Disease Name Isovaleric acidemia

Alternate name(s) Isovaleric acid CoA dehydrogenase deficiency

**Acronym** IV

Disease Classification Organic Acid Disorder

Variants Yes

Variant name Chronic intermittent form

Symptom onset Infancy (in the acute neonatal form). The chronic intermittent form presents

later in infancy or in childhood.

**Symptoms** Episodic overwhelming illness with vomiting, ketosis, acidosis and coma.

Hematological abnormalities include leucopenia, thrombocytopenia and

possible anemia.

**Natural history without treatment** About 50% of patients with the acute neonatal form will die during their first

episode. Survivors may have neurological damage though several have made complete recoveries. Patients with the chronic form may have neurologic damage, but the majority of patients are developmentally normal.

Natural history with treatment Intellectual prognosis depends on early diagnosis and treatment and

subsequently on long-term compliance. If treated appropriately, most will

have normal development.

**Treatment**Low protein diet with restricted leucine intake, glycine supplementation and

possible carnitine supplementation.

Other Sometimes a "sweaty feet" odor is reported during an acute crisis.

Physical phenotype No obvious dysmorphic features.

**Inheritance** Autosomal recessive

General population incidence 1:230,000

Ethnic differences None known

Population N/A Ethnic incidence N/A

Enzyme location N/A

Enzyme Function Isovaleryl-CoA dehydrogenase is the first step in the branched chain organic

acid metabolism of leucine.

Missing Enzyme Isovaleryl-CoA dehydrogenase

Metabolite changes Urinary isovaleryl glycine, 3-hydroxysoraline acid, increased isovaleric acid in

blood. During acute attacks, 4-hydroxyisovaleric acid, mesaconic acid, and methylsuccinic acid, isovalerylglycine and 3-hydroxyisovaleric acid are

present.

**Prenatal testing** Enzyme analysis by GCMS in amniotic fluid or CVS tissue.

MS/MS Profile Elevated C5 isovaleryl carnitine

OMIM Link http://www.ncbi.nlm.nih.gov/omim/243500

Genetests Link <u>www.genetests.org</u>

Support Group Organic Acidemia Association

www.oaanews.org

Save Babies through Screening Foundation

www.savebabies.org Genetic Alliance

www.geneticalliance.org

## American College of Medical Genetics ACT SHEET

# Newborn Screening ACT Sheet [Elevated C5 Acylcarnitine] Isovaleric Acidemia

Differential Diagnosis: Isovaleric acidemia (IVA), 2-Methylbutyrylglycinuria (2MBG) (also referred to as short/branched chain acyl-CoA dehydrogenase deficiency or SBCAD deficiency); antibiotic-related (pivalic acid derived) artifact.

Condition Description: IVA and 2MBG result from different defects in the metabolism of the branched chain amino acids, leucine (isovaleryl-CoA dehydrogenase in IVA), and isoleucine (short/branched chain acyl-CoA dehydrogenase in 2MBG). In both conditions, specific metabolites accumulate and are potentially toxic.

#### 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, odor of sweaty feet).
- Consult with pediatric metabolic specialists
- Evaluate the newborn; if infant is ill, initiate emergency treatment as indicated by metabolic specialist and transport IMMEDIATELY to tertiary center with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- Educate family about signs, symptoms and need for urgent treatment of metabolic acidosis (poor feeding, vomiting, lethargy, tachypnea, odor of sweaty feet).
- Report findings to newborn screening program.

**Diagnostic Evaluation:** Plasma acylcarnitine analysis confirms the increased C5. Urine organic acid analysis-will show isovalerylglycine in IVA and 2-methylbutyrylglycine in most cases of 2MBG. Urine acylglycine and acylcarnitine analysis may also be informative.

Clinical Considerations: Isovaleric acidemia presents in the neonate with metabolic ketoacidosis, a "sweaty feet" odor, dehydration, hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive. Milder variants without neonatal illness exist. Long-term prognosis of IVA with appropriate therapy is good. The clinical spectrum of 2MBG is variable. To date, most patients identified by newborn screening with 2MBG are of Hmong descent and remain asymptomatic.

#### Additional Information:

New England Consortium of Metabolic Programs Gene Reviews Genetics Home Reference

### Referral (local, state, regional and national):

Testing Clinical 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 patricular 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.

 $\textbf{@} \ American \ College \ of \ Medical \ Genetics, \ 2010 \ (Funded \ in \ part \ through \ MCHB/HRSA/HHS \ grant \ \#U22MC03957)$ 

