Isovaleric Acidemia: Quick reference guide

Introduction

Isovaleric acidemia (IVA) is an inborn error of the leucine pathway caused by defects of the isovaleryl-CoA-dehydrogenase (IVD). The clinical presentation of patients with IVA is highly variable, ranging from severely affected to asymptomatic.
IVA may present either in the neonatal period or later in infancy. In the neonatal period it can present with an acute episode of fulminant metabolic acidosis, which can lead to coma or death if left untreated. Late onset of IVA can manifest at any age in infancy with a chronic intermittent form, which can be associated with developmental delays, with or without recurring acidotic episodes during periods of infections.
Recently, a new form of IVA has been identified by newborn screening (NBS). Individuals with this new type of the disease were found to have less accumulation of the respective metabolites at the time of NBS diagnosis. In the vast majority of cases, the underlying genotype relates to the presence of a certain missense mutation, c.932C>T (p.A282V), in either homozygous or compound heterozygous state.
Currently, though IVA has been known for over 40 years, data on treatment and management of IVA appears to be scarce. Further, the rarity of the disease does generally not allow single centers to gain extensive personal experience with the entire spectrum of the disease and respective management strategies. Therefore, universal treatment recommendations are urgently required, considering that IVA screening is part of NBS in many countries worldwide to date.

Clinical presentation

C	**In any newborn with a poor clinical condition and/or suspicion of sepsis, isovaleric aciduria must be considered in the differential diagnosis.** **After the neonatal period, the clinical presentation of IVA may imitate other more common conditions. Affected systems are:** • **Neurological system: severe to mild mental retardation** • **Gastrointestinal tract: vomiting with ketoacidosis, abnormal feeding behavior, failure to thrive, pancreatitis** • **Immune system: (pan)cytopenia** • **Endocrinology: mimicking ketoacidosis**
D	**Classical triggers are any situation inducing catabolic stress and excessive protein intake.**
D	**NBS, though patients can be either symptomatic or asymptomatic, can help prevent serious outcome of IVA patients.**
C	**After diagnosis, a wide variation from severe neurological impairment and multiple episodes of metabolic derangements to an asymptomatic state may occur.**

Diagnosis

B	**Determination of organic acids in urine and the acylcarnitine profile in blood are the recommended investigations to detect IVA.**
B	**NBS for IVA is technically feasible.**
C	***IVD* gene mutation analysis can be used for diagnostic confirmation of IVA.**
D	**Enzyme analysis in cultured fibroblasts can be used for diagnostic confirmation of IVA.**

C	Metabolic acidosis (with elevated anion gap), elevated lactate, hyperammonemia, elevated urinary ketone bodies (in particular in newborns) are laboratory hallmarks of organic acidurias, including IVA, and therefore should be investigated in any critically ill patient or unexplained condition.

Acute management

D	In case of severe metabolic decompensation of an IVA patient, therapy must not be delayed and emergency treatment should be started as follows: • Rehydration of dehydrated patients • Supplementation/ increase of carnitine and/or glycine • Decrease of protein intake, or total stop of protein intake in severe cases • Supply of adequate calories
D	Measurement of ammonia and lactate in blood and blood gas analysis should be performed, as they are valuable markers for acute treatment.
D	During minor illnesses (e.g. rhinitis without fever), the metabolic physician should be contacted by the family and, in accordance with his/her judgement, the management may be initiated at home. This should include a decrease in protein intake, increase in caloric intake as well as increase in glycine or carnitine dosages. If symptoms persist or deteriorate over the following hours, the patient needs to be presented to the hospital for intravenous glucose and possibly also insulin and lipids. If the child is less than 1 year old, it should always be presented to the hospital without any delay.

Long-term management

D	A moderate restriction of dietary protein provides the basis for optimal long-term therapy in patients with IVA.
D	Natural Protein intake should be restricted to reduce the isovaleric acid burden but should supply at least the safe levels of intake advocated by FAO/WHO/UNU 2007. Over-restriction of natural protein could lead to catabolism, compromised growth and metabolic instability (Table 1 and 2).
D	Leucine intake should supply at least the safe levels of intake advocated by FAO/WHO/UNU 2007 and any restriction should be supported by age appropriate energy requirements being met. Over-restriction of leucine could lead to catabolism, weight loss and metabolic instability (Table 3).
D	L-Carnitine is recommended in long-term treatment of IVA patients for acid conjugation. Doses should be adjusted to keep an adequate free carnitine level in blood. Metabolically severe types of IVA should be treated with both L-carnitine and L-glycine.
D	Medication is well tolerated.

Follow up

D	Amino acids and carnitine in plasma should be monitored during treatment. Monitoring and interpretation of urinary isovalerylglycine and plasma isovalerylcarnitine levels should be tailored on an individual basis.
D	Most of the IVA patients who have been diagnosed early (< 6 weeks of life) and fewer patients with a late diagnosis develop normally. If diagnosed early, IVA outcome is much better than if diagnosed late (Figure 1).
D	Death most commonly occurs in the newborn period. Acute forms of metabolic decompensation are the most common causes of death in the newborn period.

Table 1 - FAO/WHO/UNU 2007 safe levels of protein intake in different age groups

Age	1mo	2mo	3mo	6-12mo	1-10y	11-16y	>16y
(g/kg/d)	1.77	1.5	1.36	1.31	0.92-1.14	0.84-0.90	0.84-0.87

* The FAO/WHO/UNU (2007) have set safe levels of protein intake titrated as an age adjusted mean + 2 SD

Table 2 - Amount of natural protein for age as a result of the literature review performed by the IVA guideline group

Age	1-12 months	1-10 years	11-16 years	> 16 years
Natural protein (g/kg/d)	0.9-3.0 [a]	0.8-2.0 [b]	1.0 [c]	0.6-0.8 [d]

[a] Levy et al. 1973, Cohn et al. 1978, Bakkeren et al. 1982, Wolff et al. 1985, Berry et al. 1988, Pesce et al. 1991, Orban et al. 1994, Gilbert-Barness and Barness 1999, Loots et al. 2007
[b] Budd et al. 1967, Guibaud et al. 1973, Levy et al. 1973, Krieger and Tanaka 1976, Cohn et al. 1978, Duran et al. 1979, Chalmers et al. 1985, Berry et al. 1988, Elsas and Naglak 1988, Hou and Wang 1990, Mayatepek et al. 1991, Ito et al. 1995, Fries et al. 1996, Erdem et al. 2010
[c] Lee, P. J. et al. 1998
[d] Martin-Hernandez et al. 2009

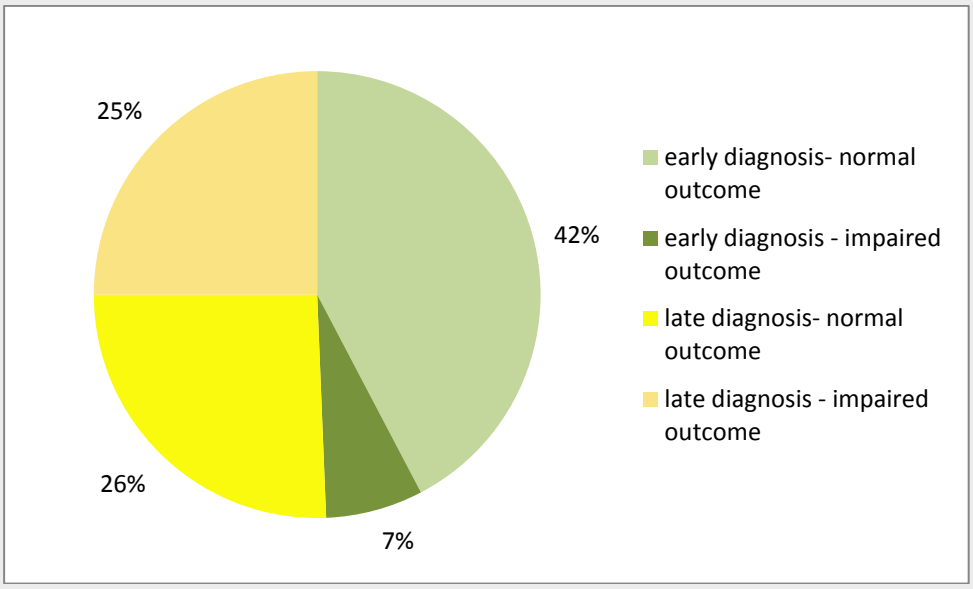
Table 3 - Leucine requirements for the normal healthy population and reported leucine intakes in IVA

	Leucine **WHO/UNU/FAO 2007 for normal healthy population** **mg/kg/day**	**Reported leucine intake from reported case studies**	**Marriage et al., 2010 (USA)** **mg/kg/d**
Tissue amino acid pattern	75		
Maintenance amino acid pattern	59		
0-1y	73 (0.5y of age)	50-155 mg/kg/day	0-6 m : 65-120 7-12m : 50-90
1-2y	54	45-185 mg/kg/day	1-3y: 40-90
3-10y	44	55-185 mg/kg/day	40-60
11-14y	44	Unreported	11-12y: 40-60 13-14y: 30-60
15-18y	42	Unreported	30-60

>18y	39	30 mg/kg/d	30-60

Marriage B (2010): "Nutrition management of patients with inherited disorders of branched-chain amino acid metabolism" Acosta pb (ed): Nutrition management of patients with inherited metabolic disorders, Massachusetts: Jones and Bartlett: 175-236

Figure 1 - Outcome of patients with IVA according to the literature review performed by the IVA guideline group



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.