Disease monitoring and management among pediatric patients with pyruvate kinase deficiency: real-world practices from pyruvate kinase deficiency registries prior to 2024 international expert guidelines

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, genetic disease that leads to chronic hemolytic anemia[1]
- Complications of the disease and its treatment are associated with significant morbidity and potentially life-limiting consequences[2,3]
- To facilitate best management and improve patient outcomes, international expert guidelines for the diagnosis and management of PK deficiency were published in 2024[4]
  - Recommendations within the guidelines are grouped alphabetically and cover five key topics:
    - Diagnosis and genetics (A1–A5)
    - Monitoring and management of chronic complications (B1–B10)
    - Standard management of anemia (C1–C6)
    - Targeted and advanced therapies (D1–D8)
    - Special populations (E1–E2)

OBJECTIVE

To characterize the disease monitoring and management practices for pediatric patients with PK deficiency in the NHS and Peak Registry up to May 2023 and compare the findings with the 2024 guideline recommendations

METHODS

- This observational study was a retrospective analysis of real-world data for pediatric patients from two PK deficiency registries (**Supplemental Figure 1** [via QR code])
  - PK Deficiency Natural History Study (NHS; NCT02053480): 2014-2017 plus 2-year follow-up
  - Pyruvate Kinase Deficiency Global Longitudinal Registry (Peak; NCT03481738): 2018–ongoing
- Patients were eligible for inclusion in this analysis if they:
  - Were aged 1–17 years at the last documented visit (index date)
  - Were not homozygous for p.R479H mutation
  - Were never enrolled in Agios interventional trials prior to the index date
  - Had known transfusion status in the year prior to the index date: not regularly transfused (NRT; <6 transfusions) or regularly transfused (RT; ≥6 transfusions)
  - Had at least 1 year of retrospective data prior to the index date, to ensure adequate time for monitoring to occur
- Data specific to the documentation of clinical monitoring and disease management activities recorded during NHS and Peak Registry participation up to May 2023 were utilized to analyze trends in management and monitoring practices prior to the publication of the guidelines
- Data collected from both registries were merged where possible, and analyzed for the study population by transfusion status
  - The definitions used for iron overload and endocrine complications are shown in **Supplemental Table 1** (via QR code)
- Data were summarized descriptively and compared with the 2024 guidelines,[4] focusing on recommendations for:
  - Iron overload: B1–B3
  - Chelation: B4
  - Vitamin D and bone health: B7
  - Endocrine function: B9

RESULTS

Patient inclusion

- In total, 140 pediatric patients were included (**Supplemental Figure 2** [via QR code])
  - The majority, 107 (76.4%) were NRT; 33 (23.6%) were RT
  - In terms of registry participation, 59 (42.1%) had only participated in the NHS; 56 (40.0%) were unique to the Peak Registry, and 25 (17.9%) participated in both registries (**Table 1**)

Demographics and clinical characteristics

- At the index date, median age of patients was 8.5 years (range 1–17) (**Table 1**)
  - Patients who were NRT were older than patients who were RT (median age 10 and 5 years, respectively)
  - Most patients were White (82.4%); 47.9% were female; the majority were enrolled from North America (57.1%)
  - *PKLR* genotype distribution:
    - 53.3% missense/missense
    - 31.4% missense/non-missense
    - 15.3% non-missense/non-missense

Table 1. Demographics and clinical characteristics among pediatric patients with PK deficiency

Demographics and clinical characteristics	Total N=140	NRT N=107	RT N=33
Age in years, median (range)			
Age at enrollment	5.0 (0.0, 15.0)	6.0 (0.0, 15.0)	3.0 (0.0, 15.0)
Age at index date	8.5 (1.0, 17.0)	10.0 (1.0, 17.0)	5.0 (3.0, 17.0)
Sex, n/N (%)			
Female	67/140 (47.9)	51/107 (47.7)	16/33 (48.5)
Race, n/N' (%)			
Asian	9/131 (6.9)	5/103 (4.9)	4/28 (14.3)
Black or African American	5/131 (3.8)	5/103 (4.9)	0/28 (0.0)
White	108/131 (82.4)	85/103 (82.5)	23/28 (82.1)
Other	9/131 (6.9)	8/103 (7.8)	1/28 (3.6)
Ethnicity, n/N' (%)			
Hispanic or Latino	24/125 (19.2)	16/99 (16.2)	8/26 (30.8)
Not Hispanic or Latino	101/125 (80.8)	83/99 (83.8)	18/26 (69.2)
Region of enrollment, n/N (%)			
Asia	5/140 (3.6)	4/107 (3.7)	1/33 (3.0)
Northern Europe	10/140 (7.1)	9/107 (8.4)	1/33 (3.0)
Central Europe	33/140 (23.6)	24/107 (22.4)	9/33 (27.3)
Southern Europe	12/140 (8.6)	9/107 (8.4)	3/33 (9.1)
North America	80/140 (57.1)	61/107 (57.0)	19/33 (57.6)
Age at PK deficiency diagnosis[a]			
Age in years, median (range)	0.0 (-1.0, 14.0)	0.0 (-1.0, 13.0)	1.0 (-1.0, 14.0)
Time from symptom onset to PK deficiency diagnosis[b]			
Time in months, median (range)	3.5 (-2.1, 107.3)	3.5 (-2.1, 107.3)	3.5 (-0.1, 74.1)
Genotype, n/N' (%)			
Missense/missense	73/137 (53.3)	56/104 (53.8)	17/33 (51.5)
Missense/non-missense	43/137 (31.4)	32/104 (30.8)	11/33 (33.3)
Non-missense/non-missense	21/137 (15.3)	16/104 (15.4)	5/33 (15.2)
Registry cohorts, n/N (%)			
NHS only	59/140 (42.1)	43/107 (40.2)	16/33 (48.5)
Peak Registry only	56/140 (40.0)	42/107 (39.3)	14/33 (42.4)
NHS and Peak Registry	25/140 (17.9)	22/107 (20.6)	3/33 (9.1)

N represents the number of patients in each group. N' was used if there were any missing data.
[a]Age of PK deficiency diagnosis of –1 represents patients diagnosed in utero. [b]Data on time from symptom onset were only available for patients who participated in the Peak Registry (N=56).
NHS, Natural History Study; NRT, not regularly transfused in 12 months prior to the index date; Peak, Pyruvate Kinase Deficiency Global Longitudinal Registry; PK, pyruvate kinase; RT, regularly transfused in 12 months prior to the index date.

Lifetime history of comorbidities (Supplemental Table 2 [via QR code])

- Over patients' lifetime history, comorbidities included iron overload (69.6%), jaundice (45.0%), hepatomegaly (21.3%), gallstones (18.5%), and cardiac complications (9.7%)

Laboratory values and blood transfusions (Table 2 and Supplemental Table 3 [via QR code])

- Median hemoglobin values were similar in NRT and RT patients (8.5 and 8.0 g/dL, respectively)[a]
- On average, patients who were NRT received <1 transfusion (range 0–5) in the year prior to the index date
- Patients who were RT received an average of 9.8 transfusions

Table 2. Laboratory values and blood transfusion details among pediatric patients with PK deficiency

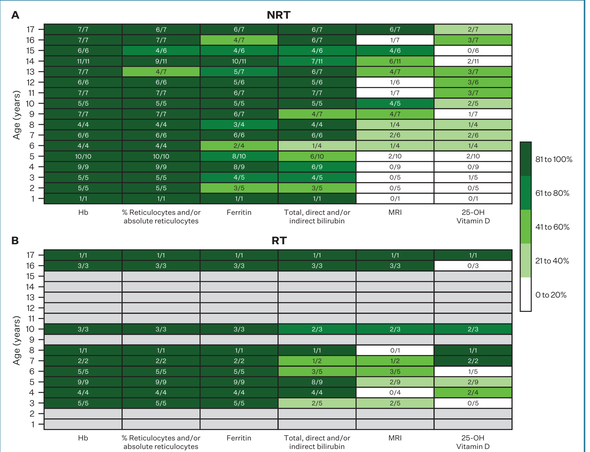
	Total N=140	NRT N=107	RT N=33
Laboratory values, median (Q1, Q3)[a]			
Hemoglobin, g/dL	8.4 (7.5, 9.6)	8.5 (7.6, 10.0)	8.0 (7.2, 8.8)
Reticulocytes/erythrocytes, %	11.0 (5.1, 30.0)	11.4 (5.1, 27.0)	8.9 (5.5, 30.0)
Absolute reticulocyte count, 10^9/L	241.2 (156.1, 532.5)	281.8 (167.6, 663.6)	204.0 (124.5, 269.0)
Indirect bilirubin, mg/dL	3.5 (2.3, 5.2)	3.4 (2.1, 5.2)	4.0 (2.9, 5.5)
Lactate dehydrogenase, IU/L	661.0 (314.0, 1068.0)	583.4 (291.9, 957.0)	897.0 (653.0, 1430.0)
Ferritin, ng/mL	581.0 (199.0, 1084.4)	480.4 (135.5, 1058.9)	774.6 (503.0, 1239.0)
Transfusion details			
Never transfused, n/N (%)	13/140 (9.3)	13/107 (12.1)	0/33 (0.0)
Number of transfusions 12 months prior to the index date, mean (SD)	3.0 (4.3)	0.9 (1.4)	9.8 (3.4)
Ever regularly transfused in any 12 months, n/N (%)	95/140 (67.9)	62/107 (57.9)	33/33 (100.0)

N represents the number of patients with data available. 'Never transfused' included in 'NRT' cohort.
[a]Last measurement closest to the index date in the NHS and Peak Registry merged data.
NRT, not regularly transfused in 12 months prior to the index date; PK, pyruvate kinase; Q1, first quartile; Q3, third quartile; RT, regularly transfused in 12 months prior to the index date.

Monitoring practices (Figure 1 and Supplemental Table 4 [via QR code])

- Patients underwent monitoring activities that included assessment for iron levels, bone health, growth and development, and endocrine function, with some variability observed across age groups

Figure 1. Disease monitoring[a] among pediatric patients with PK deficiency by age in years: A) NRT; B) RT



[a]Number of patients ever receiving the above-mentioned disease monitoring activities. No data for the specified age group are colored gray.
25-OH, 25-hydroxy; Hb, hemoglobin; MRI, magnetic resonance imaging; NRT, not regularly transfused in 12 months prior to the index date; PK, pyruvate kinase; RT, regularly transfused in 12 months prior to the index date.

Management practices (Table 3)

- Among NRT patients (median age 10 years), 43.3% had a history of splenectomy and 43.4% had received chelation therapy
- Among RT patients, 27.3% (median age 5 years) had a history of splenectomy and 84.8% had received chelation therapy
- One-quarter of all patients (25.2%) had undergone cholecystectomy
- In total, 27.2% were taking vitamin D and analogs

Table 3. Disease management among pediatric patients with PK deficiency

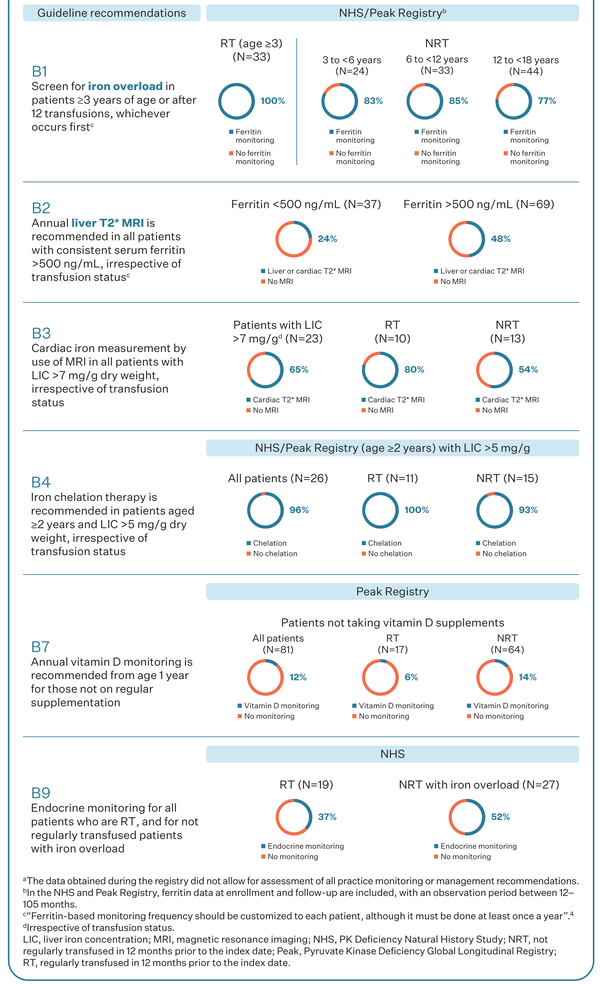
Disease management	Total N=140	NRT N=107	RT N=33
Interventions (ever), n/N' (%)			
Splenectomy	54/137 (39.4)	45/104 (43.3)	9/33 (27.3)
Cholecystectomy	34/135 (25.2)	27/102 (26.5)	7/33 (21.2)
Chelation treatment	74/139 (53.2)	46/106 (43.4)	28/333 (84.8)
Phlebotomy treatment	0/130 (0.0)	0/99 (0.0)	0/31 (0.0)
Alternative treatments (alternative, non-traditional, or investigational therapies, stem cell transplant)[a]	3/84 (3.6)	2/65 (3.1)	1/19 (5.3)
Other treatments, n/N' (%)			
Treatment for depression and/or anxiety	4/140 (2.9)	4/107 (3.7)	0/33 (0.0)
Folic acid/multivitamin containing folic acid	99/140 (70.7)	75/107 (70.1)	24/33 (72.7)
Currently taking vitamin D and analogs[b]	22/81 (27.2)	16/64 (25.0)	6/17 (35.3)
Prophylactic antibiotics after splenectomy[c]	43/54 (79.6)	36/45 (80.0)	7/9 (77.8)

N represents the number of patients in each group. N' was used if there were any missing data.
[a]NHS data; [b]Peak Registry data; [c]Only patients with a history of splenectomy were included in the percentage calculations.
NHS, Natural History Study; NRT, not regularly transfused in 12 months prior to the index date; Peak, Pyruvate Kinase Deficiency Global Longitudinal Registry; PK, pyruvate kinase; RT, regularly transfused in 12 months prior to the index date.

Comparisons of monitoring and management practices with guidelines

- Real-world practices reported in the NHS and Peak Registry prior to the publication of the 2024 guidelines for PK deficiency identified notable areas for improvement (**Figure 2**), including:
  - Monitoring of iron overload, and liver or cardiac iron levels by T2* MRI (B1, B2, and B3)
  - Management of chelation therapy (B4)
  - Annual vitamin D monitoring (B7)
  - Endocrine monitoring (B9)
- Study limitations are summarized in **Supplemental Materials** (via QR code)

Figure 2. Monitoring and management practices compared with 2024 guidelines[4,a]



[a]The data obtained during the registry did not allow for assessment of all practice monitoring or management recommendations.
[b]In the NHS and Peak Registry, ferritin data at enrollment and follow-up are included, with an observation period between 12–105 months.
[c,d]Ferritin-based monitoring frequency should be customized to each patient, although it must be done at least once a year".[4]
[d]Irrespective of transfusion status.
LIC, liver iron concentration; MRI, magnetic resonance imaging; NHS, PK Deficiency Natural History Study; NRT, not regularly transfused in 12 months prior to the index date; Peak, Pyruvate Kinase Deficiency Global Longitudinal Registry; RT, regularly transfused in 12 months prior to the index date.

CONCLUSIONS

- **Real-world practices reported in the NHS and Peak registries prior to the publication of the 2024 guidelines in PK deficiency[4] identified notable areas for improvement in the management of pediatric patients, including monitoring of bone health, endocrine dysfunction, and iron overload in patients who were NRT**
- **The findings emphasize the need for consistent care and appropriate monitoring for all pediatric patients with PK deficiency, regardless of transfusion status or perceived severity of disease**

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References: 1. Grace RF, et al. *Am J Hematol* 2015;90:825–30; **2.** Fattizzo B, et al. *J Blood Med* 2022;13:461–71; **3.** Glenthøj A, et al. *Brit J Haematol* 2024;205:613–23; **4.** Al-Samkari H, et al. *Lancet Haematol* 2024;1:e228–e239.

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Supplemental materials are available via the QR code