# Orotic Acid and Orotidine

**FOR PATIENTS WITH A SUSPECTED UREA CYCLE DISORDER, UNEXPLAINED HYPERAMMONEMIA, OR SUSPECTED HEREDITARY OROTIC ACIDURIA**

## Disease Overview
- Orotic acid may be elevated in patients with urea cycle disorders, hereditary orotic aciduria, and other causes of elevated ammonia.
- The urea cycle is the body’s primary system for removing waste nitrogen produced by the metabolism of protein and other nitrogen-containing molecules. Defects in the urea cycle can lead to life-threatening accumulations of ammonia. Several enzymes, each encoded by a different gene, are involved in the urea cycle; mutations in any of the urea cycle genes may cause a urea cycle defect.
  - Classic urea cycle disorders are characterized by hyperammonemia, cyclical vomiting, seizures, lethargy, coma, and neonatal death if not treated.
  - Elevated levels of orotic acid appear in many urea cycle disorders, including ornithine transcarbamylase (OTC) deficiency, citrullinemia type I, argininosuccinate lyase deficiency, arginase deficiency, lysinuric protein intolerance, and hyperornithinemia-hyperammonemia-homocitrullinemia.
- Hereditary orotic aciduria is a rare condition caused by deficiency of the enzyme uridine-5-monophosphate. Symptoms include megaloblastic anemia, neutropenia, crystalluria, and susceptibility to infection.

## Epidemiology
- Incidence of urea cycle disorders is approximately one in 25,000 overall but may be higher due to partial deficiencies.
- Hereditary orotic aciduria is very rare.

## Genetics
- Most urea cycle disorders are autosomal recessive; OTC is X-linked.
- Hereditary orotic aciduria is autosomal recessive.

## Indications for Ordering
- In patients with elevated ammonia, initial testing often includes plasma amino acids (AA) and urine organic acids (OA).
- Orotic acid testing may be ordered subsequent to or in conjunction with testing for AA and OA.

## Contraindications for Ordering
- Not recommended as a stand-alone test to evaluate patients with hyperammonemia.
- This test will not determine carrier status.

## Methodology
- Liquid chromatography/tandem mass spectrometry to quantify orotic acid and orotidine.
- Standard orotic acid methodologies do not separate orotidine and orotic acid.
- Separation of orotidine from orotic acid by ARUP’s test allows for more precise orotic acid measurement.

## Interpretation
- Normal concentrations of orotic acid and orotidine do not exclude a urea cycle disorder.
- Other disorders causing hyperammonemia may also show elevated orotic acid levels.
- Pregnant women may have higher-than-normal orotic acid excretion.

## Limitations
- This test cannot predict disease severity.
- This test cannot determine carrier status.

## Related Tests
- 0080710 Amino Acids Quantitative, Plasma
- 0098389 Organic Acids, Urine
- 2004896 Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication

## References
**Test Information**

<table>
<thead>
<tr>
<th>Test Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0092458</td>
<td>Orotic Acid and Orotidine, Urine</td>
</tr>
</tbody>
</table>

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com. For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

**AUTHORS**

Amanda Openshaw, MS, LCGC  
Marzia Pasquali, PhD  
Nicola Longo, MD, PhD