



CYSTADANE®
betaine anhydrous

CYSTADANE® (betaine anhydrous)
ADJUNCTIVE TREATMENT OF HOMOCYSTINURIA

Involving deficiencies or defects in:

- / cystathionine beta-synthase (CBS),
- / 5,10-methylene-tetrahydrofolate reductase (MTHFR),
- / cobalamin cofactor metabolism (cbl).

Cystadane should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.^{ref SPC}

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Treatment of Homocystinuria

CYSTADANE[®]
betaine anhydrous

**Classical
homocystinuria**

**MTHFR
deficiency**

**Cobalamin
disorders**



Classical homocystinuria

***Dietary
Modifications***

***Vitamin
Therapy***

Betaine



GOAL of treatment

☞ *Biochemical targets*

☞ *Clinical targets*

*Treatment
according
to how
patients
may be
diagnosed?*

- *Through Newborn screening*
- *A family history of homocystinuria*
- *Children are often diagnosed following dislocation of the optic lens, by which time they may have some learning difficulties.*
- *Adults are usually diagnosed after a thromboembolic event.*

Clinical targets of treatment

CYSTADANE[®]
betaine anhydrous

“For early diagnosed patients”

- *Prevent all the complications*
- *Maintaining normal growth and nutrition*
- *Allowing the patient normal opportunities for social and family life*

“For late-diagnosed patients”

- *Prevent further complications, especially thromboembolic disease.*



Biochemical target of treatment

✓ *lowering the plasma tHcy*

☞ *below 50 $\mu\text{mol/L}$ in fully pyridoxine responsive patients*

☞ *below 100 $\mu\text{mol/L}$ in pyridoxine non-responsive patients*

☞ *tHcy concentrations are lower in DBS. If these are used for monitoring, the target below is about 60-70 $\mu\text{mol/L}$.*



Vitamin therapy

***Pyridoxine or
B6***

B12

Folate

***B6
treatment***

*Is the patient responsive
to B6?*



*Start a trial B6 treatment
after diagnosis of
homocystinuria while the
patient is stable.*

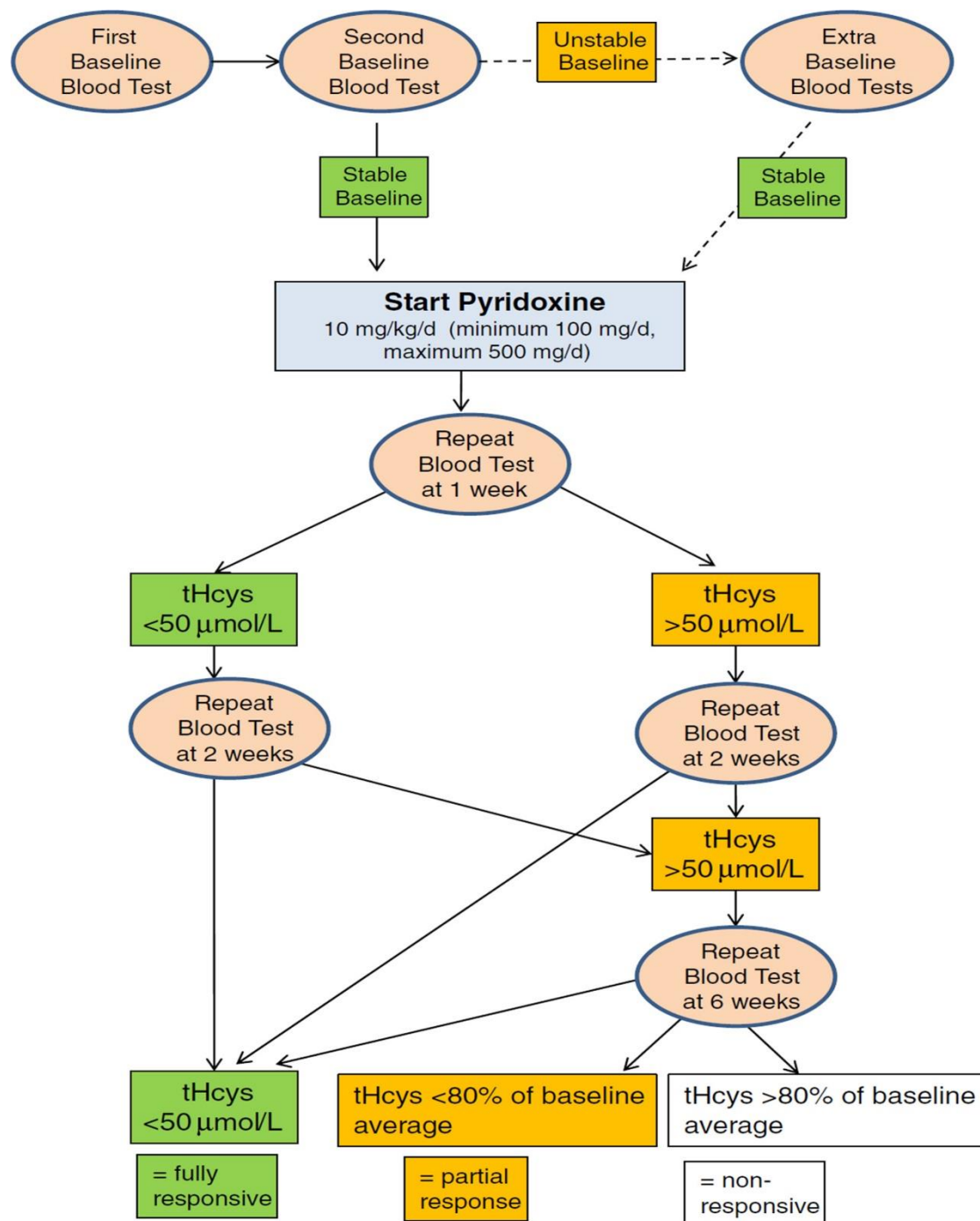
Conditions before test

The plasma tHcy concentration should be measured at least twice before treatment

The test should not be done if the patient is in the catabolic state.

The protein intake should be normal,

folate supplements should be given and vitamin B₁₂ deficiency should be corrected prior to testing



Patients detected by newborn screening rarely respond to pyridoxine

Using a relatively high dose **30** mg/kg/d (100 mg/day) for a shorter period (**2** weeks)

Measurement of the plasma tHcy at the end of the **first** and **second** weeks.

If a patient shows an equivocal fall in Hcy, the trial should be continued for **longer**, to confirm that the fall is not just due to anabolism.

✓ If **cystathionine** is measured, a rise in this metabolite provides extra evidence for a genuine response to pyridoxine.

B6 adverse effects

Peripheral neuropathy

- ✓ *The most important adverse effect of pyridoxine.*
- ✓ *In patients treated with long-term high doses of pyridoxine >900 mg/day.*
- ✓ *It has not been found in patients treated with less than 500 mg/day*
- ✓ *Withdrawal of pyridoxine has led to improvement of the neuropathy in some patients*

B6 adverse effects

- ✓ *Periods of **apnea** have been reported in a few neonates following large oral doses of pyridoxine (500 mg/d)*
- ✓ ***Rhabdomyolysis** has also been reported.*

Long-term treatment of B6



For long-term treatment, the pyridoxine dose should be the lowest that achieves the biochemical targets (plasma total homocysteine $<50 \mu\text{mol/L}$)



Using doses up to 10 mg/kg/day and avoiding doses above 500 mg/day

Pyridoxine doses of 10-40 mg can achieve biochemical targets in some patients with the p.P49L and p.I278T mutations

B12 and folate treatment

Cause of deficiency

- ✓ *Increased flux through the remethylation pathway and use of the cofactors*
- ✓ *Inadequate intake of the vitamins in patients on restricted diets*





folic acid (5–10 mg/d) or folinic acid (1–5 mg/d) in single dose



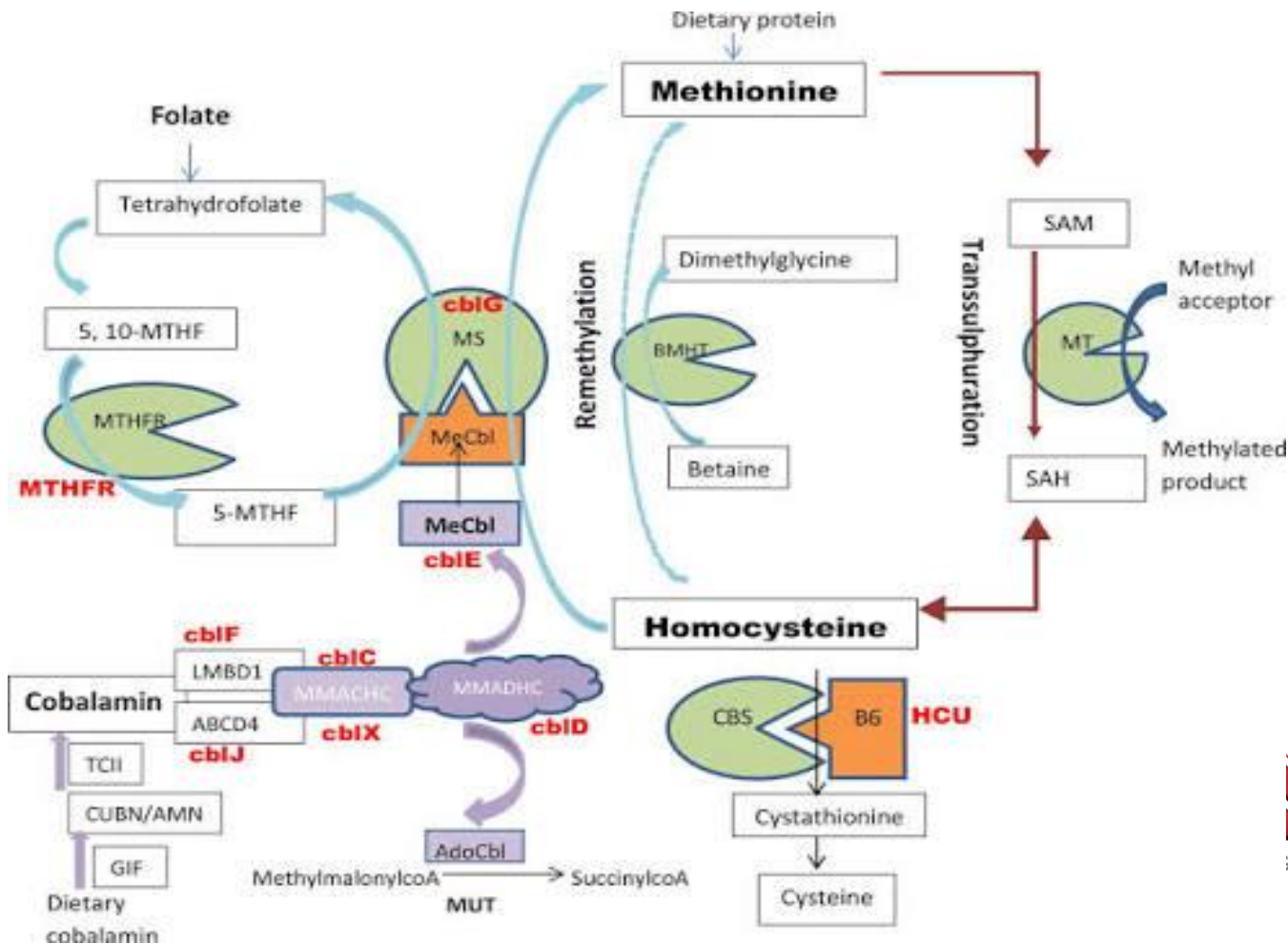
vitamin B12 is given as hydroxycobalamin at 1 mg IM per month or 1mg/oral/daily



Vitamin C 1 g/day

Betaine treatment

- Betaine (N,N,N-trimethylglycine) is a substrate for the enzyme, betaine-homocysteine methyltransferase $\longrightarrow$ remethylate homocysteine to methionine:



Effects of betaine

- **Lowers** homocysteine concentration more than 70%
- clinical improvement in approximately three-quarters of cases including reduced seizures and improved cognition
- **Increases** cysteine levels.
- Betaine may also act as a chemical **chaperone** and correct partial misfolding of the protein

EFFICACY OF CYSTADANE®

THE BIOCHEMICAL EFFICACY OF CYSTADANE®

- Cystadan® effectively lowers homocysteine levels in **pyridoxine-responsive patients** as demonstrated by the effects of oral methionine loads before and after adding betaine to patients' standard vitamin supplementation. When betaine was added to the patients' pyroxine treatment, the **homocysteine responses to the methione load were reduced to nearer to normal**.^{15,16}

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Cystadane® is effective in both pyridoxine-responsive and pyridokine non-responsive classical homocystinuria

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- Cystadane also lowers homocysteine in **pyridoxine non-responsive patients**. For example in a group of 10 patients with classical homocystinuria unresponsive to high doses of pyridoxine 3-4 weeks of treatment with betaine 6 g/day, added to continued pyridoxine 100 mg/day and folic acid 5 mg/day, **reduced plasma homocysteine levels by a mean of 77%**.¹⁷

Effect of an oral methionine load on total homocysteine levels in **pyridoxine-responsive patients** with homocystinuria treated or not with betaine. ¹⁷

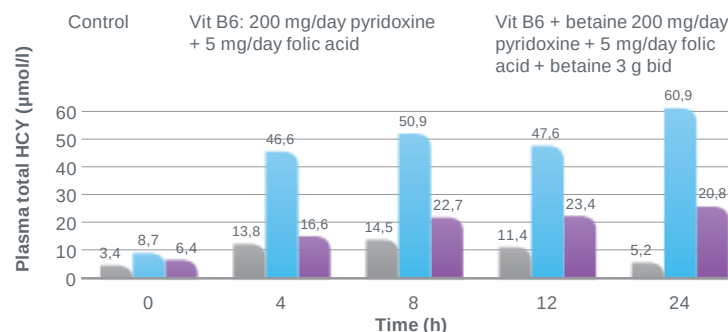
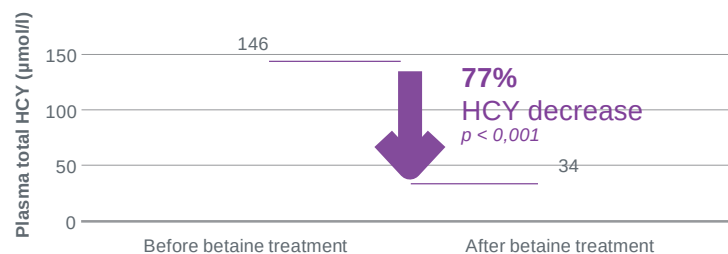


Figure drawn from data in table 1 of reference 17

Effect of betaine treatment on total homocysteine levels in **pyridoxine-non-responsive patients** with homocystinuria. ¹⁸



HCY = homocysteine

Figure drawn from data in table 1 of reference 18

Betaine treatment

*Dose : 150-200 mg/kg/day divided into two daily doses
as the half-life is >14 hours*

- *For children the initial betaine dose is **50 mg/kg twice daily**, adjusted according to response (increased weekly by 50 mg/kg increments).*
- *For adults the initial dose is **3 g twice daily**.*
- *The dose and frequency are adjusted according to biochemical response.*

Cystadane®

betaine anhydrous

Adjunctive treatment for
homocystinuria

APPROVED
in all EU countries



*For a Future,
for a Life...*

Posology for
1 administration
(morning + evening)

Body weight  kg

Spoon 100 mg 

Spoon 150 mg 

Spoon 1g 

Cystadane®

betaine anhydrous

POSOLGY

Paediatric patient less than 10 years of age: 100 mg/kg/day given in 2 doses daily

Adult and paediatric patient over 10 years of age: 6 g per day given in 2 doses of 3 g daily

ADMINISTRATION

Oral administration;

The bottle should be lightly shaken before opening. Three measuring spoons are provided which dispense either 100 mg, 150 mg or 1 g of betaine anhydrous.

The powder should be mixed with water, juice, milk, formula or food until completely dissolved and ingested immediately after mixing.



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Proper Dissolution & Immediate Ingestion (Key to Absorption)

- **Dissolve Completely in Liquid:** Measure the prescribed dose using the standard graduated scoop and dissolve the powder completely (**120–180 mL**) of liquid before drinking.
- **Suitable liquids:** Water, fruit juice, milk, or specialized metabolic formula **Or Mix with Soft Food:** It can be mixed into soft foods like applesauce, yogurt, or mashed potatoes.
- **Immediate Ingestion:** The solution/mixture must be consumed **immediately**. Do not prepare betaine drinks in advance to sit in the refrigerator or at room temperature, as betaine is highly hygroscopic and chemically sensitive in aqueous solutions over extended periods.
- **Splitting the Daily Dose:** In intestinal transport, betaine is absorbed via specific amino acid/betaine transporters (such as **BGT-1** and **PAT2 / IMINO** carriers). These transporters can become saturated with very large single boluses.

Take With or Immediately After Food: While betaine is absorbed well on an empty stomach, taking it **with or right after a meal** minimizes common gastrointestinal side effects (nausea, mild stomach cramping, or loose stools).

- **Storage to Prevent Moisture Degradation**
- **Hygroscopic Nature:** Betaine anhydrous rapidly absorbs atmospheric moisture, causing clumping and degraded potency.
- Always keep the bottle **tightly closed**
- Store in a dry place at controlled room temperature (15°C to 30°C)

Betaine side effects

Metabolism and nutrition disorders	Uncommon: anorexia
Psychiatric disorders	Uncommon: agitation, irritability
Nervous system disorders	Uncommon: brain oedema*
Gastrointestinal disorders	Uncommon: diarrhoea, glossitis, nausea, stomach discomfort, vomiting
Skin and subcutaneous tissue disorders	Uncommon: hair loss, hives, skin odour abnormal
Renal and urinary disorders	Uncommon: urinary incontinence
Investigations	Very common: blood methionine increased*

Betaine side effects



Some affected individuals develop a detectable body odor (fishy odour), resulting in reduced compliance



The increase in methionine produced by betaine is usually harmless; however, cerebral edema has occurred when hypermethioninemia is extreme ($>1000 \mu\text{mol/L}$)

Dietary Modifications

Low-methionine diet (restricting high-protein foods like meat, eggs, dairy)



Cysteine supplementation (to compensate for deficiency)

** Indication of dietary modifications:*

- *Dietary treatment should be considered for all patients with CBS deficiency who unresponsive to pyridoxine supplementation.*
- * Diet may be used either as a sole treatment or adjunctive therapy along with pyridoxine and/or betaine*
- * This dietary includes: very low in natural protein, with supplements of a Met-free L-AA mixture.*
- * Lifelong treatment is required*

Effects of methionine restriction diet on management of homocystinuria

- Methionine-restricted diet with methionine-free amino acid supplements lowers tHcy 38–67%
- Prevents thromboembolism and lens dislocation when started early (Park 2020 , Morris 2025, Majtan 2019).
- Early treatment through newborn screening dramatically reduces complications: risk ratios of 0.073 for thromboembolism and 0.069 for lens dislocation compared to clinically detected patients (Morris 2025).
- In pyridoxine-nonresponsive patients, betaine added to diet produced a 74% mean decline in homocysteine with no vascular events over 258 patient-years (Wilcken 1997).

Methionine restriction plus betaine normalized endothelial dysfunction and carotid injury responses in HCU models (Park 2020)

Over time, however, isolated long-term betaine became less effective because BHMT-mediated remethylation fell, and rising homocysteine was accompanied by return of a hypercoagulative phenotype (Maclean2012, Maclean2019).



The amount of Met that a patient can take depends on various factors:

- *The degree of residual CBS enzyme activity*
- *The responsiveness to pyridoxine*
- *The use of betaine*
- *The patient's age*
- *Growth rate*



Estimated methionine and cystine requirements

Age	Methionine mg/kg/ day	Cystine mg/kg/ day
0–6 months	15–60	85–150
6 months – 1 year	12–43	85–150
1–4 years	9–28	60–100
4–7 years	7–22	50–80
7–11 years	7–22	30–50
Women		
11–15 years	7–21	30–50
15–19 years	6–19	25–40
>19 years	5–19	20–30
Men		
11–15 years	7–22	30–50
15–19 years	7–21	25–40
>19 years	5–19	20–30

Diet modification during infancy

- *For infants diagnosed through NBS in the UK, the supply of Met/natural protein (from breast milk or formula) is stopped (after the pyridoxine test) and a Met-free complete infant is given for 2-4 days to reduce Hcy levels*
- *Met in the form of breast milk or infant formula is then introduced, divided into several feeds, in conjunction with the Met-free formula.*



- ✓ 1 liter cowmilk= 800-1000 mg methionine
 - ✓ 1 liter breastmilk= 300 mg methionine
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- ✓ The Met allowance is then titrated against the patient's plasma tHcy levels
- ✓ Measured volumes of a Met-free infant formula are given prior to breast-feeds, thereby limiting the amount of breast milk (and Met) taken.



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- * Weaning should begin at the usual time and progress through stages as normal*
 - * Gradually the Met allowance of breast milk or standard formula is replaced with protein/Met containing foods.*

** Naturally low protein foods or manufactured low protein foods are introduced first.*

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	Abbott	Cambrooke	Mead Johnson	Nutricia	Vitaflo
Infant 0–1 year	Hominex-1		HCY-1	HCU Anamix early years	
Toddler & young children	Hominex-2	Homactin AA plus	HCY-1 HCY-2	HCU Anamix next	HCU gel HCU express 15 HCU cooler 15
Older children & adults		Homactin AA plus	HCY-2	HCU Anamix next XMET Maxamum HCU LQ	HCU express 15,20 HCU cooler 15



For older children and adults, the diet is either based on ?

- 1- **Met-restriction**: calculated by estimating the daily Met intake
 - 2- **Natural protein-restriction**: based on the intake of natural protein and the assumption that 1 g (20-25 mg) of protein provides a specific quantity of Met.
- ✓ For **practical** reasons, a combination of the two is often used
 - ✓ In **theory**, the Met-restricted diet is preferable because the Met content of different foods varies relative to their protein content.

Management of late diagnosed patients:

- *The introduction of dietary restriction is extremely difficult in this patients and is best done gradually.*
- *If a Met-free L-AA supplement is likely to be required, this should be started first to ensure nutritional adequacy whilst reducing the Met/protein intake*



Challenging with diet modification

- *Nearly 95% of patients report diet-related challenges, with 50% listing dietary restrictions among their most bothersome impacts (R. Pokrzywinski et al 2025)*
- *Many patients describe being hungry "all the time" but unable to eat beyond their daily protein allotment (R. Pokrzywinski et al 2025)*
- *Restricting intake of the essential AA, Met, reduces the precursor load on the transsulfuration pathway, thereby reducing Hcy production but amino acid mixtures cause more problems than the protein restriction itself due to poor palatability, and only half of patients consistently take their prescribed formula (Morrison2021).*



L-AA mixtures

- *In CBS deficient individuals, the natural protein/Met allowance from food may be too low to support a normal growth rate in infants and children and to meet protein requirements in adults.*
- *In these instances a cystine-containing, Met-free L-AA formula/supplement should be used.*



- *These are often supplemented with fat, carbohydrate and micronutrients and are available in a variety of forms with age-specific micronutrient provision*
- *It is recommended that the L-AA supplement is split into three to four doses throughout the day to maximise nitrogen retention and achieve appropriate growth*



- *It is important to avoid both **inadequate** and **excessive** intake of the L-AA supplement.*
- ***Inadequate intake***
 - * may be due to being insufficiently prescribed or poor adherence and can result in poor biochemical control, poor growth and malnutrition*
 - * Adherence to Met-free L-AA supplements can be poor due to their taste*



- Patients who are *partially* pyridoxine-responsive may achieve target tHcy levels with a relatively mild protein restriction and may not require Met-free L-AAs supplements
- ***Late-diagnosed pyridoxine-unresponsive patients are also sometimes managed with a relatively mild protein restriction and betaine, if they cannot adhere to a stricter diet.***



Cysteine

- *Normally formed from methionine via the transsulfuration pathway.*
- *Cysteine is essential AA in CBS deficiency and low concentrations may contribute to the pathogenesis.*
- *Cysteine, like Hcy, contains a thiol group and is present in different reduced and oxidised forms.*



Cysteine

- *The binding capacity of plasma proteins for thiols is limited, grossly elevated Hcy concentrations lead to a decrease in plasma total cysteine, as often seen in poorly controlled patients.*
- *Improving Hcy control as total cysteine levels increase when Hcy levels fall*



Cysteine

- *Cysteine deficiency can cause poor weight gain and growth even in the presence of adequate energy intake*
- *Cystine is added to most Met-free L-AA supplements but the quantities are sometimes no greater than in supplements for other AA disorders, such as PKU.*
- *It is not clear if this is sufficient.*
- *Cystine supplementation can be difficult to administer due to its poor solubility and unpleasant taste*



Cysteine

- *Further research is needed addressing the accurate cysteine levels in treated patients and whether additional L-cystine supplementation improves the outcomes of patients with good Hcy control*
- *Cysteine dose: 200 mg/kg/day*



Energy requirement and micronutrient supplements

- *is unknown in CBS deficiency*
- *Many L-AA supplements now contain long chain polyunsaturated fatty acids, as strict low protein/Met diets are usually deficient in essential fatty acids.*
- *Separate supplements could be considered if they are not included in the L-AA supplement*



Monitoring

Area	Tests	Frequency
Anthropometry	Height & weight	Every clinic visit
Dietary	Dietary intake analysis	Every clinic visit if on dietary treatment
Biochemical–metabolic control	tHcy, Met	See text
Nutritional	Vitamin B ₁₂ , folate	At least annually
	Blood count, albumin, plasma AA, ferritin, zinc, 25-hydroxyvitamin D	At least annually if on dietary treatment
	Selenium, essential fatty acids	If concerns about intake
Neurodevelopmental/ neurological	Clinical examination	Annually
	MRI/EEG	Only if new CNS symptoms
Ophthalmological	Eye examination	At least annually
Neuropsychological function	IQ	At least every 5 years during childhood
Psychological	Clinical psychology or psychiatric assessment	As required
Bone density	DEXA	Every 3-5 years from adolescence—unless clinically indicated earlier
Cardiovascular	Lipid profile, cardiovascular risk factor review	Once in childhood, annually in adulthood

Monitoring

- *Plasma aminoacids and total homocysteine in infancy every 1–3 months, is indicated even more frequently, later every 3–6 months.*



Management of intercurrent illness

- *During intercurrent illness, patients should continue their regular treatment (such as pyridoxine, betaine, their L-AA mixture and adequate energy).*
- *Dehydration and immobilization should be avoided to reduce the risk of thromboembolic disease.*
- *Venous thrombosis is the main acute concern and the risk of this should be minimised by avoiding dehydration or immobilisation.*
- *Intractable vomiting may necessitate intravenous fluids*



Management of intercurrent illness

- *None of the treatments for homocystinuria need to be stopped during intercurrent illnesses.*
- *More frequent nutritional monitoring may be needed in patients on dietary treatment who have prolonged or recurrent illnesses.*



Management of surgery and anaesthesia

- *Surgery and anaesthesia pose an additional risk of thrombosis in CBS deficiency.*
- *Biochemical control, dietary management and nutrition should be optimised before elective procedures.*
- *Hydration should be maintained with intravenous fluids.*



Management of surgery and anesthesia

- *Standard antithrombotic measures such as elastic stockings, pneumatic leg compression systems and early mobilization should be followed during and after surgery.*
- *Low molecular weight heparin is recommended in cases of prolonged immobilisation.*
- *Nitrous oxide increases Hcy concentrations and should be avoided.*



Management of surgery and anesthesia

- Intravenous fluids containing 5% dextrose in 0.5 N saline at 1.5 times maintenance should be administered before, during, and after surgery until fluids can be taken orally*



Management of Cobalamin C Disorder

Restrict: No dietary restriction indicated

Supplement:

- Hydroxocobalamin injection
- Folic acid
- Carnitine
- Betaine
- Methionine to correct deficiency

hydroxocobalamin is typically started at 1 mg daily or 0.33 mg/kg/day : Plasma vitamin B12 concentrations >1,000,000 pg/m

betaine is dosed at 100–250 mg/ kg divided into two doses

L-carnitine supplementation ranging from 50 to 200 mg/kg/ day

folinic acid range from 5–15 mg/day to 5–30 mg divided 2–3 times per week



MTHFR deficiency

- *The goal of treatment is to reduce plasma tHcy, normalize the levels of Met and folate, especially in CSF, and so presumably alleviate clinical symptoms.*
- *Treatment involves the administration (suggestive doses) of betaine (100–250 mg/kg/day in children and 5–20 g/day in adults) to provide an alternative pathway for Hcy remethylation.*
- *In addition, OHcbl (1-2 g/d) and folinic acid (400 mg/d) are prescribed.*

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MTHFR deficiency

Pyridoxine, as a cofactor for CBS, may be administered to maximize the transsulfuration pathway and riboflavin as cofactor of the MTHFR enzyme

psychomotor development

Regarding the infantile forms, the only patients who have done well are those who were treated from birth. Early treatment with betaine following prenatal diagnosis has resulted in the best outcome.[98] Without treatment, these early-onset forms may rapidly progress to coma and potentially death by central respiratory failure



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