New Family Diagnosis Guide for Cobalamin Disorders

What is a Cobalamin (Cbl) disorder?

Cobalamin (Cbl) is another name for vitamin B12. A Cbl disorder occurs when the body cannot completely metabolize or process vitamin B12 (an important cofactor needed for breaking down certain amino acids, which are building blocks of protein) and homocysteine. There often is a buildup of certain compounds including homocysteine and methylmalonic acid* in the blood and urine. Cbl disorders are the result of genetic variations in one of the genes necessary for B12 metabolism. Cbl disorders are most often inherited in an autosomal recessive pattern, meaning that both parents are carriers and each pregnancy has a 25% chance of being affected. Depending on which step in the B12 metabolism pathway is affected, Cbl disorders can have different findings: Homocystinuria (HCU), Methylmalonic Acidemia (MMA) or a combined disorder (HCU + MMA).

Cobalamin disorders were named in the order they were discovered using letters of the alphabet, which can be confusing. The following chart displays the different Cbl disorders divided into groups. Symptoms and treatment may vary depending on which Cobalamin disorder you or your child has been diagnosed with. Understanding which disorder you or your child was diagnosed with will help you take steps to ensure the proper care is provided.

Type	Associated Disorder	Definition
cblD-Hcy, cblE, cblG	Homocystinuria (HCU)	Buildup of homocysteine and inability to process homocysteine to methionine
cblA, cblB, cblD-MMA	Methylmalonic Acidemia (MMA)	Cannot break down certain proteins and fats causing a buildup of methylmalonic acid
cblC, cblF, cblJ, cblX	Combined Disorder (HCU and MMA)*	Buildup of homocysteine and methylmalonic acid and decreased methionine

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What medications are used to treat Cbl disorders?

The following medications are recommended for the treatment of Cobalamin disorders. Work closely with your medical professional to confirm the medication, dose, and frequency of administration.

**** Current guidelines recommend beginning Hydroxocobalamin injections as soon as a cobalamin defect is suspected — *BEFORE* diagnosis is confirmed! ** (Huemer et al. 2017)**

Medication	Purpose	Method Administered	Helpful Information
Hydroxocobalamin (OHCbl) ** 1 mg/ml, 5mg/ml or up to 25mg/ml concentration	Helps make methylcobalamin and adenosylcobalamin, which help keep levels of homocysteine and MMA down and levels of methionine normal	Injection (Intramuscular or Subcutaneous)	Specially compounded for concentrations above 1mg/ml. Many insurance policies will not cover compounded formulation. Dark red liquid; needs to be kept refrigerated and out of direct light
Betaine (aka Cystadane)	Provides an alternate remethylation pathway to convert excess homocysteine into methionine	Oral	Distributed through Anovo pharmacy as Cystadane (https://www.cystadane.com/ contact info 844-288-5007) Generic Betaine may also be available through local pharmacy
Folinic Acid (aka Leucovorin)	Providing active forms of folic acid helps bypass the folate cycle and optimize the conversion of homocysteine to methionine	Oral	Distributed through your local pharmacy Folic and folinic are vitamins (chemically different from each other but work in a similar way)
L-Methionine	Amino acid responsible for brain growth and development	Oral	Distributed through a reputable supplement provider
L-Carnitine	Prevents secondary carnitine deficiency that can occur	Oral	Distributed through your local pharmacy or a reputable supplement provider

*** CYANOCOBALAMIN is contraindicated and ORAL hydroxocobalamin is ineffective for the treatment of Cbl disorders
***Avoid the use of nitrous oxide
***Avoid protein restriction or use of MMA/PA medical foods that contain no methionine
For more information regarding medications visit https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5203859/

Who will be involved in my child's care?

Finding a health care team that suits all your child's needs will be one of the most important steps to ensure your child is being cared for appropriately. Specialists may not be available locally as this is a rare disorder. Consider how you can travel often or whether you need to move closer to a location that can meet your child's needs, as they will be integral to your child's health; and you will be visiting with them often as your child grows and develops. Based on symptoms and concerns related to Cobalamin disorders, this may include:

Team Member	Role
Metabolic Specialist, Geneticist, Dietician and Genetic Counselor	• Provide medication prescriptions (dosage and frequency) • Order regular labs to monitor biochemical labs (MMA, homocysteine, amino acids) • Creating sick day protocols • Monitoring growth and development
Pediatrician	• Maintaining regular well child visits and preventative care • Providing support to family and referrals as needed
Laboratory or Phlebotomy services	• Depending on your child's age, ensure a provider is comfortable drawing blood from an infant, toddler, etc. • Ensure lab results will be directed to your child's care team
Neurologist	• Monitor neurological development and brain growth • Support the family/child if neurological symptoms are present (seizures, etc.) • Provider prescriptions to treat neurological symptoms, if needed
Ophthalmologist	• Monitor growth and development of vision • Common symptoms include progressive maculopathy/retinopathy, and blindness
Cardiologist	• Monitor cardiac health, hyperlipidemia • Screen and monitor for non-compaction cardiomyopathy, chronic risks related to hyperhomocysteinemia
Nephrologist (cblA, cblB, cblD-MMA)	• Cbl disorders associated with isolated methylmalonic acidemia are associated with chronic kidney disease and require regular follow-up by nephrology
Occupational, Physical, Speech and Low Vision Therapy	• Depending on your child's age, related services are available to support your child's development and support the family as problems or concerns arise • Services are available through Early Intervention, your local school district or privately through your insurance provider

Where can I go for help understanding my child's diagnosis?

- Join support groups through various social media channels (such as Facebook) to connect with people who share your or your child's diagnosis
    - Homocystinuria Support Facebook Group
      https://www.facebook.com/groups/45912445029/
    - MMA Group Support for Families Facebook Group
      https://www.facebook.com/groups/MMAFamilyGroup/
    - Organic Acidemia Association Facebook Group
      https://www.facebook.com/groups/33534928222/

- Familiarize yourself with articles, publications, and studies posted on national organization websites
    - HCU Network America
      https://hcunetworkamerica.org/
    - Organic Acidemia Association
      https://oaanews.org
    - HCU Network Australia
      https://hcunetworkaustralia.org.au
    - European Network and Registry for Homocystinurias and Methylation Defects
      http://www.e-hod.org
    - Genetics Home Reference
      https://ghr.nlm.nih.gov/
    - NORD (National Organization for Rare Disorders)
      https://rarediseases.org/
    - Clinical trials.gov
      https://clinicaltrials.gov
    - Participate in the natural history study of the National Institutes of Health, Bethesda, MD:
        - Depending on your level of support, you may consider secondary insurance through Medicaid (Waiver or Buy-in Programs) to help with medical costs

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