in Brief

Galactosemia

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AUTHOR DISCLOSURE
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Hereditary Galactosemia. Demirbas D, Coelho AI, Rubio-Gozalbo ME, Berry GT. *Metabolism.* 2018;83:188–196

Congenital Galactosemia. Grady NEG, Millard D. *NeoReviews.* 2017;18(4):e228–e233

International Clinical Guideline for the Management of Classical Galactosemia: Diagnosis, Treatment, and Follow-up. Welling L, Bernstein LE, Berry GT, et al. *J Inherit Metab Dis.* 2017;40(2):171–176

Galactosemia, first described in the early 1900s by von Reuss, is an autosomal recessive inborn error of carbohydrate metabolism characterized by the inability to convert galactose to glucose. In 1970, Louis Leloir won the Nobel Prize in Chemistry for defining the pathway of galactose catabolism. Three galactose-metabolizing enzymes are active in the Leloir pathway: galactokinase (GALK), galactose-1-phoshate uridyltransferase (GALT), and uridine diphosphate (UDP)-galactose 4-epimerase (GALE). When any of these enzymes is deficient, galactose accumulates and galactosemia is the consequence.

Classic galactosemia, resulting from any of more than 250 mutations in the *GALT* gene, initially presents in the newborn period with subtle, nonspecific clinical signs, such as feeding intolerance, jaundice, lethargy, hypotonia, vomiting, and poor weight gain. If left untreated, it advances to a severe life-threatening event progressing to hepatomegaly, hepatic failure, bleeding diatheses, renal dysfunction, encephalopathy, *Escherichia coli* sepsis, shock, and, ultimately, death. Galactosemia occurs throughout the world, but its incidence varies widely: in the United States and Europe it affects approximately 1:40,000 to 1:60,000 newborns; Ireland has the highest reported frequency (1:20,000) and Japan the lowest (1:1,000,000).

The primary sources of galactose in the human diet are milk and milk-containing products: galactose and glucose together form the disaccharide lactose, which is present in both human and bovine milk. Galactose is an important carbohydrate for infants because it is a source of energy and is used for the synthesis of glucoconjugates such as galactoproteins, galactolipids, and mucopolysaccharides (Fig).

Galactose is first phosphorylated and converted to galactose-1-phosphate (Gal-1-P) by the enzyme GALK. GALT then converts Gal-1-P and UDP into glucose-1-phosphate and UDP-galactose. The third enzyme in the pathway, GALE, is responsible for maintaining appropriate concentrations of UDP-glucose and UDP-galactose; it works through a seesaw reaction between UDP-glucose and UDP-galactose, converting each to the other as needed for the synthesis of galactoproteins, galactolipids, and mucopolysaccharides (Fig).

In classic galactosemia, Gal-1-P is the major toxic metabolite, and it serves as both the primary marker to identify affected patients and then as

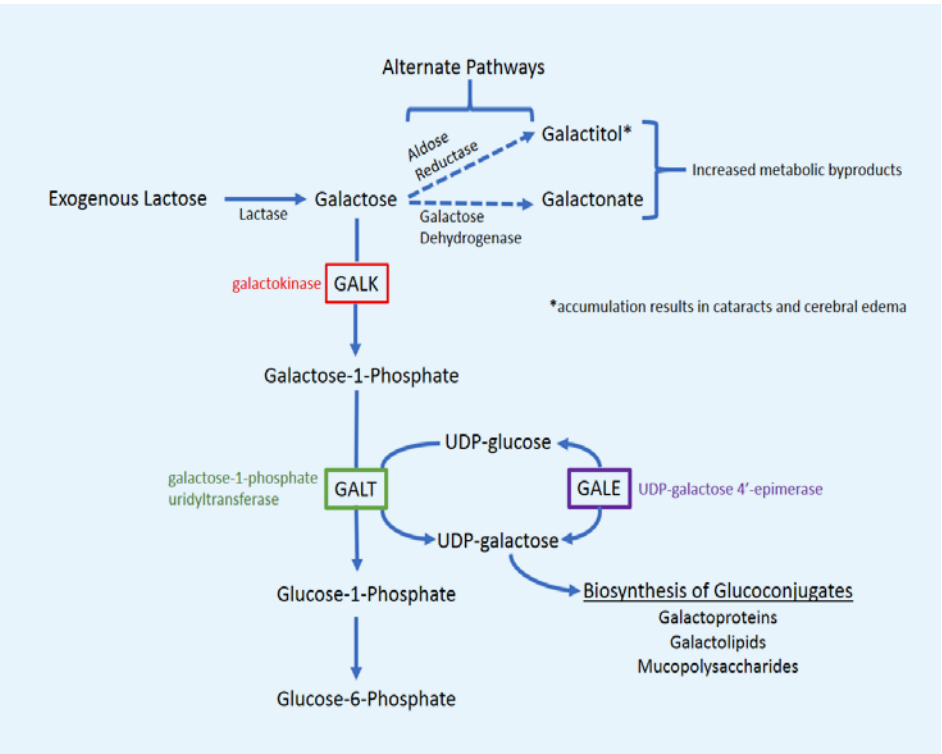

Figure. Pathway of galactose metabolism.
UDP=uridine diphosphate.

Table 1. Recommended Formulas for Infants with Galactosemia

MANUFACTURER	SOY-BASED FORMULAS	ELEMENTAL FORMULAS
Mead Johnson Nutritionals, Evansville, IN	ProSobee®	PurAmino®, Nutramigen®, Pregestimil®
Abbott Nutritionals, Columbus, OH	Similac Isomil®	EleCare®, Alimentum®
Nutricia North America, Rockville, MD		Neocate®

a therapeutic guide in their management. Unfortunately, there is little correlation between the concentration of Gal-1-P and long-term outcomes. Although restriction of galactose intake results in a rapid decrease in Gal-1-P, levels remain elevated compared with controls because of endogenously manufactured galactose, a process that is increased in infants and children compared with adults.

Based on the amount of enzyme activity, GALT deficiency can be stratified into 3 categories. The most severe form is classic galactosemia, where enzyme activity is absent or barely detectable (≤1% enzyme activity) in erythrocytes and liver tissue. Second is clinical variant galactosemia, typically exhibiting 1% to 10% enzyme activity. Clinical variant differs from classic galactosemia by the presence of elevated enzyme levels in other organs, namely, the brain, liver, and intestines. Last is the biochemical variant, referred to as Duarte galactosemia, distinguished by retaining 15% to 35% enzyme activity. Duarte galactosemia affects approximately 1:4,000 newborn infants, making it far more prevalent than classic and clinical variant galactosemia. It occurs when a child is born to a parent who is heterozygous for the Duarte allele and the other parent is heterozygous for classic galactosemia. The variability among classical, clinical, and biochemical GALT deficiency reflects the residual enzyme activity.

GALK deficiency results in galactose metabolites produced via alternative pathways with toxic accumulation of galactitol and galactonate (Fig). Galactitol targets the eyes and brain, leading to the formation of cataracts and, less frequently, to cerebral edema. Early dietary restriction of galactose prevents these complications. GALE deficiency ranges from clinically mild to severe, depending not only on enzyme activity but also on whether the deficiency is isolated to erythrocytes or is more generalized in affecting tissues and organs. Severe GALE deficiency mimics classic galactosemia, presenting with similar clinical manifestations in the newborn period.

Galactosemia is often identified through state newborn screening programs. Most newborn state screening programs start by measuring GALT activity in erythrocytes, followed by galactose levels when GALT levels are low. Because state newborn screening results can take up to 7 days to return, many states expedite the screen if galactosemia is clinically suspected. Definitive diagnosis is made by measuring galactose-1-phosphate levels and GALT enzyme activity and with molecular genetic testing. When galactose levels are high and GALT activity is normal, GALK and GALE deficiencies should be considered, as well as other disorders that result in liver failure. If galactosemia is suspected before newborn screening results are available, analyzing urine for reducing substances (galactose, glucose, and fructose) and simultaneously measuring point-of-care glucose can be helpful. A newborn with galactosemia will have elevated levels of reducing substances in the urine because of spilled galactose along with a normal or low blood glucose level. At this point, a galactose-restricted diet should be initiated immediately and confirmatory testing performed. Infants should be closely monitored for hyperbilirubinemia, sepsis, and clotting abnormalities. Coagulopathy resulting from hepatic damage can be treated with vitamin K and fresh frozen plasma.

Galactosemia can be prenatally diagnosed through amniocentesis or chorionic villus sampling when there is a family history of or strong suspicion for disease. Despite prenatal recognition of galactosemia and immediate institution of a galactose-restricted diet, affected infants may exhibit long-term complications. A soy-based or elemental formula should be initiated immediately (Table 1). Powdered formula is preferable to ready-to-feed or liquid concentrate because galactose-containing emulsifiers are added to these liquid forms. Initiating a galactose-restricted diet is paramount in preventing acute life-threatening events in the newborn period but does not prevent long-term complications such as cognitive dysfunction, ovarian damage, and growth complications. Although a galactose-restricted diet is recommended beyond infancy, for how long the restriction continues to offer

benefit is unclear, resulting in wide variations in clinical practice.

Physicians should meticulously monitor patients for long-term complications of classic galactosemia, which involve neurologic, reproductive, and faltering growth issues, by ensuring proper screening of infants, children, and adults. Because there have been conflicting reports on neurodevelopmental outcomes in children with Duarte variant, these patients should also be followed carefully. The exact causes of long-term complications remain unclear; abnormal glycosylation of galactoproteins, mucopolysaccharide, and galactolipids has been postulated as a possible mechanism. Central nervous system involvement may present with cognitive defects as early as age 18 to 36 months; symptoms include intellectual

Table 2. Outline on Galactosemia

	GALK	GALT	GALE
Enzyme deficiency	Galactokinase	Galactose-1-phosphate uridyltransferase	Uridine diphosphate -galactose-4-epimerase
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
Incidence	1:100,000–1,000,000	1:40,000–1:60,000	Mild form: 1:6,200 in African Americans to 1:64,000 in non–African Americans Severe form: 1:23,000
Chromosomal location	17q24	9p13	1p36
Newborn screen results	↑Galactose Normal GALT	↑Galactose ↓GALT	↑Galactose Normal GALT
Laboratory tests	↑↑Plasma galactose ↑↑Plasma galactitol ↑↑Plasma galactonate ↑↑Urine galactitol, galactose, galactonate Normal erythrocyte galactose-1-phosphate	↑↑Plasma galactose ↑Plasma galactitol ↑Urine galactitol, galactose, galactonate ↑↑ Erythrocyte galactose-1-phosphate	↑Plasma galactose ↑Plasma galactitol ↑Erythrocyte galactose-1-phosphate ↑Urine galactose, galactitol, galactonate
Definitive diagnostic tests	↓RBC GALK enzyme deficiency GALK mutation analysis	↓RBC GALT enzyme activity GALT mutation analysis	↓RBC GALE enzyme activity GALE mutation analysis Some cases discovered retrospectively in neurodevelopmentally delayed patients
Common mutations	P28T	Classic: Q188R, K285N, L195P Clinical variant: S135L Biochemical (Duarte): N314D/Q188R	Severe form: V94M, K257R, R335H, L183P Mild form: L313M, D103G
Symptoms	Bilateral cataracts	Initial presentation: Feeding intolerance, jaundice, poor growth, and lethargy Late presentation: Hepatic failure, coagulopathy, renal dysfunction, cataracts, *Escherichia coli* sepsis and death	Can be asymptomatic or present similar to classic galactosemia, including learning deficits, poor growth, and neurologic delays
Prognosis	Cataracts fully preventable with early galactose-restricted diet	Prompt galactose-restricted intake will bypass severe life-threatening events, all patients at risk for long-term complications: premature ovarian failure, impaired neurodevelopment, speech problems, extrapyramidal abnormalities, and diminished bone mineral density	Long-term prognosis has not been elucidated

RBC=red blood cell.

impairment (45%), verbal dyspraxia (90%), and delayed language and motor dysfunction (ataxia, extrapyramidal impairments). Long-term psychiatric and behavioral disorders are not uncommon. All patients require assessment for cognitive, developmental, intellectual, speech, and motor function using well-validated testing measures. Referral to a developmental pediatrician and early intervention services should be initiated during the first year of life.

Primary ovarian insufficiency or failure affects 80% of women with classic galactosemia, presenting clinically with absent or delayed puberty, amenorrhea, and infertility. Affected females should be referred to a pediatric endocrinologist for hypergonadotropic hypogonadism screening. Hormonal analysis should include follicle-stimulating hormone, which may be elevated as an indication of failing ovarian function. Although a decreased anti-Mullerian hormone level has been thought to indicate diminished ovarian reserve and an inability to produce good-quality eggs, studies have revealed a lack of accuracy in predicting pubertal development and fertility outcomes. Referral to a reproductive endocrinologist and fertility specialist should be considered to provide counseling for reproductive fertility options, hormone replacement, and birth control. Primary ovarian insufficiency has not been reported in females with the Duarte variant. In males, despite reports of cryptorchidism, galactosemia is not associated with gonadal dysfunction.

Reports of delayed growth in childhood and decreased bone mineral density in adolescents and adults mandate accurate monitoring of growth parameters, nutrition, and bone health. Bone mineral density should be evaluated using dual-energy x-ray absorptiometry. Dietary assessment and nutritional screening of calcium, phosphorous, and 25-hydroxyvitamin D levels should occur regularly, coupled with optimal intake of calcium and vitamin D3. Approximately 15% to 30% of patients with classic galactosemia develop cataracts. Regular ophthalmologic evaluation should occur during infancy and continue until resolution of cataracts.

Health-care providers are challenged when confronted with a newborn infant who presents with nonspecific clinical signs such as lethargy, poor intake, and failure to gain weight. These clinical signs are encountered in a wide array of disorders, including sepsis, congenital cardiac disease, endocrine disorders, and inborn errors of metabolism. Therefore, it should become common practice for health-care providers to include inborn errors of metabolism such as galactosemia in the differential diagnosis with other more common conditions. Expeditious recognition of galactosemia and the prompt initiation of treatment can spare the newborn infant from significant brain damage and ultimately death. Table 2 provides an outline on galactosemia. ■

HELPFUL LINKS

Providing newborn screen contact information for each US state,
National Newborn Screening and Global Resource Center
http://genes-r-us.uthscsa.edu

When newborn screens return with an actionable result,
American College of Medical Genetics
http://www.ncbi.nlm.nih.gov/books/NBK55827

For both parents and clinicians, this link provides thorough and comprehensive handouts on galactosemia and other inborn errors of metabolism,
Screening Technology and Research in Genetics (Star-G)
http://www.newbornscreening.info

Comment: *Newborn screening has, over the years, proved to be one of our most effective health-care interventions, saving thousands of lives and improving the quality of thousands more. We have Dr Robert Guthrie to thank for introducing the first newborn screening test in the early 1960s. The father of a son with intellectual disability and the uncle of a niece with phenylketonuria, he developed a simple test needing only a few drops of blood on filter paper to detect elevated levels of phenylalanine, which reversed a growth inhibitor and allowed bacteria on an agar plate to multiply. With identification of affected children as neonates, early removal of phenylalanine from their diet limited the devastating neurologic damage of untreated phenylketonuria. Dr Guthrie saw that his technique could be a paradigm applicable to other inborn errors of metabolism, and the second test he went on to develop was the newborn screen for galactosemia.*

—*Henry M. Adam, MD*
Associate Editor, In Brief