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FEATURE REVIEW

Cyclic Vomiting Syndrome

Background

Cyclic vomiting syndrome (CVS) is a chronic, functional gastrointestinal disorder characterized by recurrent episodes of nausea and vomiting.[1] It was first described by a pediatrician in the 1800s affecting children; however, it also occurs among adults. The prevalence of CVS in children is estimated at 1.9 to 2.3%; the prevalence in adults appears to be similar, however the data is more scarce.[1, 2]

The pathogenesis of CVS is likely multifactorial. Theories that have been proposed include dysregulation of the brain-gut axis, genetic abnormalities (e.g., mitochondrial mutations, polymorphisms involving the cannabinoid and mu-opioid receptors), dysfunction of the endocannabinoid system and the hypothalamic-pituitary-adrenal axis.[1] CVS may be considered a variant of migraine. As a result, many conventional treatments for migraine have demonstrated efficacy in treating CVS based on open-label and retrospective studies.[1]

There is significant variation in the recognition, diagnosis and management of CVS.[3] The Rome criteria may be used for diagnosis, last updated in 2016 (Rome IV).[4] For CVS in adults, the Rome IV criteria include: Stereotypical episodes of acute onset vomiting and short duration (less than 1 week) with:

1. At least one discrete episode in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart, and
2. Absence of vomiting between episodes, but other milder symptoms can be present between cycles.

A personal or family history of migraine headaches supports the diagnosis.[4]

Cannabinoid hyperemesis syndrome (CHS) may be a subset of CVS associated with chronic cannabis use.[2] For a brief review of management of CHS, see the “You Asked Us” section in the October 2021 newsletter.

Approach to Treatment

Evidence-based consensus guidelines for the treatment of CVS were published by the American Neurogastroenterology Motility Society and the Cyclic Vomiting Syndrome Association in 2019.[3] The guideline committee described a biopsychosocial care model for treatment, which integrates lifestyle modification (e.g., identification and avoidance of triggers), prophylactic and/or abortive medications, and psychotherapy (to treat frequently co-morbid psychiatric disorders).

Abortive medications should be offered to all patients, while prophylactic medications should be considered only in moderate to severe CVS. Severity criteria (mild vs. moderate to severe) were assigned based on the frequency and duration of episodes and health care utilization (i.e. emergency department visits or hospitalizations for CVS). A treatment algorithm is included in Figure 1 of the guidelines.[3]

The guideline committee established 10 recommendations for the management of CVS.[3] These are condensed on the following page for convenience.

IN THIS ISSUE:

Treatment Recommendations for CVS[3]

Prophylactic medications in adults with moderate to severe CVS

- Strong recommendation for tricyclic antidepressants (e.g. amitriptyline) as first-line
- Conditional recommendations for topiramate, aprepitant, zonasimide or levetiracetam as alternative prophylactic medications
- Conditional recommendations for the supplements co-enzyme q10 or riboflavin as alternative prophylaxis, and mitochondrial supplements as concurrent prophylaxis

Abortive medications in adults with mild or moderate to severe CVS

- Conditional recommendations for use of triptans (e.g. sumatriptan intranasal or injection), serotonin antagonists (e.g. ondansetron) or aprepitant

Non-pharmacologic interventions

- Screening, referral and treatment for co-morbid conditions (e.g. psychiatric disorders, migraines, autonomic dysfunction and substance use)
- Complementary therapies (e.g. meditation, relaxation, biofeedback)

Table 1: Pharmacotherapy of CVS

Drug	Quality of evidence[3]	Usual adult maintenance dose[3]	Cost* ($) for 1 month (prophylaxis) or 1 dose (abortive)	Public Drug Funding (Ontario Drug Benefit)
Prophylactic medications				
amitriptyline	Very low	75 to 100 mg daily	7.46	General benefit
aprepitant (*Emend*)	Very low	125 mg twice weekly (adults > 60 kg) or 80 mg twice weekly (adults 40 to 60 kg)	146.84 (80 mg dose)	Not a benefit for CVS
topiramate	Very low	100 mg daily	13.75	General benefit
levetiracetam	Very low	1000 to 2000 mg daily	21.66	Not a benefit for CVS
zonisamide	Very low	400 mg daily	Not available in Canada	Not applicable
coenzyme Q10	Very low	200 mg bid	26.78	Not a benefit
riboflavin	Very low	200 mg bid	18.95	Not a benefit
Abortive medications				
sumatriptan	Moderate	20 mg nasal spray or 6 mg SC injection	34.62 (injection)	General benefit for injection only
ondansetron	Consensus	8 mg oral disintegrating tablet	4.99	Not a benefit for CVS
aprepitant (*Emend*)	Very low	125 mg on day 1, then 80 mg on days 2 and 3	104.39	Not a benefit for CVS

*cost based on manufacturer's listed/wholesale price (Ontario Drug Benefit or McKesson); prices may vary based on individual institutional contracts (does not include professional dispensing fee)

YOU ASKED US

Question: What is the current evidence for use of direct oral anticoagulants (DOACs) in obese patients for the treatment of acute venous thromboembolism (VTE)?

Answer summary: Thrombosis Canada's guidance statement on DOACs in obese patients states that there is increasing comfort in using DOACs for patients with a body mass index (BMI) between 30 and 39.9 kg/m^2 for treatment of VTE.[1] Similarly, the International Society on Thrombosis and Haemostasis (ISTH) 2021 Guidelines concluded that any DOAC is appropriate for patients with a BMI up to 40 kg/m^2 or weight up to 120 kg.[2] For patients with a BMI over 40 kg/m^2 or weight over 120 kg, the ISTH suggests that standard doses of rivaroxaban or apixaban are appropriate regardless of BMI or weight for VTE treatment.[2] At this time, less supportive data is available for apixaban than rivaroxaban. Consult the ISTH Guidelines for recommendations around anticoagulation in the setting of bariatric surgery.[2]

Background

Health Canada defines obesity as a body mass index (BMI) over 30 kg/m^2.[3] Obesity can be categorized as Class I (BMI 30 to 34.9 kg/m^2), Class II (BMI 35 to 39.9 kg/m^2) and Class III (BMI ≥40 kg/m^2).[4] Obesity is associated with an increased risk of both first and recurrent VTE.[5]

DOACs are used as first-line agents for both treatment and prophylaxis of VTE. Obesity and its treatments (i.e. bariatric surgery) can have an impact on the pharmacokinetics and pharmacodynamics of DOACs.[5] There are currently no routine laboratory tests that can reliably assess the anticoagulant effect of DOACs.[6] Obese patients, especially those with a BMI ≥40 kg/m^2 or weighing >120 kg, are underrepresented in clinical trials. A high weight alone does not always indicate obesity, which limits the interpretation of certain trials that reported weight and not BMI.[1] To date, no randomized controlled trials have specifically studied the safety of DOACs in obese patients.

Evidence

Observational studies support the use of apixaban or rivaroxaban for VTE treatment in obese patients.[2] These are summarized briefly below.

Apixaban

A single-center, retrospective study including 47 patients with a BMI ≥40 kg/m^2 found a similar incidence of VTE recurrence and major bleeding compared to warfarin.[7]

An observational study from U.S. databases including 43,000 patients with VTE in obesity Class I-III found no significant difference in recurrent VTE or major bleeding compared to warfarin. A slightly lower risk for both outcomes was found with apixaban.[1]

Rivaroxaban

The EINSTEIN thromboembolism trials demonstrated that rivaroxaban was an effective and safe alternative to standard anticoagulant in adult patients. A post-hoc analysis of this data, including 861 patients with a BMI ≥35 kg/m^2, found no significant difference in the incidence of recurrent VTE and major bleeding.[8]

Observational studies comparing rivaroxaban and warfarin in patients with Class I-III obesity demonstrated similar rates of VTE recurrence and bleeding outcomes.[2]

Pooled DOACs

A meta-analysis of five observational studies compared DOACs (apixaban, rivaroxaban and dabigatran) with warfarin in 6585 patients with a BMI ≥40 kg/m^2 or weighing >120 kg. The analysis demonstrated non-inferiority of DOACs for VTE recurrence and risk of major bleeding.[9] Several observational studies pooling DOACs (mostly rivaroxaban and apixaban) have shown similar rates of VTE recurrence and bleeding risk across the obesity classes.[2]

Summary of relevant ISTH Guidance Statements[2]

For patients with BMI >40 kg/m^2 or weight >120 kg:

- For treatment of VTE, standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA (i.e. warfarin), weight-based LMWH, and fondaparinux are also options.
- For primary prevention of VTE, standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight.
- Suggest avoiding use of dabigatran and edoxaban for VTE treatment and prevention in obese patients given unconvincing data for dabigatran, and lack of data for edoxaban.
- Suggest avoiding monitoring peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.

RESOURCES OF INTEREST

NOTE: These resources may be out of date by the time of publication. For the latest Ontario Ministry of Health COVID-19 documents, please visit: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/covid19_vaccine.aspx

COVID-19 Vaccine Third Dose Recommendations. The Ministry of Health. December 14, 2021. Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/COVID-19_vaccine_third_dose_recommendations.pdf

Highlighted Changes

- Immunocompromised individuals who are eligible for a three-dose primary series may receive a booster dose ≥6 months (168 days) after completion of the primary series
- Updated to include booster dose eligibility for adults ≥50 years of age
- Preferential recommendation for Pfizer-BioNTech for individuals aged 18 to 29
- New Table 2: Options for Vaccine Type and Dose offered for COVID-19 Vaccine Booster Doses

COVID-19 Recommendations for Special Populations. The Ministry of Health. December 2, 2021. Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/COVID-19_vaccination_rec_special_populations.pdf

Highlighted Changes

- Information on re-vaccination for stem cell transplant and CAR-T therapy recipients
- Updated guidance for those with allergies to COVID-19 vaccines
- New guidance on COVID-19 vaccination for children, adolescents and young adults

Rapid Antigen Tests for Voluntary Screen Testing. Ontario Science Advisory Table. Updated December 10, 2021. Available from: https://covid19-sciencetable.ca/sciencebrief/rapid-antigen-tests-for-voluntary-screen-testing/

Brief Summary

Using studies on people carrying a range of SARS-CoV-2 viral loads, this brief
(1) confirmed that people with high viral loads are likely to transmit the virus to the people around them, and
(2) established that rapid antigen tests can reliably detect those cases.

Rapid antigen tests could therefore help interrupt the chain of transmission by identifying infectious cases of COVID-19 quickly, leading to prompt isolation of the infected person.

Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19. Ontario Science Advisory Table. November 24, 2021. Available from: https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-5-0/

Ontario clinical practice guideline update for COVID-19 therapeutics (includes antiviral and antibody medications) in adult patients.

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Cyclic Vomiting Syndrome

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MetroDIS Holiday Hours

Fri Dec 24: 8:30am to 2pm

Mon Dec 27: stat holiday

Tues Dec 28: stat holiday

Fri Dec 31: 8:30am to 2pm

Mon Jan 3: stat holiday

Happy Holidays

You Asked Us

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3. Obesity. Health Canada. Published October 5, 2006. Accessed October 14, 2021. https://www.canada.ca/en/health-canada/services/healthy-living/your-health/lifestyles/obesity.html

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