



comida HCys^A formula

This practical guide is an introduction to the use of **comida-HCys A formula**, an amino acid based methionine free* formula, suitable from birth to 12 months of age.



*No added methionine.



Enhancing Lives Together



Important information

PURPOSE

This practical guide is for the use of **comida-HCys A formula** in the dietary management of an infant with Homocystinuria.

INTENDED USERS

This practical guide is:

- for use by **healthcare professionals** working with infants diagnosed with Homocystinuria.
- **not** for use by parents/caregivers with Homocystinuria or patients themselves.
- for **general information** only and must not be used as a substitute for professional medical advice.

TARGET POPULATION

This practical guide is for use in infants with diagnosed/proven Homocystinuria.

PRODUCT INFORMATION

comida-HCys A formula is a food for special medical purposes.

Any product information contained in this practical guide, although accurate at the time of publication, is subject to change. The most current product information may be obtained by referring to product labels and **www.comidamed.com**. Please refer to these sources for information regarding allergens.

DISCLAIMER

The information contained in the practical guide is for general information purposes only and **does not** constitute medical advice. The practical guide is not a substitute for medical advice or care provided by a licensed and qualified healthcare professional and Vitaflo does not, in the absence of negligence on Vitaflo's part, accept any liability arising from reliance on information contained in this guide and or the incorrect use of **comida-HCys A formula** product.

This practical guide should be read in conjunction with local, national and international guidelines and best practice for the dietary management of Homocystinuria. Information contained within the guide is based on the most recent scientific evidence available on the management of Homocystinuria as of date of publication.

COLLABORATORS

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Introducing and adjusting **comida-HCys A formula** is dependent on the individual patient. Practical examples are given in this guide; however, it is the responsibility of the managing healthcare professional to use clinical judgement to introduce and adjust **comida-HCys A formula** in the most appropriate way for individual patients and it may not always be appropriate to use the practical guide.

IMPORTANT NOTICE

- **comida-HCys A formula** must only be used under medical supervision.
- Suitable from birth to 12 months of age.
- Not suitable for use as a sole source of nutrition.
- **comida-HCys A formula** must only be consumed by infants with proven Homocystinuria.
- **comida-HCys A formula** must be used in conjunction with breast milk or infant formula to provide the methionine, fluid and general nutritional requirements of the infant in quantities as advised by a clinician or dietitian.
- For enteral use only.

This practical guide does not establish or specify particular standards of medical care for the treatment of any conditions referred to in this practical guide.

Vitaflo International Limited **does not** recommend or endorse any specific tests, procedures, opinions, clinicians or other information that may be included or referenced in this practical guide.

Symbols and Abbreviations

Symbol	Abbreviation	Definition
	HM	Human milk
	BF	Breastfeed
	HCP	Healthcare Professional
	MET	Methionine
	tHcy	Total homocysteine
	MET-free formula	MET-free formula (comida-HCys A formula)
	SIF	Standard infant formula
	CBS	Cystathionine beta-synthase

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Features of comida-HCys A formula

comida
HCys^A
formula

comida-HCys A formula a methionine free* amino acid based powdered formula containing essential and non-essential amino acids, carbohydrate, fat, vitamins, minerals, trace elements, arachidonic acid (ARA) and docosahexaenoic acid (DHA).

comida-HCys A formula provides all the essential nutrients required by an infant, with the exception of methionine.

comida-HCys A formula is for use in the dietary management of Homocystinuria (HCU) suitable from birth to 12 months of age.



*No added methionine.

Overview of feeding an infant with HCU

Infants newly diagnosed with HCU are typically trialed on pyridoxine for two weeks, while on a standard diet to determine responsiveness. If an infant is deemed unresponsive or partially-responsive with total homocysteine (tHcy) levels above 50 $\mu\text{mol/L}$ ¹, they are prescribed a methionine-free formula (**comida-HCys A formula**), indicated for infants, as medically appropriate pending the clinical status of the infant¹.

Feeding an infant with HCU is a balance between providing methionine-free formula alongside adequate amounts of methionine from human milk (HM)/standard infant formula (SIF), with the goal of keeping methionine (MET) levels and homocysteine (tHcy) levels within target therapeutic ranges. The goal range for methionine in patients on betaine is <1000 $\mu\text{mol/L}$. The goal ranges for tHcy are <100 $\mu\text{mol/L}$ in non-pyridoxine responsive patients and <50 $\mu\text{mol/L}$ in patients who are responsive¹.

In HCU, cystathionine beta-synthase (CBS) is the deficient enzyme. In normal metabolism, this enzyme converts homocysteine to cysteine. Elevated homocysteine and MET occur when the body cannot convert excess homocysteine into cysteine. Homocysteine is the amino acid that is toxic to the body in HCU. Limiting MET in the diet limits homocysteine production as methionine is a precursor in the impaired pathway¹.

Since MET is an essential amino acid (cannot be produced by the body, therefore dietary intake is required) the body requires a small amount for normal growth and development. This is provided through either HM or SIF as the source of MET. A family should be supported to make the appropriate choice for their family and their infant, with relevant healthcare professionals' input as appropriate.

comida-HCys A formula may be used, after confirmation of the HCU diagnosis and the following pyridoxine trial, in combination with HM/SIF. Alternatively, it may be used as a sole source of nutrition for a brief period known as a "washout" for 2-4 days¹ in order to achieve a rapid reduction in blood tHcy levels. This "washout" regimen should only be used by the metabolic healthcare provider, if diagnostic blood tHcy levels are found to be significantly elevated on laboratory results, or if there is concern for significant tHcy elevation. It is important that blood MET and tHcy levels are monitored very closely to prevent MET deficiency. After this "washout" period, determined by the metabolic healthcare provider, a source of MET, either HM or SIF, is reintroduced and given in combination with **comida-HCys A formula**.

Breastfed infants

Healthcare providers should support a family's decision to BF or provide HM, as the MET / intact protein source for an infant with HCU, whenever possible. **comida-HCys A formula** combined with bottle-fed HM or feeding at the breast may be used to maintain satisfactory blood MET and tHcy control, provided there is adequate HM available for the infant and blood MET and tHcy levels can be closely monitored¹⁻³. Feeding at the breast may not always be possible with HCU. Families should discuss what is best for them and their infant with their metabolic healthcare provider. HM offers nutritional benefits including higher long chain polyunsaturated fatty acid concentrations and a lower MET content. MET in HM is 21 mg/100 ml⁴ compared with approximately 30-35 mg/100 ml in SIF (values for SIF are taken from three common SIF available in the USA, retrieved October 2024). Breastfeeding an infant with HCU is based on the principle of giving a measured volume of **comida-HCys A formula** to offset the infant's appetite for breastfeeds.

Feeding a measured amount of **comida-HCys A formula** alongside each breastfeed, or alternating measured feeds of **comida-HCys A formula** with breastfeeds, decreases the total amount of HM consumed and therefore decreases total MET intake. Infants can still feed on demand, varying the quantity of feeds from day to day provided that the prescribed quantity of **comida-HCys A formula** is given throughout the day³. Successful HCU management with breastfeeding is achieved via close monitoring of blood MET and tHcy levels and adjustment of the prescribed volume of **comida-HCys A formula** by the managing metabolic healthcare professional in order to maintain blood MET and tHcy control. See sections 1.1-1.4 for more details. In practice, we start by alternating between breastfeeding and formula feeding. We then adjust the amount of formula according to laboratory results and the rate of lactation.

SIF fed infants

There are various options for feeding an infant with SIF and **comida-HCys A formula**. With the help of managing healthcare professional, families may choose a SIF supplemented with DHA and ARA that is best for their infant and family circumstances. SIF and **comida-HCys A formula** may be given in separate or mixed bottles, depending on specific clinic protocol and preference, with a variety of feeding approaches capable of optimizing blood MET and tHcy control and catering to a family's individual circumstances. See Sections 1.1 - 1.4 for more details.

Overview of feeding an infant with HCU

Blood MET and tHcy Level Monitoring

Blood MET and tHcy levels are used to determine whether the volume of **comida-HCys A formula** and HM/SIF should be adjusted; as discussed earlier, tHcy is the most dangerous metabolite in HCU, but MET deficiency must be avoided in order to promote normal growth and neurodevelopment. Expect to adjust the feeding plan often, most likely weekly, especially during the first two months of life.

Blood MET and tHcy levels should be checked at least weekly throughout infancy^{1, 5}. The quantity of MET tolerated by infants will vary and be guided by blood MET and tHcy levels. Individual MET tolerance will vary significantly throughout infancy with changes in growth and development. It is vital to investigate all the possible causes for changes in MET and tHcy levels before adjusting the feeding plan. Consider waiting for two consecutive blood MET and tHcy levels to indicate the need for a feeding plan adjustment, unless the blood MET level is very low or blood tHcy very high.

Progression

A combination of HM/SIF and **comida-HCys A formula** may continue to provide 100% of the infant's nutrition requirements until the age of 6 months, or when the infant is developmentally ready for the introduction of solids. Complementary feeding should be supported by the metabolic healthcare provider.

IMPORTANT NOTICE

Breastfeeding can continue for as long as the mother and infant wish, provided that growth, blood MET and blood tHcy levels are satisfactory. SIF should be introduced if there is inadequate HM to provide enough MET or liquid nutrition volume for age, in combination with **comida-HCys A formula**. If the mother wishes to wean the infant from HM, then a gradual approach is recommended, if possible.

Overview of feeding an infant with HCU

PRINCIPLES OF INITIATING NUTRITION MANAGEMENT

If tHcy levels > 50 $\mu\text{mol/L}$ and if medically appropriate given clinical status after diagnosis and pyridoxine trial, **comida-HCys A formula** can be used to reduce tHcy levels rapidly.

Depending on diagnostic MET and tHcy levels and clinical circumstances, the metabolic team may consider the following strategies for initiating **comida-HCys A formula**:

- Temporarily stop HM/SIF and use **comida-HCys A formula** as sole nutrition source for 2-4 days¹ as a "washout" to quickly decrease tHcy.
- Introduce **comida-HCys A formula** in combination with HM/SIF.

If a "washout" is pursued and if HM/SIF has been stopped, reintroduce MET to tolerance.

Intact protein intake is adjusted based on individual blood MET and tHcy levels. For breastfed infants, **comida-HCys A formula** volumes will be adjusted with the intended effect of modifying the infant's appetite for HM.

Continue to give a combination of **comida-HCys A formula** and HM/SIF to provide 100% of the infant's requirements and to achieve optimal growth, MET and tHcy levels.

HM/SIF and **comida-HCys A formula** should provide 100% of the infants' nutrition needs until approximately the age of 6 months when solids are introduced or when the infant is developmentally ready for the introduction of solids.

Monitor blood MET and tHcy levels weekly to achieve stability in blood MET and tHcy. Guidelines recommend aiming for a MET treatment range of <1000 $\mu\text{mol/L}$ and tHcy treatment range of <100 $\mu\text{mol/L}$ in non-pyridoxine responsive infants or <50 $\mu\text{mol/L}$ in pyridoxine responsive infants^{1, 5}.

- **comida-HCys A formula** and MET source (HM/SIF) may be given together at each feed, or at alternating feeds to ensure nutrient availability throughout the day.
- If the prescribed volume of **comida-HCys A formula** is not taken, it may cause a rise in blood MET levels, leading to a rise in tHcy levels, which is very dangerous for the infant.
- Blood MET and tHcy levels are used to determine whether **comida-HCys A formula**, SIF/HM prescription should be adjusted.
- The infant should be weighed at each clinic visit or more frequently if there is a clinical concern.

Nutrition prescription using comida-HCys A formula at diagnosis after the pyridoxine trial

The aim is to achieve a rapid reduction in blood tHcy levels. Reducing MET intake will in-turn reduce tHcy levels.

If temporarily stopping intact protein and using **comida-HCys A formula** alone to lower very high blood MET levels, a two-step method is used:

Step 1 - Introduction of **comida-HCys A formula**

- Use **comida-HCys A formula** as a sole source of nutrition for 2-4 days as directed by the managing healthcare professional depending on the infant's response to a trial of pyridoxine¹.
- **comida-HCys A formula** should be offered on demand to the infant if medically appropriate to do so.

Feeding plan and considerations:

- Mix desired amount of **comida-HCys A formula** per feed (see example feeding plans which follow).
A 3 to 4 week-old infant will typically take about 90-120 ml (3-4 fl oz) per feed.
- Encourage family to track number of wet and soiled diapers to ensure intake adequacy.
- Feeding frequency may need to be higher for infants who have not yet regained their birth weight.
 - Family should consult with their managing healthcare professional.
- Encourage mothers breastfeeding to express breast milk when the infant feeds to establish and protect breast milk supply during the washout regimen.
- Maternal-infant skin-to-skin contact and/or a small number of short duration breastfeeds (if approved by metabolic healthcare provider), may be continued to help promote breast milk supply and bonding during the period when breastfeeding is stopped.

Step 2 - Reintroduction of HM/SIF

- In 2-4 days at the discretion of the managing healthcare professional.
- See example feeding plans over the following pages.

Example feeding plans

If a washout regimen is not required or reintroducing intact protein source, the following feeding plans illustrate 2 methods for calculating the feeding plan whether breastfeeding or bottle-feeding with expressed HM or SIF.

Also note, many factors can affect blood MET and tHcy levels. Always check for causes of high or low blood levels before making a change to the nutrition prescription.

Example using a 3-week-old infant diagnosed with HCU with insufficient reduction of tHcy following a pyridoxine trial, therefore requiring dietary restriction of MET, weight 4,2 kg.

1.2.1 If breastfeeding:

As we don't know how much human milk is consumed, start by adding in one feed of **comida-HCys A formula** from a bottle (see 1.2.2 for guidance on volume) and feeding at the breast with other feeds. Let the infant take as much as they want at each feed.

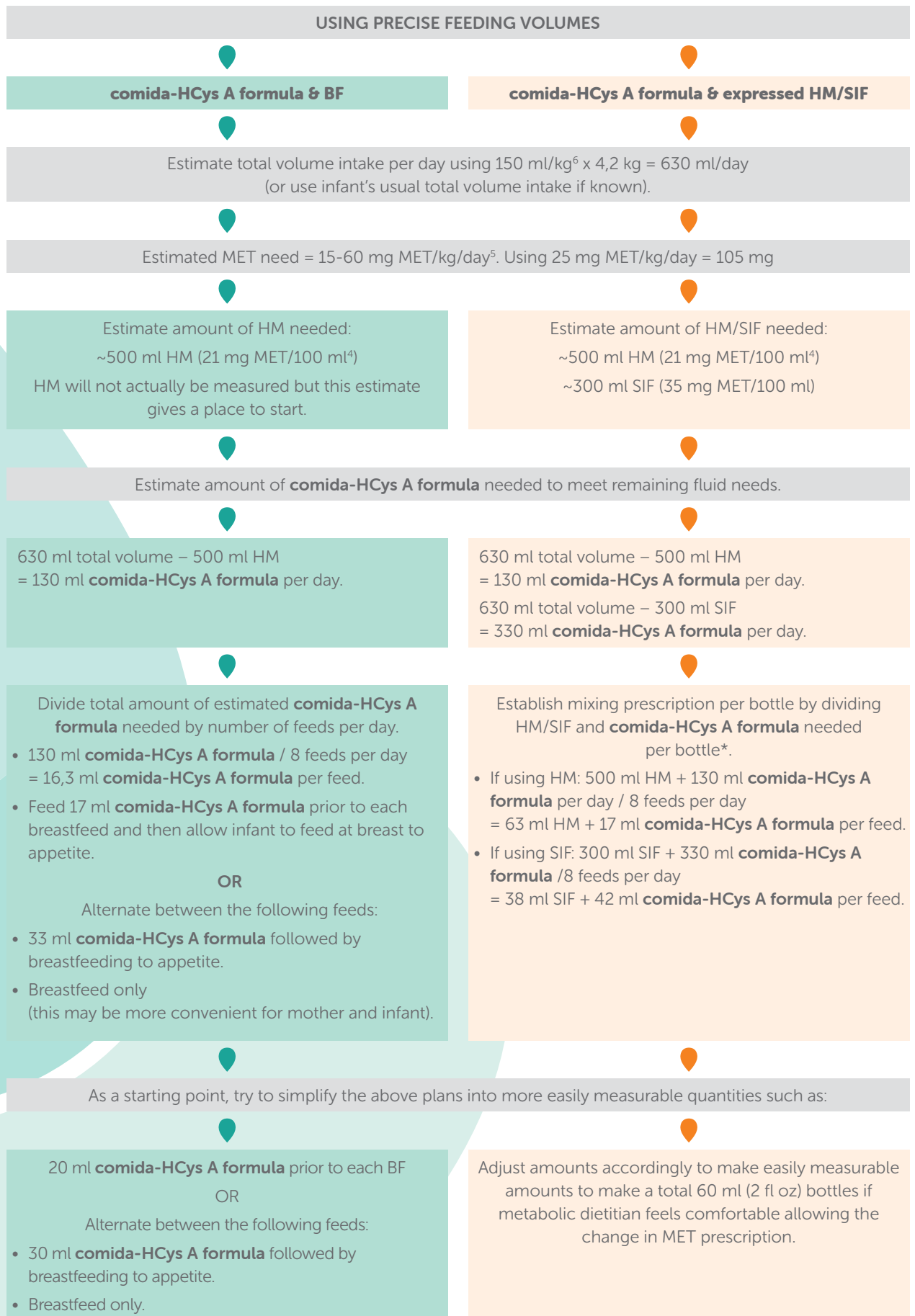
Parents should keep a meal/feed diary, noting the time of each meal (breastfeeding or bottle-feeding) and the precise amount consumed when **comida-HCys A formula** milk is given.

1.2.2: If maternal milk is given by bottle feed:

Estimate amount of HM needed for a 4,2 kg infant, consider: **(*calculations in green)**

- MET requirements for 0-6 months = 15-60 mg/kg/day⁵, **using an assumed average tolerance 25 mg/kg/day**
(25 x 4,2 = 105 mg/day) = 105 mg MET/day
- HM = 21 mg MET/100 ml
(105/21 x 100 = 500 ml HM) = 500 ml HM/day.

Example feeding plans



* Infants should be fed to appetite when hungry and total liquid volume per day should not be limited to establish MET and tHcy level control. If the estimated volume intake does not satisfy the infant, then additional feeds either of **comida-HCys A formula** alone or mixed **comida-HCys A formula** + HM/SIF may be given depending on what is clinically appropriate.

Check list for blood MET and tHcy monitoring

Many factors can affect blood MET and tHcy levels. Always check for causes of high or low blood MET level or high tHcy before making a change to the nutrition prescription.

Considerations for high blood MET or tHcy levels:

POSSIBLE CAUSE	ACTION
Excess intake of intact protein (HM/SIF)	• Confirm feeding preparation and provision is consistent with prescription. • Review mixing and measuring of feeds/formula. • Adjust prescription of HM/SIF and comida-HCys A formula to meet infants MET tolerance.
Inadequate intake of comida-HCys A formula	• Ensure that adequate comida-HCys A formula supply is available. • Address symptoms that may affect tolerance such as colic, constipation, or reflux by seeking appropriate medical advice. • Determine presence of short-term symptoms affecting intake such as illness, pain, teething, or vaccination. • Monitor weight and increase comida-HCys A formula prescription as needed.
Catabolism or slow weight gain	• Monitor weight frequently to better understand growth trajectory. • Rule out illness or infection and encourage appropriate medical treatment. • Encourage optimal total volume intake and adjust feeding intervals and frequency as needed to achieve goals. • Cross-check MET and calorie intake to ensure infant is meeting requirements.
Change in blood monitoring routine	Encourage consistent timing of blood MET and tHcy level within family's and infant's specific circumstances.
Betaine usage	Betaine remethylates homocysteine into methionine which results in reduced homocysteine but an increase in MET. Confirm medication changes in line with lab results if MET is higher than expected given tHcy.

Check list for blood MET and tHcy monitoring

Considerations for low blood MET levels:

POSSIBLE CAUSE	ACTION
Inadequate intake of intact protein (HM/SIF) or Excessive intake of comida-HCys A formula	• Confirm feeding preparation and provision is consistent with prescription. • Review mixing and measuring of feeds/formula. • Ensure adequate HM available if applicable, supplement SIF as needed. • Adjust prescription of HM/SIF and comida-HCys A formula to meet infants MET tolerance.
Anabolism or rapid growth phase	• Monitor weight frequently to better understand growth trajectory. • Increase MET source if blood MET level is very low; consider continuing prescription and repeating level if blood MET level is in an acceptable low range.
Change in blood monitoring routine	• Encourage consistent timing of blood MET and tHcy level over the day within family's and infant's specific circumstances.

MONITORING TIPS

For all infants, frequent monitoring of MET and tHcy levels is key, but try not to make changes to a feeding plan too frequently.

Consider:

Many factors affect MET and tHcy levels; review all causes in this section.

- Monitor MET and tHcy level trends
 - Unless MET level is very low or very high or tHcy is very high, consider:
 - Continuation of the current plan
 - Awaiting 2 consecutive MET and tHcy levels before adjusting prescription
- In general, do not make more than 1 change to the plan in 1 week

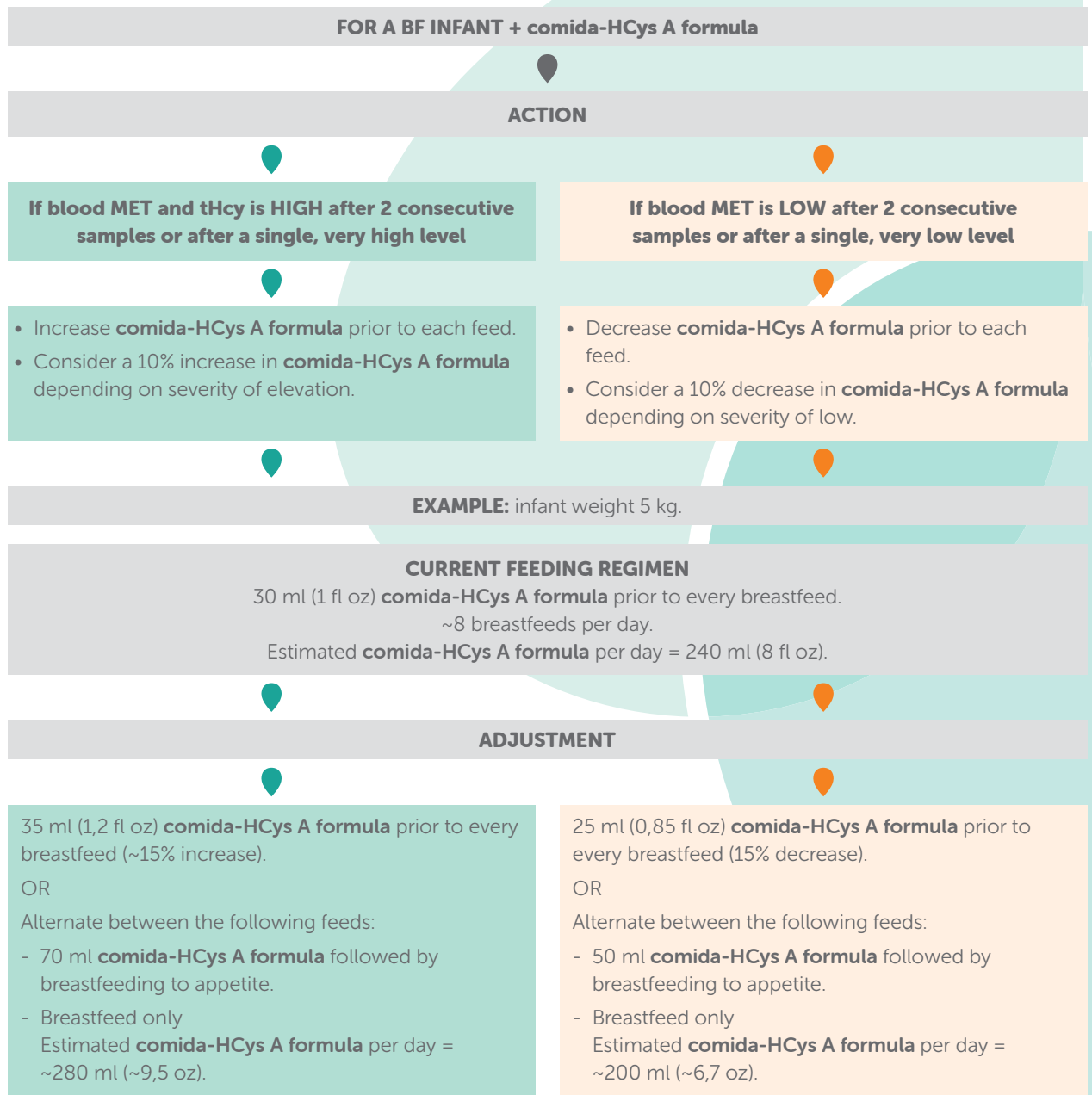
For MET levels that ARE very low or very high:

- Consider repeating blood MET level sooner than 1 week to guide interventions or other intervention as recommended by metabolic healthcare professional.

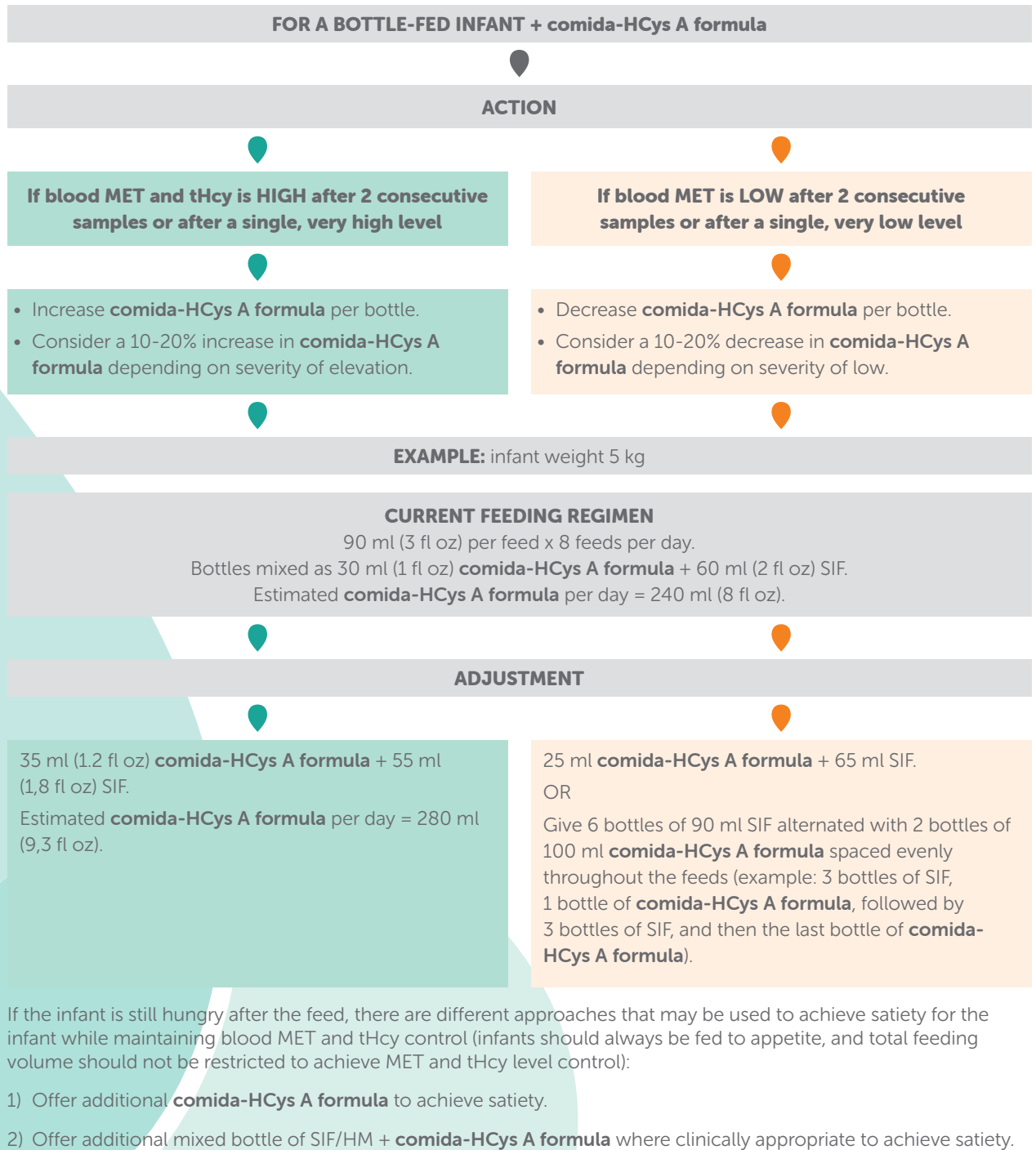
REMEMBER:

Sick day protocols are not addressed in this guide because guidelines for incurrent illness in HCU recommend continuing the infant's standard treatment regimen, whilst avoiding dehydration and immobilization¹. Seek advice from healthcare professionals as needed.

Fine-tuning the nutrition prescription



Fine-tuning the nutrition prescription



Practical feeding strategies to use with caregivers



Be prepared with feeding supplies. It is important for HCPs to know what supplies the family/caregivers have on-hand and to ensure they can get proper supplies when needed.

These Include:

Feeding bottles with necessary measurement markings (demarcation) for infant's recipe

- Appropriately staged nipples for infant feeding
- Adequate supply of **comida-HCys A formula**
- HM pump and supplies if needed to express
- Adequate supply of SIF (if using)

FORMULA MIXING INSTRUCTIONS:

- Use **comida-HCys A formula** scoop (or gram scale) to mix **comida-HCys A formula**. Do not use scoops from other formula containers to mix **comida-HCys A formula**
- Ensure family has access to a safe water source for formula mixing
- Inquire about the most effective written method for family to receive new recipes and mixing instructions. Review mixing at every visit

Confirm family/caregivers are able to procure more **comida-HCys A formula** and SIF (if using) when supplies are low. Consider providing written guidance on where families can obtain these formulas. Direct families to appropriate agencies and services if needed to obtain SIF at low-cost or for free.

Practical points for effective communication between HCPs and caregivers

ESTABLISH LINES OF COMMUNICATION BETWEEN HCP AND CAREGIVER/FAMILY

Phone calls, e-mail, text and/or the medical record portal may all be used. Ensure caregivers/families are comfortable using communication method.

KEEP INFORMATION SIMPLE AND PRACTICAL AND CHECK FAMILY/CAREGIVER UNDERSTANDING OF INFORMATION.

Allow time for questions and encourage questions between visits.

Consider written feeding plans.

ENCOURAGE QUESTIONS

Caregivers should be encouraged to ask questions and speak up whenever they do not understand. Effective and open lines of communication as well as appropriate teaching methods are critical for caregiver success.

EDUCATE ALL CAREGIVERS

Let primary caregiver(s) know that anyone taking care of the infant is welcome at clinic visits and education pieces may be provided for all caregivers depending on their needs.

ESTABLISH FREQUENCY OF REVIEWING MET AND tHcy LEVELS AND CLINIC VISITS

Ensure caregivers understand what communication method will be used to report results and adjust the diet between visit.

INFORM OTHER HCPS, INCLUDING THE PRIMARY CARE PHYSICIAN, OF THE MANAGEMENT PLAN

DIRECT CAREGIVERS TO APPROPRIATE PATIENT/FAMILY SUPPORT GROUPS AND APPROPRIATE INFORMATION PLATFORMS

REMEMBER THAT DIFFERENT PATIENTS/FAMILIES SUCCEED WITH DIFFERENT COMMUNICATION METHODS;

Be as adaptable as you can within your clinic's capabilities.

Directions for preparation, use, and storage of comida-HCys A formula

PREPARATION GUIDELINES

Follow the instructions exactly and feed immediately. Incorrect preparation can make your infant ill.



Wash hands well.



Sterilise bottle, teat and cap by boiling in water for five minutes. Leave covered until use.



Boil drinking water for five minutes. Allow to cool to lukewarm drinking temperature, i.e., water that feels warm on the wrist but not hot.



Pour exact amount of lukewarm water into the bottle.



Using the scoop provided, add the prescribed number of scoops of **comida-HCys A formula** to the water, levelling each scoop off with the back of a clean dry knife. Do not press the powder into the scoop.



Shake well until the powder is fully dissolved.



Always test the temperature before feeding by shaking a few drops onto the inside of your wrist - the feed should feel warm but not hot.

It is important for caregivers to carefully follow the instructions for the preparation, use and storage of **comida-HCys A formula**. Use only the scoop provided in the can or a gram scale for greatest accuracy.

- Any formula remaining in the bottle after 1 hour should be discarded.
- Do not reheat **comida-HCys A formula**.
- Do not heat **comida-HCys A formula** in a microwave as uneven heating may occur and could cause scalding.
- Do not boil **comida-HCys A formula**.
- Infants should be supervised at all times when feeding.
- Regular teeth cleaning is recommended.

Preparation Guidelines

Water (ml)	comida-HCys A formula no. scoops	comida-HCys A formula (g)	Drinking volume (ml)	Protein equivalent (g)
30	1	4,7	35	0,67
90	3	14,1	100	2
180	6	28,2	200	4

STORAGE

UNOPENED: **comida-HCys A formula** should be stored in a cool, dry place.

OPENED: Use within 3 weeks.

Always replace container lid after use.

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All information correct at the time of publication.