BIMDG

British Inherited Metabolic Disease Group

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This protocol has 5 pages

ISOVALERIC ACIDAEMIA –ACUTE DECOMPENSATION

(standard version)

- **Please read carefully. Meticulous treatment is very important as there is a high risk of neurological complications including cerebral oedema.**

- **If the instructions do not make sense or a problem is not addressed you must discuss your concerns with the consultant on call.**

1. Background

Isovaleric acidaemia is caused by a deficiency of isovaleryl CoA dehydrogenase, an enzyme on the catabolic pathway of leucine. Treatment is aimed at reducing production of isovaleric and increasing its removal. The patients are treated with a low protein diet, glycine and carnitine.

Decompensation is often triggered by metabolic stress such as febrile illness, particularly diarrhoea or vomiting, fasting, or constipation, but an obvious cause is not always apparent. The early signs of decompensation may be subtle. Vomiting is common and should always be taken seriously. However the signs may be difficult to assess such as irritability or just 'not right'. Always listen to parents carefully as they probably know much more than you do.

2. Admission

Most patients who present to hospital will require admission. Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child does not improve.

- **If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.**

3. Initial plan and management in hospital

⇨ If the child is shocked or clearly very ill arrange for admission to ITU/High dependency unit.

⇨ If admitted to metabolic/general ward make a careful clinical assessment including blood pressure and even if the patient does not appear encephalopathic enter a Glasgow coma score (for details click here). This is very important since should the child deteriorate particularly around the time of a change of shifts, the new team will recognise any change.

The following tests should be done:

BLOOD:	pH and gases
	Ammonia
	Glucose (laboratory and bedside strip)
	Urea and electrolytes
	Calcium, Phosphate and Alkaline phosphatase
	Full blood count
	Lactate
	Amylase/lipase *(if pancreatitis a possibility)*
	Blood spot acylcarnitines
	Blood culture
URINE TESTS	ketones

Complications

Pancreatitis. This is probably more common than recognised, partly because it is not easy to diagnose with confidence. It should be suspected if there is abdominal pain, shock out of proportion to other symptoms or hypocalcaemia. Plasma lipase and amylase activity may not be raised, particularly at an early stage. Abdominal ultrasound may be helpful.

4. Management

Management decisions should be based primarily on the **clinical** status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- Factors that will influence the decision include, how ill is the child and have they deteriorated suddenly in the past?

- Can the child tolerate oral fluids?

If the child is relatively well - may be treated orally but assess very carefully.
If the child is obviously unwell - must be treated with intravenous fluids

- **If there is any doubt at all, put up an intravenous line.**

A. ORAL.

If the child is relatively well and not vomiting oral feeds may be given.
The emergency regimen should be used. This may be given as regular frequent drinks but if the patient is at risk of vomiting or is nauseated fluid should be given either continuously or as small boluses more frequently. For more information about the emergency oral management click here

Age (years)	Glucose polymer concentration (g/100ml)*	Total daily volume**
0-1	10	150-200 ml/kg
1-2	15	100 ml/kg
2-6	20	1200-1500 ml
6-10	20	1500-2000 ml
>10	25	2000 ml

* If necessary, seek help from your local dietitian. In an emergency a heaped 5 ml medicine spoon holds approximately 7g of glucose polymer.

**For each drink the volume will generally be this figure divided by 12 and given 2 hourly but if the patient is nauseated or refuses try frequent smaller drinks or a continuous naso-gastric infusion.

Electrolytes should be added to the drinks if vomiting and/or diarrhoea is a problem using standard rehydration mixtures following manufacturer's instructions but substituting glucose polymer solution for water.

Medicines

Glycine should be given 300 mg/kg/24h in 4 divided doses
Carnitine is normally added - 100 mg/kg/24h in 4 divided doses

B INTRAVENOUS.

If the child is unwell

- Give Glucose 200 mg/kg **at once** (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg.. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h **ONLY until next solution is ready– do not leave on this high rate longer than necessary**. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
    - Deficit: estimate from clinical signs if no recent weight available
    - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
    - Give 0.45% saline/10% glucose (for instructions to make this solution click here).

- Having calculated the deficit and the maintenance, administer the appropriate rate of 0.45% saline/10% glucose to correct the deficit within 24 hours
- Recheck the electrolytes every 24 hours if still on IV fluids.

- Hyperglycaemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol rather than reducing the glucose intake. **Strict supervision is essential.**

-Potassium can be added, if appropriate, once urine flow is normal and the plasma potassium concentration is known.

Acidosis can be marked but sodium bicarbonate is not given routinely. However if acidosis persists after correction of blood glucose and perfusion, sodium bicarbonate may be needed if the pH <7.1 or the pH is deteriorating rapidly or the base deficit is greater than 15 mmol/l.

Initially give a half correction [0.15 x weight x base deficit (mmol/l)] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol but this solution should be diluted *at least* 1ml to 5ml of 5% glucose. Then review and check U&E and pH & blood gases. The acidosis normally corrects fairly quickly so that repeat doses of sodium bicarbonate should only occasionally be needed.. If further doses of sodium bicarbonate appear to be needed, discuss with the consultant. Before doing so ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is haemofiltration (possibly haemodialysis), assisted ventilation and inotropes. Such treatment should be under specialist metabolic supervision.

- Carnitine should be given intravenously - 100 – 200 mg/kg/24h either continuously or in 3 divided doses.

- An intravenous preparation of glycine is not normally available. If possible therefore give glycine enterally by continuous infusion via a nasogastric tube. The dose is the same as that given orally 300 mg/kg/d.

- Treat any infection

5. Progress:

Monitoring: Reassess after 4-6 hours or earlier if there is any deterioration or no improvement
Clinical assessment should include Glasgow coma score (for details click here) and blood pressure.

Blood tests:
- Blood pH and gases
- Ammonia
- Glucose (laboratory): high values can occur due to insulin resistance
- Urea & electrolytes,
- Full blood count
- Lactate
- Calcium, Phosphate, ALP and Amylase/lipase if pancreatitis a possibility

If improving, continue and for intravenous fluids after 6 hours please refer to the previous section

If deteriorating (clinical state, acidosis, hyperammonaemia, fluid overload), seek specialist help. Haemofiltration (haemodialysis) may need to be considered urgently. Note peritoneal dialysis is less efficient. Exchange transfusion is dangerous and should not be used.

6. Re-introduction of enteral feeds: Enteral feeds with some protein should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition. If necessary, consult your local dietitian for more details. If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition. (Note only moderate protein restriction when using TPN is necessary. Discuss with specialist metabolic team).

7. Going Home: Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child deteriorates.

For further information please refer to:

Saudubray J-M, van den Berghe G, Walter JH. (editors) Inborn Metabolic Diseases. Diagnosis and treatment. 5th Edition. Springer 2012