Newborn Screening ACT Sheet
[Decreased Citrulline]*
Urea Cycle Disorder

* A decreased Citrulline concentration alone, in most instances, is NOT informative. To better determine the risk of a newborn being affected with a relevant urea cycle disorder and to reduce the number of false positive results, several amino acid ratios (e.g., Glutamine/Citrulline and others; see Genet Med 2011: 13: 230–254) must be considered. Note that some newborn screening laboratories do not report decreased citrulline or abnormal amino acid ratios.

Differential Diagnosis: Proximal urea cycle defects, including N-acetylglutamate synthetase (NAGS) deficiency, carbamoylphosphate synthetase (CPS) deficiency, and ornithine transcarbamoylase (OTC) deficiency.

Condition Description: The urea cycle is the enzyme cycle whereby ammonia is converted to urea. Deficiencies of NAGS, CPS, and OTC interrupt early steps in the cycle resulting in reduced citrulline and hyperammonemia. The genetic disorders NAGS and CPS deficiencies are autosomal recessive, while OTC deficiency is X-linked.

YOU SHOULD TAKE THE FOLLOWING ACTIONS IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea). If any are present, refer for emergency management.
- Consult immediately with pediatric metabolic specialist.
- Assess the newborn clinically (poor feeding, vomiting, lethargy, hypotonia, tachypnea, seizures).
- Measure blood ammonia. If elevated, refer for emergency management of hyperammonemia in consultation with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- Provide family with information about signs and symptoms of hyperammonemia.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma ammonia to determine presence of hyperammonemia. In all three urea cycle deficiencies (NAGS, CPS, OTC), plasma amino acid analysis will show decreased citrulline. Orotic acid, which may be detected by urine organic acid analysis or by a specific urine orotic acid measurement, will be increased in OTC deficiency. Note: Urine organic analysis may not identify orotic acid in some laboratories because of the tests employed.

Clinical Considerations: The NAGS, CPS, OTC deficiencies can present acutely in the newborn period with hyperammonemia, seizures, failure to thrive, lethargy, and coma. Later signs include intellectual disability. Neonatal illness is rare in female carriers of OTC deficiency; some may later develop hyperammonemia in association with intercurrent illness.

Additional Information:
- Genetics Home Reference
  - CPS Deficiency
  - NAGS Deficiency
  - OTC Deficiency

Referral (local, state, regional and national):
- Testing
  - CPS Deficiency
  - NAGS Deficiency
  - OTC Deficiency
- Clinical Services
- Find Genetic Services

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.
Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

© American College of Medical Genetics and Genomics, 2012 (Funded in part through MCHB/HRSA/HHS grant #U22MC03957)