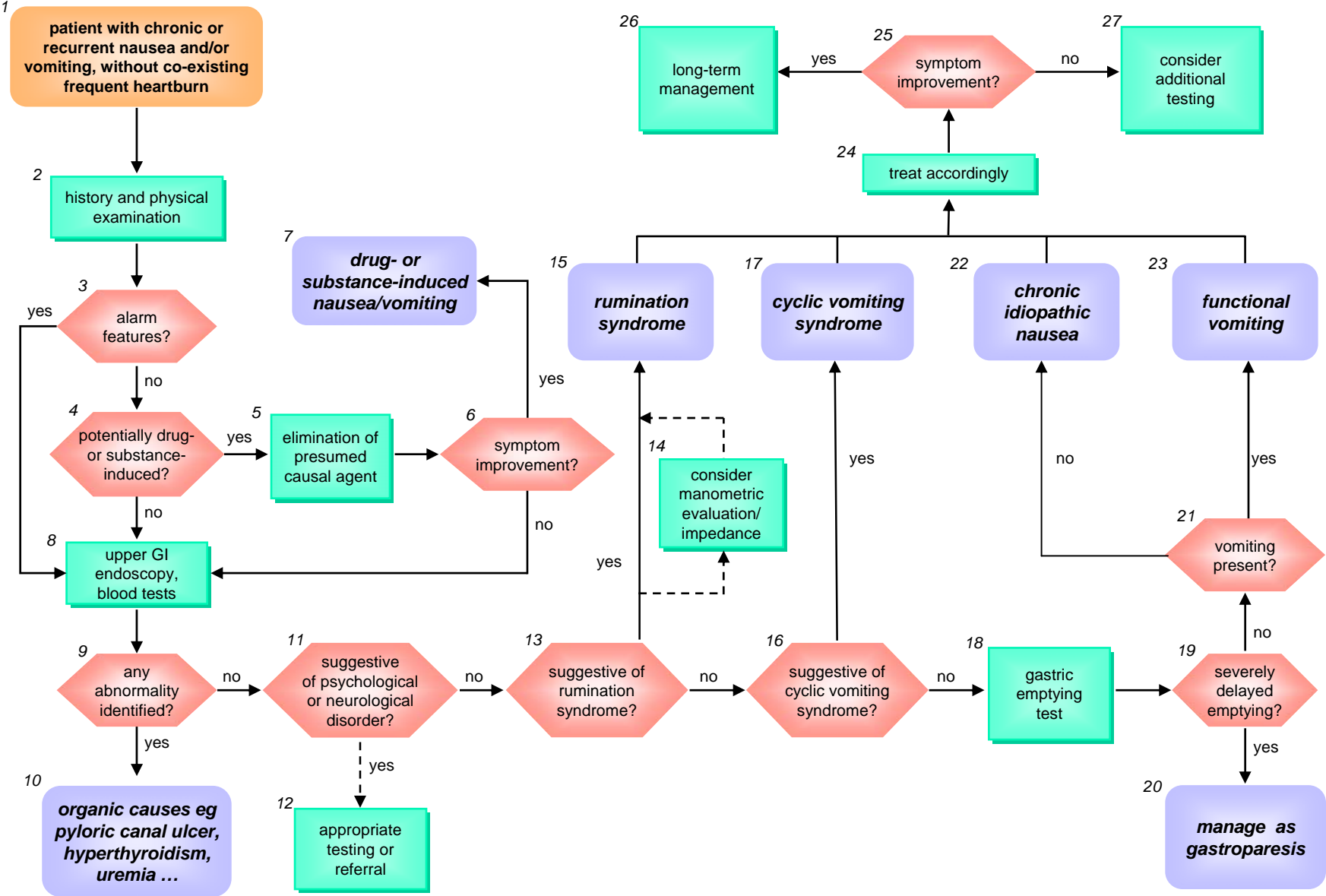


Figure 2: Recurrent nausea and/or vomiting



Recurrent nausea and/or vomiting

Case history

A 23 year old college student is referred to a gastroenterologist for refractory, persistent nausea (Box 1, Fig 2). The history (Box 2) reveals that she had been well until 14 months ago, when she became progressively nauseated over the course of a few days. Although initially present several hours per day, over the last few months the nausea has become ever present, from the moment she wakes up until the time she goes to bed. The nausea is usually not associated with vomiting though she has vomited 3 or 4 times in the last year (Boxes 1,13,16,21). There is no heartburn (Box 1) or excessive belching. The nausea interferes with her appetite, though is not worsened after meals and is not related to bowel movements, posture or exercise. She has lost 3 kg of weight over the last 6 months. There are no other alarm symptoms (Box 3). She notes occasional mild intermittent postprandial fullness, without early satiation or epigastric pain. The patient does not take NSAIDs or other medications, is a non-smoker and uses alcohol only sporadically. There is no history of substance use (Box 4). There are no associated vestibular, neurological or overt psychiatric symptoms (Box 11). There is no history of migraine and no other previous or current medical conditions that may explain the nausea. There is no relevant family history of gastrointestinal disease.

Clinical examination is negative, including the absence of vascular bruits over the abdomen, no neurological system abnormalities, and no alarm signs (Boxes 2, 3, 11). Blood tests including thyroid function tests and tests for other systemic or metabolic disorders are normal (Boxes 8, 9). An abdominal ultrasound performed 12 months ago was reported as normal. An upper GI endoscopy performed during the last year was also normal (Boxes 8, 9). A 24 hour urinary cortisol is normal.

Over the last year, she has tried several prokinetic and anti-emetic agents (including metoclopramide, domperidone, ondansetron), and also was prescribed a PPI, up to two times the standard dose, without improvement. She now takes up to four 10mg tablets of metoclopramide per day, with little or any effect, and

no other medications. The gastroenterologist also confirms that there are no specific features to suggest rumination syndrome (Box 13) or cyclic vomiting syndrome (Box 16). and also refers the patient for an ophthalmological examination to rule out signs of intracranial hypertension (Box 11). A scintigraphic gastric emptying test (Box 18) is then arranged; this reveals a half emptying time for solids within the normal range (Box 19). A diagnosis of **chronic idiopathic nausea** is made (Box 22).

A low dose tricyclic antidepressant is then prescribed for 8 weeks, with addition of chlorpromazine as a symptomatic anti-emetic agent (Box 25). The option of conducting additional diagnostic investigations, such as abdominal CT scan and MRI of the brain, in case of insufficient response to the proposed therapy, is discussed.

Figure legend

1. Nausea is a common and subjective symptom and the differential diagnosis is wide. In this context, it is assumed there are no known systemic or organic disorders such as diabetes mellitus or connective tissue disease. Nausea may accompany gastro-esophageal reflux disease (GERD) and may often respond to appropriate GERD management, which will generally consist of PPI therapy. Also see 'recurrent heartburn' algorithm (1).
2. A detailed history and clinical examination at the initial visit are essential. The history should recognize nausea as an unpleasant sensation of the imminent need to vomit typically experienced in the epigastrium or throat. Vomiting should be distinguished from regurgitation or rumination (see below). During the history taking and clinical examination, a broad list of potential causes of nausea and vomiting, including organic gastrointestinal disorders, medications and toxic agents, endocrine disorders, neurological disorders and psychogenic factors should be considered (1,11-14).
3. Alarm features include age, unintentional weight loss, nocturnal symptoms, dysphagia, lymphadenopathy, abdominal mass and evidence of anemia. If any of these symptoms or signs is present, prompt upper GI endoscopy is indicated, although the yield may be low (3,4).
4. Classes of drugs that commonly cause nausea and/or vomiting include analgesics, cardiovascular medications, hormonal preparations, antibiotics, CNS active medications, and cancer chemotherapy. Cannabis use/interruption of use has been implicated in chronic or recurrent nausea and vomiting (1).
- 5,6. If potentially relevant medications can be discontinued, and symptoms improve in temporal association with this cessation, a diagnosis of drug- or substance- induced nausea/vomiting may be considered, although longer term follow-up will be required (12).

7. Besides cancer chemotherapy agents, opioid analgesics and macrolide antibiotics are important causes of nausea and vomiting. A clue to cannabis hyperemesis is compulsive hot bathing or showering behavior.

8- Upper GI endoscopy serves mainly to exclude obstructive lesions and peptic ulceration, or rarely another organic lesion. In young patients without alarm features, empiric anti-emetic therapy may be considered prior to endoscopy and other additional investigations. In the case of frequent vomiting, esophagitis may be present, but this is a consequence of vomiting caustic gastric contents and usually does not explain chronic or recurrent nausea and vomiting. Relevant blood tests to be considered in addition to routine hematology and biochemical tests, include CRP level, thyroid function tests, blood glucose level, serum calcium, and tests to exclude Addison's disease. Celiac disease may be screened for in high prevalence areas. Further tests may be required depending on the results of these investigations. Imaging (small bowel x-ray or CT enterography) may be used to exclude mechanical obstruction in the upper gastrointestinal tract (1,12). In the setting of recent major weight loss (e.g. recent spinal cord injury, anorexia nervosa), the superior mesenteric syndrome (SMA) may develop where there is compression of the 3rd portion of duodenum by the aorta; CT is an excellent diagnostic modality at which time the superior mesenteric artery to abdominal aorta distance should be measured.

11,12. Neurological disorders that may cause chronic or recurrent nausea and/or vomiting include migraine, increased intracranial pressure, labyrinthine disorders and demyelinating disorders. Usually there are neurological symptoms and signs that clue the physician into these possibilities. Psychological conditions that may cause chronic or recurrent nausea and/or vomiting include anxiety disorders, depression, eating disorders and psychogenic vomiting. Psychogenic vomiting usually occurs in conditions of major psychological distress and is not clearly related to food ingestion. Self-induced vomiting is mainly associated with eating disorders. Appropriate testing (clinical neurological examination, exclusion of intracranial hypertension by examination of the eye fundus or by MRI scan of the brain) and/or referral may need to be considered.

13. Rumination should be suspected when there is the effortless repeated regurgitation of food (14). A typical history is generally sufficient to make a diagnosis of rumination syndrome. Key elements are the timing during and shortly after meal ingestion, the lack of prodromal nausea, the repetitive and effortless appearance of food in the mouth, and the ability to swallow the regurgitated material back into the esophagus.

14. In case of doubt or need for additional confirmation, esophagogastric manometry with administration of a meal shows a diagnostic pattern of brief intra-gastric pressure rises that are transmitted to the esophagus. Simultaneous impedance monitoring may document that these abdomino-thoracic strains push intragastric contents up into the esophagus to the pharynx (14,15).

15. Rome III diagnostic criteria for rumination are: 1) persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing, and 2) the regurgitation is not preceded by retching, and 3) these criteria are fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

Supportive criteria are that regurgitation events are not usually preceded by nausea, there is cessation of the process when the regurgitated material becomes acidic, and the regurgitant contains recognizable food with a pleasant taste.

16. Cyclic vomiting should be suspected when there are episodes of vomiting with a stereotypical onset and duration. There are varying intervals of absence of vomiting in between episodes. No structural or biochemical cause can be identified (1, 13).

17. Rome III diagnostic criteria for cyclic vomiting syndrome are: 1) stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week), and 2) three or more of these episodes in the preceding year, and 3) absence of nausea and vomiting in between episodes, and 4) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

18 - 20. Gastric emptying rates can be assessed using scintigraphy or breath test technology. Mildly delayed gastric emptying is a non-specific sign which may partly depend on the presence of nausea during the test. Severely delayed emptying suggests gastroparesis as a cause of nausea and/or vomiting. There is no consensus on a cut-off for "severely" delayed emptying using scintigraphy, enough to consider a diagnosis of gastroparesis, but we suggest using three times the upper limit of a large normal sample as the cut-off value.

21. Depending on the presence or absence of vomiting, likely diagnoses are now either chronic idiopathic nausea or functional vomiting.

22. Rome III diagnostic criteria for chronic idiopathic nausea are: 1) bothersome nausea, occurring at least several times a week, and 2) not usually associated with vomiting, and 3) absence of abnormalities at endoscopy or metabolic disease that explains the nausea, and 4) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

23. Rome III diagnostic criteria for functional vomiting are: 1) on average one or more episodes of vomiting per week, and 2) absence of criteria for an eating disorder, rumination, or major psychiatric disease according to DSM-IV, and 3) absence of self-induced induced vomiting and chronic cannabinoid use and absence of abnormalities in the central nervous system or metabolic diseases to explain the recurrent vomiting, and 4) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (1).

24. Treatment for functional nausea and/or vomiting is based on antiemetics, prokinetics or low-dose antidepressants. Dopamine-2 receptor antagonists such as domperidone, metoclopramide and chlorpromazine can be considered first-line drugs. Metoclopramide can induce parkinsonism and irreversible tardive dyskinesia; chlorpromazine causes somnolence. Tricyclic antidepressants as well as mirtazapine have nausea- and vomiting suppressing properties and can be considered second-line drugs

(2,16). In case of cyclic vomiting syndrome, anti-migraine drugs can also be considered (1,12,13). The rumination syndrome is preferentially treated by behavioral therapy (diaphragmatic breathing) (17).

25, 26. The long-term management, in case of therapeutic response, has not been established for these disorders.

27. Additional tests may include abdominal CT scan, small bowel x-ray or CT enterography, antroduodenal manometry, or esophageal pH/ impedance testing.

Psychosocial problems such as anxiety or depression may also present with nausea or vomiting. It is important to consider these early on in the course of extensive investigations, and to obtain expert opinion in case of refractoriness. A useful tool is the *Rome III psychosocial alarm questionnaire* (see Appendix A). Therapeutic trials using antidepressants can be considered with the endpoint of benefit being symptom improvement or improved daily functioning even in the presence of the symptoms.