Glutaric aciduria type I: Quick reference guide

Introduction

Glutaric aciduria type I (synonym, glutaric acidemia type I) is an autosomal recessive disease caused by inherited deficiency of glutaryl-CoA dehydrogenase. This mitochondrial enzyme is encoded by the *GCDH* gene localized on gene map locus 19p13.2 and is involved in the catabolism of L-lysine, L-hydroxylysine and L-tryptophan. Biochemically, glutaric acidurias type I is characterized by an accumulation of glutaric acid, 3-hydroxyglutaric acid, and glutarylcarnitine. These can be detected in body fluids by metabolite analysis.

Untreated, the majority of patients develop striatal injury during a finite period of brain development [age 3-36(-72) months]. This may occur acutely following an acute encephalopathic crisis often precipitated by intercurrent febrile illness, or insidiously. The characteristic neurological sequela is secondary dystonia, superimposed on axial hypotonia. With aging, there is a tendency for a fixed dystonia and akinetic-rigid parkinsonism to develop. Morbidity and mortality is high in symptomatic patients.

It has been demonstrated that early diagnosis is essential for a favourable disease course. As a consequenc, glutaric acidurias type I has been implemented in the newborn screening disease panel in some countries. Significant differences still exist in the approaches used to diagnose and manage affected patients, and there is a wide variation in the health outcome. The major aim of this guideline is to assess the common practice and to formulate recommendations for diagnosis and management of affected individuals based on the best evidence available.

Diagnostic procedure

Glutaric acidurias type I is defined as inherited deficiency of glutaryl-CoA dehydrogenase confirmed by enzyme analysis and/or demonstration of two disease-causing *GCDH* gene mutations. All other signs, symptoms and laboratory abnormalities that are found in affected patients are not pathognomonic so that the diagnosis should be suspected, but not considered as confirmed. Figure 1 summarizes the proposed diagnostic algorithm.

GCP	**The accurate diagnosis of glutaric acidurias type I has important practical implications when devising treatment plans and giving appropriate information to children and their families. The diagnostic work-up should be done by metabolic specialists**.

B	*Newborn screening* **For mass newborn screening for glutaric aciduria type I determination of C5DC in dried blood spots by tandem mass spectrometry (MS/MS).**

D	*High-risk population screening* **In a cohort with a high disease incidence due to a single common *GCDH* mutation and a low excretor phenotype, DNA-based methods should be considered for newborn screening. The use of MS/MS-based screening in such populations will likely lead to false negative results.**

D	*Confirmation of positive screening results* **For the confirmation of a positive newborn screening result, a specific diagnostic work-up is required, including a quantitative analysis of glutaric and 3-hydroxyglutaric acid in urine or blood, *GCDH* gene analysis, and, if feasible, enzyme analysis.**

D	*Metabolic testing in symptomatic patients* **In patients with signs and symptoms of glutaric aciduria type I, a specific diagnostic work-up should include quantitative analysis of glutaric and 3-hydroxyglutaric acid in urine or blood, *GCDH* gene analysis, and/or enzyme analysis**

Metabolic maintenance treatment

Table 1 summarizes a proposed protocol for maintenance treatment.

C	*Interdisciplinary team* **Metabolic treatment should be implemented by an interdisciplinary team that includes metabolic pediatricians, dietitians, and nurses. Parents and patients should have regular training and written treatment protocols.**
C	*Dietary treatment* **A low lysine diet (ie reducing lysine intake to a safe requirement) with or without additional administration of lysine-free, tryptophan-reduced amino acids supplements should be used for dietary treatment, in particular in asymptomatic patients up to age 6 years.**
C	*Carnitine supplementation* **Carnitine should be supplemented in patients with glutaric aciduria type I and should be continued lifelong**

Emergency treatment

Routine treatment does not reliably protect against striatal injury, so it is crucial to use an intensified emergency treatment protocol during episodes that are likely to induce catabolic state. Tables 2-4 summarizes proposed protocols for emergency treatment.

C	*Start of emergency treatment* **Emergency treatment should start without delay and should be performed aggressively during febrile illness, surgery and immunization within the vulnerable period for acute encephalopathic crises (up to age 6 years)**
GCP	*Emergency treatment after age 6 years* **Emergency treatment in children after age 6 years should be considered at least during severe illness. It should be performed similarly to that in the age group 0-6 years with adaptation to the individual.**

Management of neurologic complications

GCP	*Expert neurological evaluation* **In all symptomatic patients, expert neurological evaluation should be performed by a neuropediatrician and/or later on by a neurologist to identify clearly the kind and severity of movement disorder. In addition, dietitians, physicotherapists, occupational therapists, orthopedists, seating and speech specialists and providers of communication aids, should be consulted to provide multi-disciplinary support for children with movement disorders.**
D	*Antidystonic drug treatment* **Baclofen and benzodiazepines as monotherapy or in combination should be used as first line drug treatment for focal and generalized dystonia. Intrathecal baclofen should be considered as additional therapy for generalized dystonia and spasticity. Trihexyphenidyl should be considered as second line treatment for dystonia, particularly in adolescents and adults. Botulinum toxin A should be considered as additional therapy for severe focal dystonia.**
GCP	*Antiepileptic drug treatment* **Diagnosis, choice of antiepileptic drug therapy and management of seizures in GA-I should follow existing guidelines – except for the use of valproate which should be avoided in this condition. The diagnosis of epilepsy and choice of antiepileptic drugs should be made by a pediatric neurologist or pediatrician with expertise in childhood epilepsy. In adulthood, patients with epilepsy should be followed and antiepileptic therapy should be monitored by an adult neurologist.**
D	*Subdural haemorrhage* **Children with subdural haemorrhage and/or bitemporal arachnoid cysts should be investigated for glutaric aciduria type I, in particular if occuring in combination with macrocephaly and/or a movement disorder.**
D	*Shaken baby syndrome* **Glutaric aciduria type I should be excluded in children with suspected shaken baby syndrome using the**

	recommendations for selective screening.

D	*Neurosurgery* **Neurosurgical intervention for arachnoid cysts and subdural haemorrhages in affected patients should be undertaken very cautiously in close consultation with the pediatric neurosurgeon.**

Therapy monitoring

Table 5 provides a schedule for biochemical monitoring in glutaric aciduria type I.

GCP	*General statement* **Therapy should be accompanied by regular professional monitoring. Monitoring should be intensified at any age if there are new complications (disease- or therapy-related) or non-adherence to treatment.**

D	*Biochemical monitoring (organic acid analysis)* **Urine analysis of GA and 3-OH-GA is not informative for therapy monitoring.**

D	*Biochemical monitoring (amino acid analysis)* **Amino acids in plasma (ideally 3-4 h postprandially) should be monitored during dietary treatment.**

D	*Biochemical monitoring (carnitine status)* **Carnitine status in plasma should be monitored in all patients to detect secondary carnitine depletion.**

GCP	*Neuroradiologic investigations* **Neuroradiologic investigations should be performed in case of neurologic deteroriation but are not generally recommended for regular follow-up monitoring.**

Legend

Grades of recommendations

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}.
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}.
D	Evidence level 3 and 4; or Extrapolated evidence from studies rated as 2^{+}.

Good practice points

GCP	Recommended best practice based on the clinical experience of the guideline development group.

ANNEXE

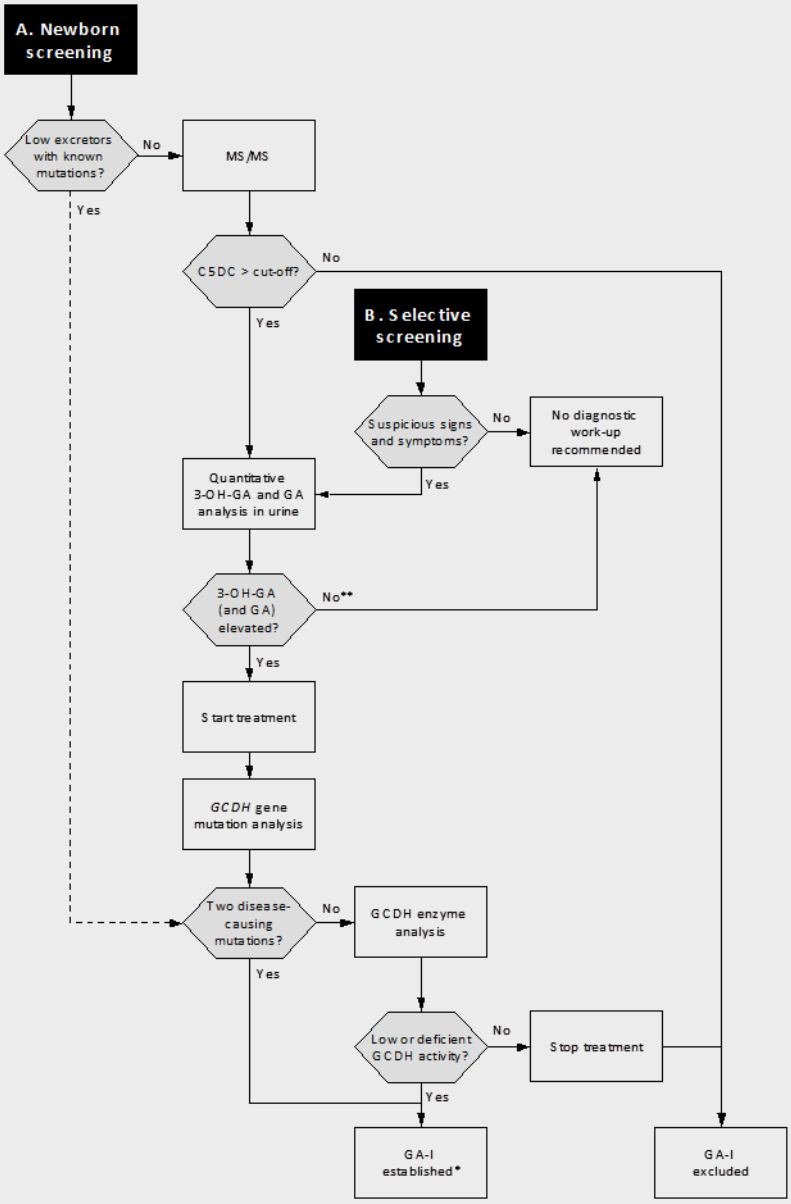

Fig 1. Diagnostic algorithm for glutaric aciduria type I

A, Newborn screening for glutaric aciduria type I is performed using MS/MS. In low excretor cohorts with known mutations, *GCDH* gene mutation analysis should be considered as alternative method (dotted line). Treatment should be started after the identification of two disease-causing mutations (*). **B, Selective screening** should be initiated if the diagnosis of GA-I is suspected clinically or there is a positive family history. Note that a few patients with a low-excreting phenotype may show (intermittently) normal urinary excretion of 3-hydroxyglutaric acid (and glutaric acid). If an individual shows normal 3-hydroxyglutaric acid (and glutaric acid) concentrations in urine (or other body fluids) but presents with highly suspicious signs and symptoms for glutaric aciduria type I, further diagnostic studies should be considered (**).

Table 1. Metabolic maintenance treatment (protocol proposed by GDG)

If normal growth and development are not achieved these recommendations should be modified according to individual needs.

Treatment		Age				
		0–6 months	7–12 months	1–3 years	4–6 years	> 6 years
1. Low lysine diet						
Lysine (from natural protein)[a]	*mg/kg per day*	100	90	80-60	60-50	Avoid excessive intake of natural protein; use natural protein with a low lysine content; according to 'safe levels' (Suppl. Table 6)
Amino acid mixtures (protein)[b]	*g/kg per day*	1.3-0.8	1.0-0.8	0.8	0.8	
Energy	*kcal/kg per day*	115-80	95-80	95-80	90-80	
2. Micronutrients[c]	%	≥ 100	≥ 100	≥ 100	≥ 100	≥ 100
3. Carnitine	mg/kg per day	100	100	100	100-50	30-50

[a]The lysine/protein ratio varies considerably in natural food and thus natural protein intake in children on a low lysine diet is dependent on the natural protein source. The natural protein intake is relatively high if patients predominantly use sources of natural protein with a low lysine content.

[b]Lysine-free, tryptophan-reduced amino acid mixtures should be supplemented with minerals and micronutrients as required to maintain normal levels. Adequate intake of essential amino acids is provided from natural protein and lysine-free, tryptophan-reduced amino acid supplements. The amount of amino acid supplements is adjusted to reach at least the 'safe levels'.

[c]According to international dietary recommendations.

Table 2. Strategies to prevent delayed start of emergency treatment

Topic	Proposed strategies to avoid delay
Education and training of parents	Parents should be informed in detail about the natural history and the particular risks of glutaric aciduria type I, in particular the manifestation and neurological sequels of an acute encephalopathic crisis. They should be instructed precisely about the management of maintenance and emergency treatment and this knowledge should be reinforced during regular visits at a metabolic center.
Treatment protocols	Written protocols for maintenance and emergency treatment should be given to all who may be involved (parents, metabolic centers, local hospitals) and kept updated. Parents should also receive an emergency card (preferably laminated) summarizing the key information on glutaric aciduria type I and basic principles of treatment. The telephone number of the responsible metabolic center/physician should be written on the protocol and the emergency card. Parents should take their emergency instructions and supplies of maltodextran and AA supplements when going to hospital.
Supplies	Parents should be advised always to maintain adequate supplies of specialized dietetic products (maltodextran, lysine-free, tryptophan-reduced amino acid mixtures) and drugs required for maintenance treatment and emergency treatment at home.
Local hospital or pediatrician	The closest hospital/pediatrician should be clearly instructed if glutaric aciduria type I has been newly diagnosed in a child. Key information (including written treatment protocols) should be provided to the local hospital/pediatrician without delay and *before* inpatient emergency treatment might be necessary. Inpatient emergency treatment should be started immediately in the closest hospital if necessary and follows the supervision of the responsible metabolic center which should be contacted without delay.
Holidays	Metabolic specialists/centers in the vicinity of the holiday resort should be informed in writing about the disease and the recent treatment *before* the start of the holidays. The emergency card and treatment protocols should be translated *before* the start of the holidarys if necessary.
Infectious diseases	During infectious disease the responsible metabolic center/metabolic specialists should be informed (by parents or local hospitals/pediatricians) without delay to allow supervision of the emergency management. Parents should be instructed to call their doctor and/or metabolic consultant as soon as a temperature of 38.5 °C is noted and an intercurrent illness is suspected either, an upper respiratory infection, gastrointestinal infection or if increased irritability develops.
Vomiting/ diarrhoea	Vomiting and diarrhoea is particularly dangerous – even in the absence of fever. Please follow the recommendations for *"infectious diseases"* (see above).
Surgery	If a surgical intervention is planned, the responsible metabolic center/specialist should be informed *before* such interventions to discuss the specific risks of affected patients with surgeons and anaesthesiologists, to recommend a protocol for the postsurgical metabolic management and to allow supervision of this period. If possible, the postsurgical metabolic management should be performed in a metabolic center. In general, fasting should be avoided, glucose infusions applied, and carnitine dosage doubled.

Table 3. Emergency treatment at home (protocol proposed by GDG)

A. Oral carbohydrates[a]	**Maltodextran**			
Age (years)	%	kcal/100 mL	KJ/100 mL	Volume (mL) per day orally
Up to 0.5	10	40	167	min. 150/kg
0.5-1	12	48	202	120/kg
1-2	15	60	250	100/kg
2-6	20	80	334	1200-1500
6-10	20	80	334	1500-2000
>10	25	100	418	2000-2500
B. Protein intake				
Natural protein	Stop for 24 to a maximum of 48 hours, then reintroduce and increase stepwise until the amount of maintenance treatment is reached within 48 (-72) hours. Prolongation of inadequately low protein intake increases the risk of protein catabolism.			
AA mixtures[b]	If tolerated, amino acid mixtures should be administered according to maintenance therapy (see also Table 1)			
C. Pharmacotherapy				
L-Carnitine	Double carnitine intake: eg 200 mg/kg per day p.o. in infants			
Antipyretics	If body temperature raises above 38.5 °C (101 F), antipyretics, such as ibuprofen or paracetamol (each 10-15 mg/kg per single dose, 3-4 doses daily, maximum daily dose 60 mg/kg body weight) should be administered.			

[a]Solutions should be administered every 2 hours day and night.

[b]If neonates and infants also receive a lysine-free, tryptophan-reduced amino acid supplement, this can be continued but should be fortified by maltodextran. Patients should be re-assessed every 2 hours.

Table 4. Emergency treatment in hospital (protocol proposed by GDG)

A. Intravenous infusions		
Glucose	Age (years)	Glucose (g/kg per day IV)
	0-1	(12-) 15
	1-3	(10-) 12
	3-6	(8-) 10
	6-10	(6-) 8
	>10	3-6
Insulin	If persistent hyperglycemia > 150 mg/dL (> 8 mmol/L) and/or glucosuria occurs, start with 0.05 IE insulin/kg per h IV and adjust the infusion rate according to serum glucose	
B. Protein intake		
Natural protein	Stop for 24 to a maximum of 48 hours, then reintroduce and increase stepwise until the amount of maintenance treatment is reached within 48 (-72) hours. Prolongation of inadequately low protein intake increases the risk of protein catabolism.	
AA mixtures[a]	If tolerated, lysine-free and tryptophan-reduced amino acid mixtures should be administered orally or by nasogastric tube according to maintenance therapy (see also Table 1).	
C. Pharmacotherapy		
L-Carnitine	100 (-200) mg/kg per day i.v.	
Antipyretics	If body temperature rises above 38.5 °C (101 F), antipyretics, such as ibuprofen or paracetamol (each 10-15 mg/kg per single dose, 3-4 doses daily, maximum daily dose 60 mg/kg body weight) should be administered.	
Sodium bicarbonate	If acidosis; alkalination of urine also facilitates urinary excretion of organic acids	
D. Monitoring		
Blood	Glucose, blood gases, electrolytes, calcium, phosphate, complete blood cell count, creatinine, urea nitrogen, C-reactive protein, amino acids[b], carnitine, blood culture (if applicable), amylase/lipase[c], creatine kinase[c].	
Urine	Ketone bodies, pH	
Vital signs	Heart rate, blood pressure, temperature, diuresis; Glasgow Coma Scale if reduced consciousness; assessment for neurological signs (hypotonia, irritability, rigor, dystonia)	

[a]Lysine-free, tryptophan-reduced amino acid mixtures should be supplemented with minerals and micronutrients.

[b]During the recovery phase.

[c]In severe illness to detect pancreatitis (amylase/lipase) or rhabdomyolysis (creatine kinase).

Table 5. Routine biochemical monitoring in glutaric aciduria type I (basic schedule proposed by GDG)

Parameter	Rationale	Frequency at age		
		0-2 years	2-6 years	> 6 years
Amino acids (plasma)	General nutritional status	Every 1-2 months	Every 3 months	Every 6-12 months
Tryptophan (plasma; HPLC)	Tryptophan depletion	In children with feeding problems; or if clinical presentation suggests tryptophan depletion; or if amino acid supplements do not contain tryptophan.		
Carnitine (plasma or serum)	Avoid depletion, check for non-adherence	Every 1-2 months	Every 3 months	Every 6-12 months
Complete blood cell count, ferritin	Routine surveillance, avoid depletion of iron, folate, or cobalamin	Every 6 months	Every 6 months	Every 6-12 months
Albumin	General nutritional status	If concerns exist about the nutritional status and in children with feeding problems		
Calcium, phosphate, alkaline phosphatase	Bone status[a], check for compliance	Every 3 months	Every 6 months	Every 12 months
Transaminases	Routine surveillance	Every 3 months	Every 6 months	Every 12 months

[a] If inadequate bone mineralisation is suggested, additional tests are required (eg vitamin D status, parathyroid hormone, radiological investigations for bone age and density).

According to:

Stefan Kölker, Ernst Christensen, James V. Leonard, Cheryl R. Greenberg, Avihu Boneh, Alberto B. Burlina, Alessandro P. Burlina, Marjorie Dixon, Marinus Duran, Angels García Cazorla, Stephen I. Goodman, David M. Koeller, Mårten Kyllerman, Chris Mühlhausen, Edith Müller, Jürgen G. Okun, Bridget Wilcken, Georg F. Hoffmann, and Peter Burgard.
Diagnosis and management of glutaric aciduria type I – revised recommendations.
Journal of Inherited Metabolic Diseases 2011; 34: 677 – 694.