Guideline
for the diagnosis and management
of isovaleryl-CoA-dehydrogenase deficiency
(isovaleric acidemia) - a systematic review -

Guideline development group

- International interdisciplinary guideline development group (GDG) consisting of pediatric metabolic specialists, a clinical biochemist, metabolic nutritionists and a clinical research assistant
- Last follow-up meeting in 06/2018
- Establishment of working groups focusing on the members' respective specialization
- Systematic discussion of evidence on key questions in the GDG

Development process

- The **Scottish Intercollegiate Guideline Network (SIGN, 2015)** and **Grading of Recommendations, Assessment, Development and Evaluation (GRADE)** concepts were used to structure the development process of the guideline

- Development of the guideline
  - Identification of 22 structured key questions by the GDG
  - Systematic literature review covering the years 1966 to 2013, current update covering the years 2013 to 2018
  - Each study was rated according to its level of evidence. Based on the evidence table, a recommendation relating to each key question was phrased and the grade of recommendation was defined according to SIGN and GRADE.

Key questions

A) Clinical symptoms, incidence & diagnosis

Clinical diagnosis

1. What were the clinical signs and symptoms that led to the suspicion of IVA?
2. Which trigger factors for metabolic crises/episodes are reported?
3. Did patients identified by newborn screening (NBS) present with any symptoms at the time of diagnosis?
4. Did patients develop any symptoms (acute or chronic) after the diagnosis was made (either by selective screening or NBS)?
5. How often did the respective patients (see question 4) have symptomatic episodes?

Incidence

6. What is the reported incidence of IVA?

Biochemical analysis

7. How was the diagnosis or conformational diagnosis made?

B) Treatment & monitoring

Emergency (sick-day hospital)

8. Which emergency treatment regimens were used? Did they change with age?
9. Which laboratory investigations were used to help guiding acute treatment?
10. Was extracorporeal detoxification used?

Sick-day home management

11. Which treatment regimens were used? Did they change with age?

Diet (long-term therapy)

12. Was dietary protein restriction part of the long-term treatment of IVA?
13. Which amount of natural (complete) protein for age was used?
14. What was the age-related leucine intake?
15. What was the age-related amount of amino acid supplement?

Medication (long-term therapy)

16. Were carnitine and/or glycine used in managing IVA in the long-term? Did medication change with age?
17. What other therapeutic approaches were used in treating IVA?
18. Which side effects of medication are reported?

Monitoring

19. Which metabolic/biochemical tests were used to monitor therapy (e.g. urea/IVG; C5-AC in blood, urine)?

C) Outcome

20. What was the long-term outcome of the different forms of IVA (diagnosis by NBS vs. selective screening) in terms of morbidity?
21. What was the clinical outcome in prenatally diagnosed patients?
22. Which information has been reported on mortality and cause and age of death?

SIGN Grading System (2015): Levels of evidence

Levels of evidence

1++	High quality meta-analyses, systematic reviews and randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies OR high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Sytematic literature review

- A systematic review of the literature on IVA was carried out using **Medline, Embase, the Cochrane Collaboration, Google Scholar, Ovid** and **Pubmed**
- Search terms: “isovaleric acidemia”, “isovaleric aciduria”, “isovaleric acid”, “isovaleryl-CoA dehydrogenase”, “IVD gene”, “isovaleryl glycine”, “isovaleryl-glycine”, “isovalerylglycine”, “isovaleryl carnitine”, “isovaleryl-carnitine”, “isovalerylcarnitine”, “newborn screening AND metabolic disease”, “neonatal screening AND metabolic disease”, “newborn screening AND biochemical genetics”, “neonatal screening AND biochemical genetics”, “newborn screening AND inborn error of metabolism”, “neonatal screening AND inborn error of metabolism”, “newborn screening AND inborn errors of metabolism”, “neonatal screening AND inborn errors of metabolism”, “newborn screening AND inherited metabolic disease”, “neonatal screening AND inherited metabolic disease”.

Statement 1

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

Statement 2

Classical triggers are any situation inducing a catabolic state and excessive protein intake.

Statement 3

NBS, though patients can be either symptomatic or asymptomatic, can help prevent serious outcome of IVA patients.

Statement 4

After diagnosis, a wide variation from severe mental handicap and multiple episodes of metabolic derangements to an asymptomatic state may occur.

Recommendation 1

Recommendation for

Level of evidence: low (SIGN level 3)

Clinical relevance: high

Any critically ill patient or unexplained condition should be investigated for metabolic acidosis (with elevated anion gap), elevated lactate, hyperammonemia, elevated urinary ketone bodies (in particular in newborns) as these parameters are laboratory hallmarks of organic acidurias, including determination of organic acids in urine and the acylcarnitine profile in blood as the recommended investigations to detect IVA.

Recommendation 2

Strong recommendation for

Level of evidence: high to moderate (SIGN level 2++ to 4)

Clinical relevance: high

In case of positive newborn screening or selective screening (elevated C5 carnitine in blood and isovalerylglycine in urine), IVD gene mutation analysis and / or IVD enzyme analysis can be used for diagnostic confirmation of IVA.

Recommendation 3

Strong recommendation for

Level of evidence: moderate to low (SIGN level 2- to 4)

Clinical relevance: very high

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 AND
- Anabolic therapy by administering high-energy intake (glucose, insulin, lipid) AND
- Supplementation/ increase of carnitine and/or glycine, according to their previous treatment regime AND
- Decrease of protein intake, or total stop of protein intake in severe cases AND / OR
- Carglumic acid can be used initially
- Extracorporal detoxification (when indicated)

Recommendation 4

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: High

The response to the medical management should be evaluated after four hours.

If the response is regarded inadequate, extracorporal detoxification should be started to decrease ammonia levels rapidly. Delay of any kind of treatment which prolongs the time of hyperammonemia affects outcome.

Recommendation 5

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: very high

Measurement of ammonia and lactate in blood and blood gas analysis should be performed, as they are valuable markers for acute treatment.

Recommendation 6

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: high

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.

If symptoms persist or deteriorate over the following hours, the patient needs to be hospitalized for adequate emergency treatment. If the child is less than 1 year old, early hospitalization should be seriously considered.

Recommendation 7

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: moderate to high

A moderate restriction of dietary protein provides the basis for optimal long-term therapy in patients with IVA.

Recommendation 8

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: moderate to high

Natural protein or leucine intake should be restricted but should cover at least the safe levels of intake advocated by WHO/FAO/UNU 2007.

Any restriction should be combined with sufficient energy supply meeting age-depending requirements .

Over-restriction of leucine or natural protein could lead to catabolism, compromised growth, weight loss and deterioration of metabolic stability.

Recommendation 9

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: high

Leucine-free L-amino acid supplements should be part of the total protein intake, if natural protein tolerance is below WHO/UNU/FAO (2007) safe levels of protein intake.

Recommendation 10

Recommendation for

Level of evidence: low (SIGN level 3 to 4)

Clinical relevance: high

L-Carnitine (100 mg/kg*d) 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 additionally treated with 150-250 mg/kg*d of oral glycine.

Medication is well tolerated.

Recommendation 11

Recommendation for

Level of evidence: (literature check ongoing)

Clinical relevance: high

Amino acids and carnitine in plasma should be monitored during treatment to evaluate nutritional status and supplementation.

Recommendation 12

Strong recommendation for

Level of evidence: high to moderate (SIGN level 2++ to 3)

Clinical relevance: high

Most of the IVA patients who have been diagnosed early (acute neonatal) and fewer patients with a late diagnosis (chronic intermittent) develop normally. If diagnosed early, IVA outcome is much better than if diagnosed late (figure 1). These data warrant newborn screening.

Statement 5

Mild type IVA with the prevalent phenotype p. A282V identified by newborn screening have not experienced any metabolic crises in the first decade of life. Relaxation of the initial dietary treatment and continuation of emergency treatment has not led to metabolic crises.