Glucose-6-phosphate dehydrogenase deficiency (G6PD) is intravascular hemolytic anemia. It is inherited in an X-linked recessive manner. Patients have episodic hemolysis due to an identified oxidative stressor that causes damage to red blood cells (RBCs) which lack sufficient NADPH.

Epidemiology and Etiology

Epidemiology

- Found in Malarial Endemic regions; Mediterranean, African, Middle Eastern descent
- Present exclusively in males as it is X-linked Recessive
- Females can be silent carriers

Etiology

- Mutation in the Glucose-6-phosphate dehydrogenase(G6PD) enzyme
- A single-base change that results in a single amino-acid substitution
- Mutation lowers the half-life of the enzyme
- G6PD deficiency results in a defect of the Pentose Phosphate Shunt during glycolysis
- Inheritance is X-linked Recessive (band Xq28)
G6PD deficiency is an X-linked disorder found on Band Xq28.
Pathophysiology

- G6PD is the rate-limiting enzyme in the Pentose Phosphate Pathway.
- G6PD enzyme is responsible for:
  - Oxidation of glucose-6-phosphate
  - Reduction of nicotinamide adenine dinucleotide phosphate (NADP+) to NADPH
- NADPH maintains glutathione in its reduced form.
- Reduced glutathione is needed to neutralize oxidative metabolites.
- In RBCs, this is the ONLY pathway that produces NADPH.
- Thus, a lack of G6PD results in a deficiency in NADPH and increased oxidative damage.
- Oxidative stressors can denature hemoglobin and cause intravascular hemolysis.
- Extravascular hemolysis would be due to splenic clearance of the deformed RBCs.

![Image: Metabolic pathways. By Lecturio.]

<table>
<thead>
<tr>
<th>Common oxidative stressors</th>
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<tr>
<td><strong>Drugs</strong></td>
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<tr>
<td>• Sulfas (TMP-SMX)</td>
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<td>• Quinolones</td>
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<tr>
<td>• Nitrofurantoin</td>
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<td>• Aspirin/NSAIDs</td>
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<td>• Methylene blue</td>
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Clinical manifestations

- History of a trigger for the oxidative stress
- **Episodic Symptoms of Anemia**
  - Pallor
- Shortness of Breath
- Fatigue
- Tachycardia
- Flow murmur (best heard at upper sternal borders)

![Image: Hematuria](https://byomicsonline.org/license/copyright)

- Intravascular Hemolysis
  - Jaundice
  - Hemoglobinuria (cola-colored urine) - Hematuria
- Neonate (Males)
  - Prolonged pathological jaundice/icterus (See [Neonatal jaundice](#))

**Video Gallery**

[G6PD Deficiency: Clinical Pathology](#) by Carlo Raj, MD

**Diagnostics**

Suspected in cases of episodic hemolytic symptoms.

- CBC
  - ↓ Hb
  - ↑ Retics
  - ↑ LDH
  - ↓ Haptoglobin
  - ↑ Bilirubin
- Peripheral Blood Smear
  - Heinz Bodies
  - Bite Cells
- Beutler test
  - Done 2-3 weeks after an acute episode
  - quantifies NADPH/G6PD levels
Treatment

- Prevention
  - Avoid oxidative stressors: infections, drugs, fava beans in the diet
- During Hemolysis
  - If Hb < 9 with hemolysis – Blood Transfusion
  - Neonatal Jaundice – Phototherapy or exchange transfusion
- Splenectomy considered in rare cases of chronic hemolytic anemia

Differential Diagnoses

- **Hemolytic Anemia**: Hemolytic Anemias encompasses anemia due to a shortened half-life of the RBC. The causes include extravascular (extrinsic/intrinsic) or intravascular. G6PD is an extravascular, intrinsic type.
- **Sideroblastic Anemia**: It is microcytic anemia in which the bone marrow produces sideroblasts (ring-shaped blood cells) due to the inability of the body to place iron properly into hemoglobin. It presents with abnormal iron studies as well as splenomegaly.
- **Sickle Cell Disease**: A hereditary hemoglobinopathy resulting in hypoxia and anemia. They share demographics however, sickle cell disease is a chronic hemolytic disorder whereas G6PD deficiency is episodic and less severe.

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