); this is particularly true in PH1, where a number of patients require dialysis up to 6 times per week (vs. the standard 3 times per week schedule in non-PH1-related ESRD)**
  - **Over a third of patients required a solid organ transplant, carrying a significant mortality risk; transplant also subjects patients to a life-long immunosuppressive regimen which increases patient morbidity (e.g., infection, malignancy) and mortality over time**
- **Earlier diagnosis and effective therapies are needed to prevent disease manifestations and progression to advanced disease and alleviate the significant time and resource burden associated with PH1**

1. Cochat P et al. N Engl J Med. 2013;369:649-658 2. Abumwais JQ. Saudi J Kidney Dis Transpl. 2012;23:158-161 **3.** Danese, D., Murray, R., Monpara, A., Ben-David, R., Crockett, T, Holloway, M.R., Barr, K., Doyle, S., Howie, K. (2019) The Importance of Evaluating for Potential Underlying Causes of Kidney Stones: A Survey of Physician Experiences in Diagnosing Primary Hyperoxaluria Type 1. Poster presentation: 56th European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Congress; 2019 Jun 13-16; Budapest, Hungary. 4. Taylor E et al. Transl Androl Urol. 2012 Dec; 1(4): 223–228. 5. Cindolo L et al. Minerva Urol Nefrol. 2017 Oct;69(5):421-431. 6. Milliner DS, Harris PC, Cogal AG, et al. Primary Hyperoxaluria Type 1. 2002 Jun 19 [Updated 2017 Nov 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1283/. 7. Gambaro G, et al. *Am J Kidney Dis*. 2001;37:233-243.