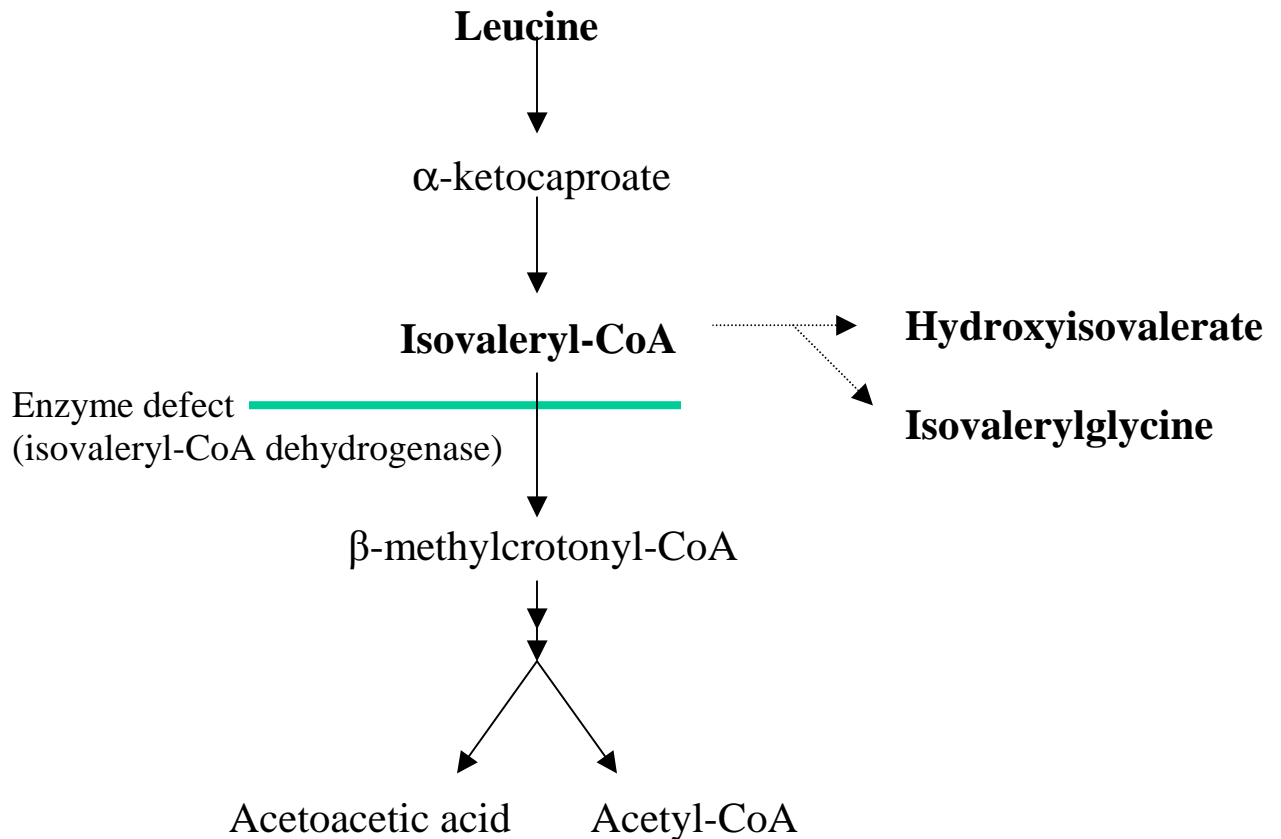


**ACUTE ILLNESS PROTOCOL
ORGANIC ACID DISORDERS**

ISOVALERIC ACIDEMIA

PATHOPHYSIOLOGY



Catabolic stress such as normal perinatal catabolism or febrile illness (e.g. infection) produces endogenous proteolysis. The released amino acids add to the amino acid pools and are degraded within the relevant pathways, producing increased amounts of the organic acid intermediates. When excessive protein is ingested, a similar increase in available amino acids occurs. When there is a metabolic defect after the amino acid has lost its nitrogen in the course of degradation (see the pathway above), the esterified organic acid-CoA

accumulates. Much of the esterified organic acid is converted to the parent organic acid and other organic acid metabolites.

The increased metabolite measured in urine and/or blood in these disorders is the organic acid per se and, in urine, the related metabolites. The increased organic acids overwhelm the body's acid-base balance, resulting in metabolic acidosis. This metabolic stress produces an increased need for cellular energy, which is provided by enhanced degradation of glucose, resulting in hypoglycemia. The hypoglycemia is exacerbated by inhibition of gluconeogenesis induced by one or more of the accumulated organic acids. The hypoglycemia sets in motion hormonal changes that cause release of free fatty acids from adipose tissue. The fatty acids are transported into mitochondria as carnitine conjugates where they are β -oxidized to ketones, producing ketosis. The increased organic acid also inhibits the urea cycle producing hyperammonemia, glycine degradation producing hyperglycinemia, and hematopoiesis resulting in neutropenia. Hence, the constellation of laboratory findings in these organic acid disorders:

Ketoacidosis
Hypoglycemia
Neutropenia
Hyperammonemia
Hyperglycinemia

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation. The ketoacidosis also produces vomiting. Mobilization of free fatty acids from stores to the liver produces a fatty liver. The increased organic acids may also be toxic to hepatocytes.