

Cyclic Vomiting Syndrome 301: a guide for patients and families

What is cyclic vomiting syndrome (CVS)?

Cyclic vomiting syndrome (CVS) is not a disease with a single cause, but rather a specific pattern of vomiting that originates in the brain. There is no proven test to diagnose CVS. Therefore, the correct diagnosis relies on a doctor to take a detailed history, perform a careful physical examination, and conduct tests to exclude other diseases that cause a similar pattern of vomiting.



How common is CVS, when does it begin and who gets it?

Some studies suggest that CVS may affect as many as 2% of school-aged children. The most common age of onset is between 3 and 7 years of age, most often during preschool. It can also begin in teenage years (lasting into adulthood) or in adulthood (average age 35 years). It occurs worldwide in all races but appears to be less common in Africa. There is a high association with migraine headaches in the family, especially on the maternal side.

What symptoms suggest CVS?

Many different conditions cause recurrent vomiting. However, in most cases, CVS can be differentiated from other causes by four main features: *repeated attacks of vomiting*, being *well in between*, *stereotypical episodes* (similar symptoms), and *rapid-fire (intense) vomiting*. If you or your child has all of these features, there is close to a 90% chance that you/they do have CVS. There are also typical accompanying symptoms during episodes: listlessness (93%), paleness (91%), unrelenting nausea (82%), loss of appetite (81%), abdominal pain (81%), retching (79%), headache (42%), diarrhea (36%), and excessive salivation (13%).

First, and most importantly, are the *repeated attacks of vomiting* in CVS. The number defined by the current North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) diagnostic criteria are a minimum of 3 over six months or 5 total attacks. The vomiting spells start suddenly, and many patients have a typical warning period of 1-2 hours of symptoms such as nausea, irritability, and abdominal pain. The attacks often begin in the early morning hours and awaken the patient from sleep. During the episode, patients often like to be left alone in a dark, quiet place. Some become dehydrated and require IV fluids in the emergency department or in the hospital. The episodes usually resolve within hours but some last up to 10 days.

Second, most patients feel completely *well in between episodes*. Once the episode resolves, the patient usually returns to their “normal self” within a few hours and can resume drinking and eating regular food. The period of normal health between episodes varies between 2 weeks to 3 months for most patients but can range from weekly to once every 6-12 months. There are several *different vomiting patterns* within CVS. About half of children vomit on a regular timetable (*cyclic*) such that you can predict when the next attack will occur. Those with an exceptionally long predictable interval of 9 weeks or more, so-called *long-cycle, calendar-timed*, are particularly difficult to treat. The other half have *sporadic* and irregular episodes, with **triggers** of excitement (birthdays, vacations), stress (school), illness, lack of sleep (sleepovers), dietary intake (chocolate, aged cheese), excessive use of cannabis, and weather changes (cold fronts). A few have 3-4 days clusters of early morning episodes with recovery by

afternoon, then restarting in the early morning (*cycle-within-a-cycle*) before returning to baseline wellness.

Third, these vomiting attacks are *stereotypical*. “Stereotypical episodes” means that each vomiting attack resembles previous ones as to time of onset, duration of the episode and accompanying symptoms. In contrast, stomach flus caused by various viruses cause different symptoms with different durations. Most often, the CVS attacks last between 6 and 48 hours which remains consistent for that individual. However, some attacks can be as brief as 2 hours, and others can last up to 10 days. Average attacks in adults tend to last for 5 days. As the patient has the identical profile of symptoms (paleness, listlessness, etc.) it is easier for you to recognize the attacks as part of the ‘same’ illness. Since no one else is usually sick at home, it is less likely due to an infection.

Fourth, the majority (77-92%) of patients have a remarkably *rapid-fire (intense) vomiting pattern*. During the worst hour, they vomit frequently, often up to once every 10 minutes. This can result in up to 20-30 times a day and even more than 100 times per episode. This is higher than most other causes of vomiting except food poisoning. Even when the vomiting has completely emptied the stomach, the retching may continue on the same pace, except when they fall asleep. The vomit may contain dark brown bile and even bright red blood. The blood results from a temporary bruising of the stomach.

How sick will my child get during an attack?

Unfortunately, CVS requires more medical intervention than even a stomach virus (rotavirus). More than half of the patients require IV hydration at least once. As many as 19% require IV hydration with every episode. Sometimes the child is so pale and listless (so-called ‘conscious coma’) that they have to be carried like a limp rag which may be mistaken for being in shock or coma. Patients can have other unusual symptoms such as extreme hot water showering/bathing or guzzling a lot of fluid and then vomiting. Some become hypersensitive to touch or develop limb pains. Some may have reduced urination due to a hormone, even after rehydration. These are not psychiatric symptoms but ones typical of CVS. The lab results which may be temporarily abnormal include a high white blood cell count, elevated blood sugar, and increased ketones in the urine and blood.

How does CVS relate to ‘abdominal migraine’ and migraine headache?

This is confusing even to doctors because of the overlap between these ‘cousin’ conditions. Of CVS patients, 80% have abdominal pain and could be reclassified as having abdominal migraine. Conversely, 50% of abdominal migraine patients have vomiting and could be rediagnosed as CVS. Although it is not perfect, we usually ask which is the most consistent and troublesome symptom – vomiting, abdominal pain, or headache – and use that to classify the patient. In one study in school children, the average ages and frequency of CVS were 5 years and 2%, abdominal migraine 10 years and 4%, and migraine headaches 12 years and 11%. As they grow older, the majority skip directly from CVS to migraine headaches whereas some go from one to the other and a few even have all three simultaneously. It is anticipated that 75% will ‘trade’ CVS for migraines by college age.

Can CVS patients have other symptoms when healthy?

Yes, as we have learned from asking more questions about other symptoms even when well. These include anxiety (47% overall, 59% of school-aged children), depression (14%), limited stamina and/or chronic fatigue (52%), poor sleep (48% - difficulty falling or staying asleep), postural orthostatic tachycardia syndrome (up to 38%), irritable bowel syndrome or constipation (41%), and complex regional pain syndrome (10%). About 12% have chronic daily nausea that has been labeled '*coalescent CVS*' that may indicate an underlying autonomic nervous system disorder. Chronic anxiety, inability to keep up with peers, poor quality sleep, feeling faint when standing up (POTS) and daily nausea can profoundly reduce quality of life.

What causes CVS?

There is no simple answer. Many studies indicate that in most patients, CVS is strongly related to *migraines*. In CVS patients, the similar sudden onset and ending of attacks, the effectiveness of anti-migraine medications, the morphing into migraines, and the positive family history of migraines (80%) link these two conditions. However, it appears even more complicated. *Autonomic system* (controls blood pressure etc.) *dysfunction* leads to overreaction to stressors. As part of its role in reducing stress, an *altered endocannabinoid system* may explain why overuse of cannabis can be a trigger. *Mitochondrial* (cell's power plant) *dysfunction* can lead to low energy and mitochondrial supplements help some patients. Other nuclear mutations that affect cell's energy production or the stress response may interact with mitochondrial mutations to lead to CVS. How all these mechanisms fit together remains to be seen.

What other conditions cause vomiting?

There is a long list of conditions that cause vomiting and make it a challenge for doctors to diagnose the cause. These include: food poisoning (*Bacillus cereus*), gastroesophageal reflux (acid reflux), stomach infections (*H. pylori*) or inflammation (gastritis or duodenitis), food allergies (eosinophilic esophagitis), pancreatic inflammation (pancreatitis), and urinary tract infections. However, most conditions that cause vomiting tend to either be short-lived (i.e. food poisoning), or chronic (i.e. acid reflux that occurs daily). Having repeated bouts of *vomiting separated by well periods* is unusual and should make a physician or family suspect the diagnosis of CVS.

How does the doctor make the diagnosis of CVS?

Diagnosing CVS is challenging for many doctors because CVS is an uncommon disorder that has no lab or X-ray to help confirm the diagnosis. As a result, it can take up to 2½ years to come to a correct diagnosis. Often, young children presenting with repeated vomiting are said to have "a stomach virus" (gastroenteritis), or, in a teenager or adult "food poisoning." Obviously, as it continues to recur, that explanation does not make sense. The health provider may then suspect a CVS diagnosis and apply the diagnostic criteria based upon the four main features we listed above.

Are there different types of CVS?

After evaluating nearly 1300 patients with CVS, Dr. B U K Li believes that there are different subtypes of CVS that may have different mechanisms and even require different treatments. The largest subgroup (80%) by far is *migraine-related*. This includes patients who have migraines themselves or in their families typically more often on the maternal side. This group responds well to anti-migraine medications. Another group includes those with *mitochondrial dysfunction*

who have limited stamina or fatigue, neurological deficits and/or confirmed mitochondrial enzyme deficiency and may benefit from mitochondrial supplements. *Catamenial* (menses)-triggered CVS responds to low-estrogen birth control pills. The *Sato-variant* has severe and prolonged (3-10 days) episodes characterized by spikes of high blood pressure. The *long-cycle calendar-timed* group is particularly refractory to therapy. Those with *autonomic dysfunction* (postural orthostatic tachycardia syndrome) may benefit from higher salt and fluid intake, exercise to improve circulation and specific medications that aid the cardiovascular system. Lastly, teenagers and adults with *cannabinoid hyperemesis syndrome* triggered by excessive recreational cannabis use over years most likely are a subset of CVS and improve upon cessation. To make matters more challenging, some instances of CVS can fall into more than one subcategory.

What testing needs to be done if CVS is suspected?

In general, the patient history will strongly suggest a diagnosis of CVS. But because there is no test to diagnose CVS and many other conditions cause recurrent vomiting, some causes may need to be excluded. How much testing to do is up to the doctor's judgment but there are recommendations in the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) guidelines. There are two important conditions that can mimic CVS and require testing. The most important includes **malrotation** where the abnormally-positioned intestines can twist and strangulate themselves. A second is **ureteropelvic junction obstruction** which blocks urine flow from the kidneys and leads to vomiting. In both, corrective surgery will resolve the vomiting. **Metabolic diseases (hereditary enzyme deficiencies)** can cause recurrent vomiting, particularly in infants and young children, where buildup of toxins from the missing enzyme causes vomiting. Very rarely, brain tumors or other lesions in the brainstem can present with recurrent vomiting.

The single most important test is the **upper GI series** (x-ray of the stomach and duodenum to exclude malrotation). The second is an **abdominal ultrasound** (ultrasound of kidneys and gallbladder). Both can be performed even when the child is well. During the episode itself, a complete blood count, electrolytes, blood sugar, blood urea nitrogen and urinalysis are recommended with or without lipase. At times, a **CT scan** or **MRI of the head** may be ordered. In some, **endoscopy** (examination of the esophagus and stomach with a scope) may be needed. Multiple studies show that in suspect CVS, the results of these tests are normal.

If I think my child has cyclic vomiting, what should I do?

The most important thing to do is to seek a physician who can take a careful history and determine if the history is consistent with CVS. Although it is ideal to be evaluated by an established CVS program, unfortunately there are only a few in the U.S. While some pediatricians are comfortable and have experience in making the diagnosis, very often a definitive diagnosis will require referral to a pediatric consultant in Canada, or a pediatric subspecialist, either a neurologist or gastroenterologist in the U.S. After the history, physical exam, and testing, if your physician feels that CVS is likely, they will discuss therapy with you. It may be helpful to bring literature such as the pediatric or adult guidelines or this guide to your physician to help advocate for the patient. It is best to do so in a spirit of partnership.

What therapies are available?

Treatments for CVS is divided into at six categories: *lifestyle changes*, *psychological support*, *abortive therapy* to break an attack, *prophylactic therapy* to prevent further attacks, *rescue therapy* to lessen the symptoms when the child's episode cannot be stopped, and the use of *dietary, supplements and complementary approaches*.

- **What are lifestyle changes can be made?**

Lifestyle changes are simple approaches that can help improve school and extracurricular participation. You'll recognize these as grandma's advice. Drinking extra fluid and adding salt to the diet can treat the dizziness that occurs on standing up and help keep extra fluid reserve for when cycles start. Eating regular meals and using protein-based snacks can help boost and sustain a child's low energy. Regular bedtimes and turning off ALL electronics (phones, tablets, computers, televisions, etc) before bedtime can help regulate the sleep pattern. Regular exercise even for those with fatigue helps not only their fitness and sleep pattern but can also increase mitochondrial function. Lastly, avoiding known triggers such as sleepovers, chocolate or aged cheese, and frequent cannabis use is important. We only recommend dietary avoidance if a specific food has been consistently eaten before episodes.

- **How do can you deal with anxiety?**

Research has confirmed that many children and adults with CVS have anxiety. In some, CVS attacks may be triggered by psychological stressors. In children happy excitement such as birthdays, holidays or vacations is more common, but school exams, bullying, and divorce can do so as well. And, of course, having CVS, going to the Emergency Room, being hospitalized and missing school adds to the stress. We recommend several *psychological support* approaches to lower the stress response. A helpful book for children is "Be the Boss of Your Stress" (Culbert and Kajander) and there are Apps that teach deep breathing techniques to calm the child. In the older child, yoga may be helpful. When the disability has reduced daily school attendance, we typically recommend a psychologist who can teach stress reducing techniques and help the child develop better coping strategies. In some cases, the effect of reducing anxiety is more powerful than the medication.

- **What abortive therapies can be used?**

Abortive therapies are treatments given to stop the episode during the warning period before the vomiting begins, or, within the first two hours of vomiting. These are given only at onset of the attacks rather than daily. There are three classes of medications that can be tried, however they are not always effective. The antimigraine nasal sprays or injections such as sumatriptan (Imitrex®) or zolmitriptan (Zomig®) may work if given early during the warning period. Anti-vomiting oral medications such as aprepitant (Emend®) or ondansetron (Zofran®) may work if given during the warning period. A few patients respond to being sedated using sedatives such as IV lorazepam (Ativan®) in the Emergency Department. If the abortive approach fails, then we move on to the rescue approach to lessen symptoms.

- **When should prophylactic therapy be used?**

Prophylactic treatments are medications given on a daily basis to try to prevent future episodes. For patients with more frequent episodes (every 1-2 months) or with severe episodes requiring medical intervention, prophylactic therapy should be considered to reduce the frequency and

severity of episodes. However, if episodes are infrequent (e.g, 3 times a year), relying on abortive therapy alone makes more sense. The most common prophylactic medications include amitriptyline (Elavil®), cyproheptadine (Periactin®), pizotifen (Sandomigran® in Canada), and propranolol (Inderal®). Other medications include anti-vomiting agent aprepitant (Emend®) and anticonvulsants (used to prevent seizures) such as topiramate (Topamax®), phenobarbital and levetiracetam (Keppra®). While these prophylactic medicines are generally safe, each has a different side effect profile, and so the benefits and risks of prophylactic therapy should be reviewed with your physician.

- **What are ‘rescue’ medications to help during an episode?**

Once a CVS episode starts, it is very difficult to stop. In an attack, the best *‘rescue’ therapy* AKA supportive treatment involves fluid replacement, anti-vomiting agents, sedatives, and, if needed, pain medications. Intravenous fluids with a high percentage of dextrose (sugar) should be started and the patient admitted to a dark, quiet room in the hospital. Anti-vomiting medicines include aprepitant (Emend® or fosprepitant IV) or ondansetron (Zofran®). If sedation using diphenhydramine (Benadryl®), promethazine (Phenergan®), or lorazepam (Ativan®) induces sleep it can stop the nausea and vomiting temporarily. Even without rescue or supportive treatment, the attack will eventually stop on its own. However, if the episode lasts longer than 10 days, it probably is not due to CVS and other causes should be investigated further.

- **Does diet play a role?**

We don’t know about the role of diet in CVS. There is a migraine diet that restricts certain foods (cheeses, chocolate, legumes, wine and other foods) but is generally not recommended unless a specific food trigger has been identified. Because energy depletion can be a trigger for episodes, most doctors recommend even pacing of meals with frequent healthy snacking. Avoiding fasting is highly recommended.

- **Can supplements be helpful?**

There is some evidence that certain supplements that help the mitochondrial (cell power plant) produce energy. These include Coenzyme Q10, Riboflavin (vitamin B2) and L-carnitine can help prevent episodes. Commonly-used dosages for the first two supplements can be found at www.cvsaonline.org. There may be some side effects from using L-carnitine.

- **Can complementary therapies be helpful?**

Acupuncture has been tried by a number of patients with mixed success. Although yoga and other stress reducing practices have not been studied, they may be helpful.

Will my child get better? Will my child outgrow CVS?

Information on the long-term natural history of CVS remains limited. However, studies do suggest most respond well to medication. A significant proportion of children with CVS will begin to outgrow it beginning at 9 years of age and we estimate that 75% will ‘trade’ their childhood CVS for adult migraines by the age of 18 years. There are those who develop CVS as teenagers and we don’t yet know if they will outgrow it like younger children or carry it with them into adulthood. From studies in adults with CVS, there are some (29%) who began to have CVS attacks as children. However, the typical adult begins to experience CVS in their 30’s.

What kind of impact will CVS have on our family?

You know better than we about the effects that CVS can have on your family. Studies demonstrate that it greatly affects the patients' quality of life. An unexpected episode can disrupt a family vacation. Missed school leads to missed work for the parents. And so on. If the child misses several weeks of school, a rehabilitation approach to return the child to school and function that involves either a psychologist or rehabilitation program may become necessary. Finding support groups like those available through the Cyclic Vomiting Syndrome Association can be helpful for adjusting and learning about ways to help cope.

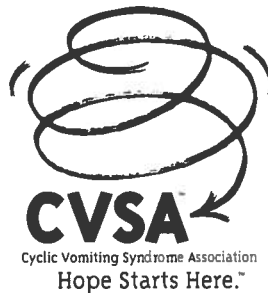
How can I learn more?

Talk to your physician, to other patients and family members, and explore the website www.cvsaonline.org. The Cyclic Vomiting Syndrome Association (CVSA) offers information, educational materials, conferences, and multiple opportunities for support (support groups) coping with this illness.

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