PYRUVATE KINASE DEFICIENCY (PKD)

TERM DEFINITION

Red cell pyruvate kinase deficiency (PKD) is a rare congenital, non-spherocytic hemolytic anemia transmitted as an autosomal recessive trait and caused by a glycolytic defect that is due to compound heterozygous or homozygous mutations in the *PKLR* gene.

PYRUVATE KINASE

2 PK GENES, 4 ISOENZYMES

- There are 2 PK genes that encode 4 PK isoenzymes.
- The *PKLR* gene encodes R-type PK in red cells and L-type PK in liver hepatocytes.
- PKD is caused by homozygous or compound heterozygous mutations in the *PKLR* gene.

***PKLR* GENE**

L-type PK
- Liver
- Renal cortex
- Small intestine

R-type PK
- Erythrocytes

***PKM* GENE**

M1-type
- Skeletal muscle
- Heart
- Brain

M2-type
- Leukocytes
- Platelets
- Lung
- Spleen
- Kidney
- Adipose tissue

PYRUVATE KINASE GENERATES ATP

- Because they lack mitochondria, red cells rely on glycolysis for ATP generation.
- Each molecule of glucose gives rise to 2 molecules of ATP.
- PK is in the glycolytic pathway and generates 50% of the ATP.
- Loss of PK activity results in ATP depletion and shortened RBC life span.

NORMAL

Glucose
ATP ← ↓ → 2,3-DPG
Phosphoenolpyruvate
ATP ← ↓ *Pyruvate kinase*
Pyruvate
↓ *Lactate dehydrogenase*
Lactate

***PK* DEFICIENCY**

Glucose
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ATP ← ↓ *Pyruvate kinase*
Pyruvate
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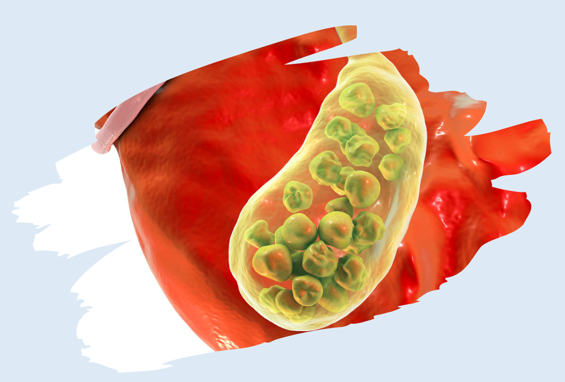
Lactate

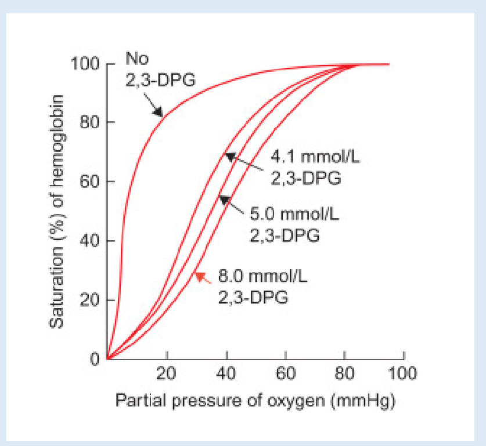
CLINICAL PEARLS

Patients with PKD may develop extreme reticulocytosis (> 50%) post-splenectomy.



Patients with PKD are prone to develop pigment gallstones even after splenectomy.

PKD is the most frequent enzyme abnormality of the glycolytic pathway causing hereditary non-spherocytic hemolytic anaemia.



Patients with PKD have elevated red cells of 2,3-DPG which shifts the oxygen dissociation curve to the right, leading to increased tolerance of anemia.

DIAGNOSIS

CONSIDER

Consider the diagnosis in a patient with:

- Non-immune hemolytic anemia, other causes ruled out.
- Patients with undiagnosed hemolytic process in whom reticulocytosis increases after splenectomy, even as the anemia improves.

CONFIRM

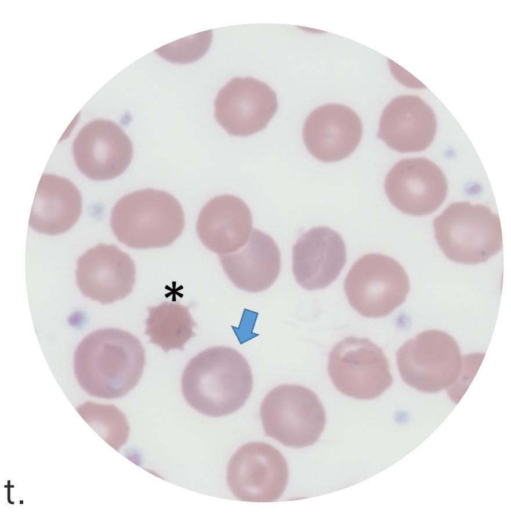
Confirm the diagnosis in a patient using:

- Direct quantitative enzyme activity.
- Molecular testing using next generation sequencing (NGS) strategies.

OTHER FINDINGS

Other findings consistent with a diagnosis of PKD:

- Peripheral smear, showing presence of
  - Polychromatophilia
  - Acanthocyte-like cells
- Iron overload (even in the absence of transfusions)



Shown here is a peripheral smear from a splenectomized patient with PKD shows an acanthocyte-like cell (asterisk) and a polychromatophilic cell (arrow). There are also target cells present.

COMPLICATIONS

Ineffective erythropoiesis
- Frontal bossing
- Spinal cord compression by extramedullary hematopoietic tissue

Iron overload
- Iron overload
- Heart failure
- Conduction disturbances
- Hypogonadism
- Hypothyroidism
- Hyperpigmentation

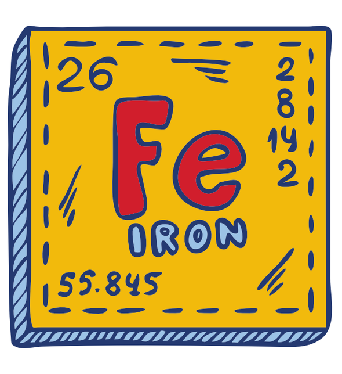
Splenectomy
- Overwhelming sepsis
- Thromboembolic events

Hemolysis
- Severe anemia
- Gallstones
- Gallstones are detected with increased frequency after the first decade of life and may occur even after splenectomy.
- Aplastic crisis following parvovirus infection
- Chronic leg ulcers

MONITORING

STUDY	ADULTS (18 YEARS AND OVER)
Complete blood counts, reticulocyte count, and bilirubin	At least annually, more often depending on hemolytic episodes and transfusion needs.
Serum ferritin and TSAT	Every 3-6 months in transfusion dependent; annually in non-transfusion dependent; every 1-3 months while on chelation.
Liver iron concentration	Annually in transfusion-dependent patients. In non-transfusion dependent, MRI frequency, if available, based on the following: annually if > 5 mg/g, every 5 years if < 5 mg/g
Abdominal US	Right upper quadrant US every 2-3 years or until cholecystectomy. After cholecystectomy, every 2-3 years if evidence of intrahepatic cholestasis.
Viral hepatitis serology	Annually in transfusion-dependent patients
Echocardiogram	Consider if age > 30 years, prior to pregnancy, & at any age if concern for cardiac dysfunction and/or pulmonary hypertension.

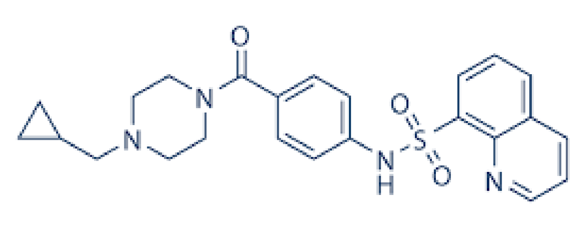
TREATMENT



Iron chelation

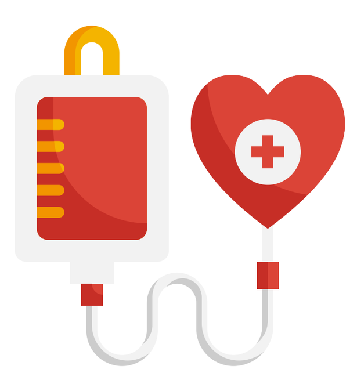
Folate supplementation

Especially important during hemolytic crises, pregnancy, and in childhood during growth and development.



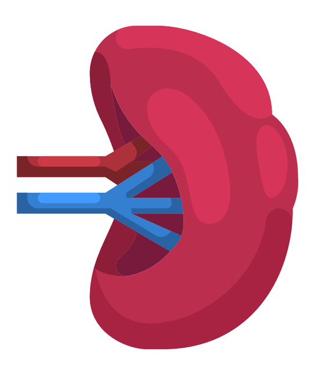
PK activator

Mitapivat, AG-348; FDA approved for the treatment of hemolytic anemia in adults with PK deficiency.



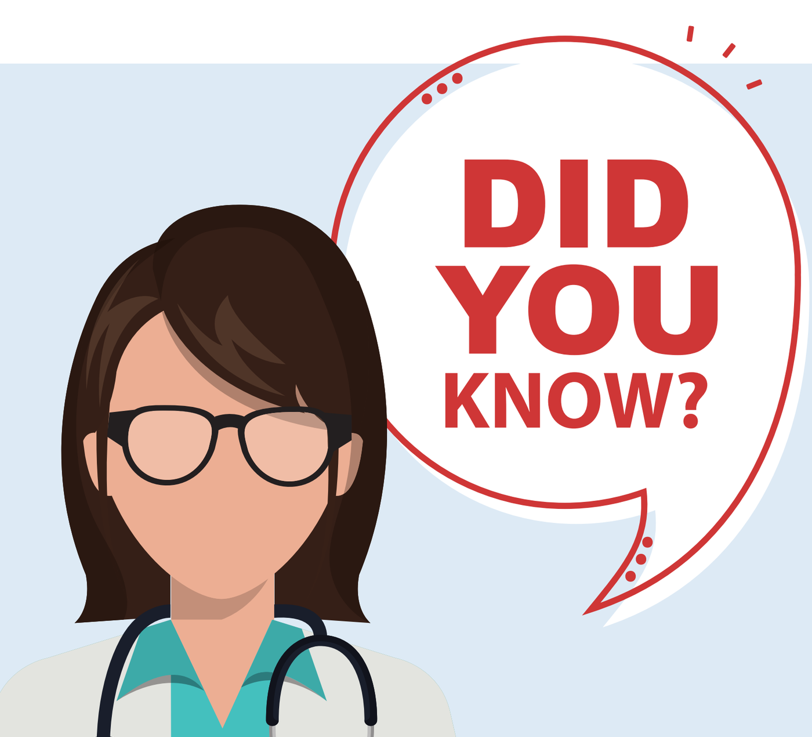
Red cell transfusion

The need for transfusions should be based on comprehensive clinical judgment regarding quality of life, growth, and symptoms and not on hemoglobin level alone.

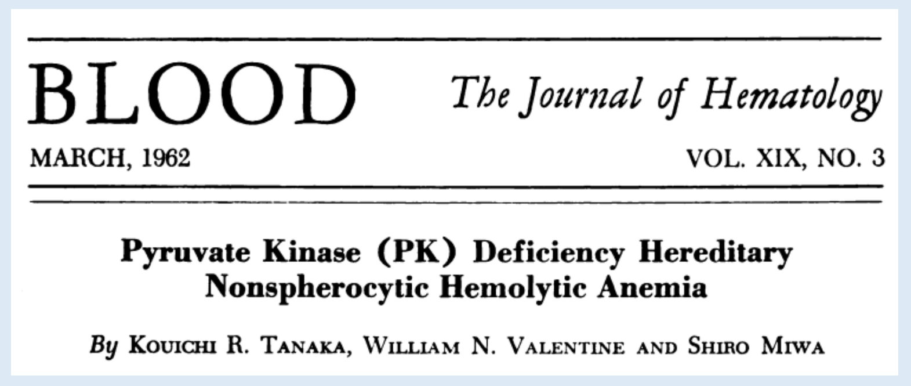


Splenectomy

Indications include patients with PKD who receive regular transfusions or are severely anemic and patients with massive splenomegaly at risk of spleen rupture due to lifestyle choices.



HISTORY OF MEDICINE



BLOOD The Journal of Hematology

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Pyruvate Kinase (PK) Deficiency Hereditary Nonspherocytic Hemolytic Anemia

By Kouichi R. Tanaka, William N. Valentine and Shiro Miwa

The first description of PK deficiency in a patient. *Blood*. 1962;19(3):267-295.

NOTES

ATTRIBUTIONS

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