

Functional Emesis

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ABSTRACT

Emesis is an essential survival response, because consumption of food is a key element in the survival behavior and the act of feeding can expose the majority of internal organs to toxins, altered food, viruses, bacteria or fungi. The relationship between visceral or vestibular stimuli and the anatomical structures of the brain-gut axis explain the modulation of the gastrointestinal response. We aimed to review comprehensively the current knowledge on emesis occurring in the disorders of brain-gut interaction (DBGI), i.e. functional conditions presenting with emesis. PubMed, Cochrane Library, EMBASE and WILEY databases were screened for relevant publications from the last 20 years regarding brain-gut disorders manifesting emesis. We included in the search also idiopathic gastroparesis, as a condition paralleling the postprandial distress syndrome. We critically analyzed 2 articles about chronic nausea and vomiting syndrome, 9 articles about cyclic vomiting syndrome, 9 articles about cannabinoid hyperemesis, 10 articles about idiopathic gastroparesis and 6 articles about gastroparesis like-syndrome. Contradictory results regarding the implication of environmental factors in the development of emesis in DBGI demonstrate that the underlying pathogenesis is still not completely understood.

Key words: emesis – vomiting – functional gastrointestinal disorders – disorders of brain-gut interaction.

Abbreviations: CHS: cannabinoid hyperemesis syndrome; CNVS: chronic nausea and vomiting syndrome; CVS: cyclic vomiting syndrome; DBGI: disorders of brain-gut interaction; ECS: endogenous cannabinoid system; FGID: functional gastrointestinal disorders; GES: gastric electrical stimulation; GP: gastroparesis; GLS: gastroparesis-like syndrome; ICC: interstitial cells of Cajal; IGP: idiopathic gastroparesis tGES: temporary gastric electrical stimulation; TSS: total symptom score.

INTRODUCTION

Emesis is a reflex which integrates a complex set of actions of the inspiratory and expiratory muscles in order to produce an involuntary, forceful expulsion of the contents of stomach through the mouth and rarely through the nose [1]. Emesis must be distinguished from regurgitation and rumination.

The first description of emesis as a “reflex arc” dates back to more than four centuries ago by the French philosopher Descartes. Charles Sherrington, an English physiologist, conducted complex experiments on spinal cord reflexes in the early years of

the XX century, demonstrating the link between the central nervous system, peripheral nervous system, vestibular function and emesis [2].

Emesis is an essential survival response, because consumption of food is a key element in the survival behavior and the act of feeding can expose the majority of internal organs to toxins, altered food, viruses, bacteria and fungi. Similar with the survival response of emesis, diarrhea has the role of removing toxins and pathological agents from the lower intestines.

The activation of the emesis reflex arc has the function of modulating the gastrointestinal function, the response to stress environmental changes, the regulation of the gastrointestinal immune system, mucosal inflammation and intestinal microbiota (Fig.1) [3-8].

Functional gastrointestinal disorders (FGID) are disorders of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormality.

Disorders of Brain-Gut Interactions (DBGI) is the new name of FGID and the diagnosis is mainly clinical [1-3]. Emesis

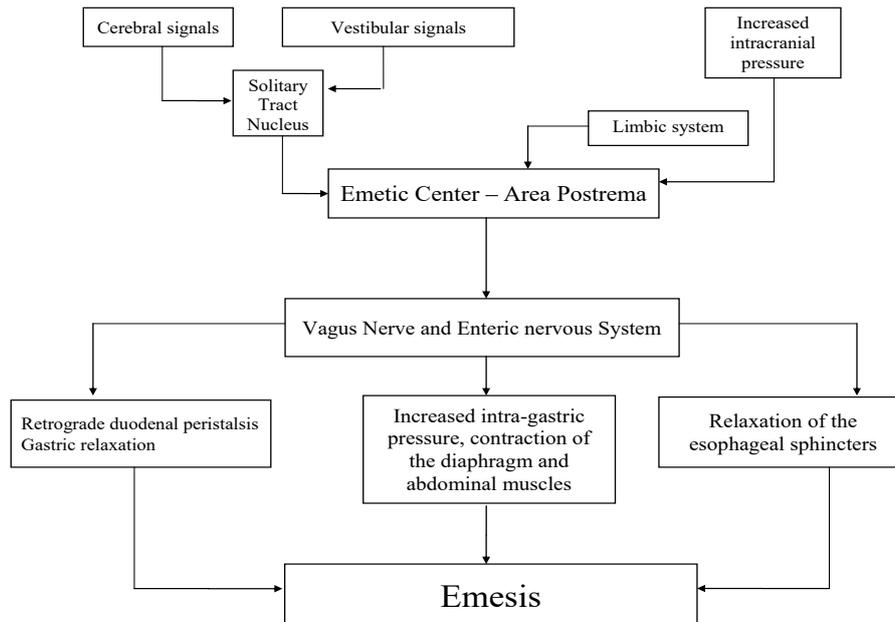


Fig. 1. The pathogenesis of emesis.

is encountered in some of these DBGI. The diagnosis of these disorders relies on the symptom-based Rome IV Criteria [3]. According to these, the DBGI presenting vomiting are included in the Gastroduodenal DBGI. They are classified in three syndromes: chronic nausea vomiting syndrome (CNVS), cyclic vomiting syndrome (CVS), cannabinoid hyperemesis syndrome (CHS) [3]. Beside this, emesis may occur accompanying nausea in postprandial distress syndrome, one of the subtypes of functional dyspepsia.

Three years have elapsed since the issue of the Rome IV Criteria and we searched for an update review on the current knowledge of the DBGI manifested with emesis. We also looked for current evidence on idiopathic gastroparesis (IGP), which is a parallel disorder to functional dyspepsia. We report additionally on the emerging entity of the gastroparesis-like syndrome (GLS).

PubMed, Cochrane Library, EMBASE and WILEY databases were screened for relevant publications regarding brain-gut disorders manifested with emesis between January 1999 and January 2019. The search terms included: (emesis OR vomiting OR vomit) AND (brain-gut OR brain OR functional gastrointestinal disorders OR FGID OR chronic nausea) AND (vomiting syndrome OR cyclic vomiting syndrome OR cannabinoid hyperemesis OR idiopathic gastroparesis OR gastroparesis like-syndrome). Exclusion criteria were: studies written in languages other than English, studies not performed in humans, abstracts, conference presentations, letters to the editor, editorials, comments and opinions and these were not taken into consideration. Articles treating the subject of rumination syndrome were also excluded. The articles included in this review refer only to DBGI that include the brain-gut axis pathology and emesis as the predominant symptom.

The initial search identified 1898 articles, out of which 257 potentially appropriate articles were reviewed. Of these 257 articles, 36 articles were retained for this review (Fig. 2). Two articles analyzed CNVS, 9 articles analyzed CVS, 9 articles

analyzed cannabinoid hyperemesis, 10 articles analyzed IGP and 6 articles analyzed GLS.

Chronic nausea and vomiting syndrome

According to the Rome IV Diagnostic Criteria, all the following clinical and lab criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis of CNVS: bothersome nausea (severe enough to impact on usual activities), occurring at least 1 day per week and/or one or more episodes of emesis per week. It should be differentiated from self-induced vomiting, eating disorders, regurgitation or rumination. No evidence of organic, systemic or metabolic diseases should be found on routine investigations including upper endoscopy [9].

The prevalence of CNVS is unknown, although nausea is reported at least weekly by 3% of normal population [9].

The treatment options include antiemetic agents divided into 5 classes: 1) histamine H1 antagonists (meclizine, promethazine); 2) muscarinic M1 antagonists (scopolamine); 3) dopamine D2 antagonists (prochlorperazine); 4) serotonin 5-HT3 antagonists (ondansetron, granisetron), neurokinin NK1 antagonists (aprepitant); 5) cannabinoids (dronabinol) [3, 9, 10]. Clinical trials and therapeutic guidelines are lacking.

Cyclic vomiting syndrome

Cyclic vomiting syndrome was first described in children by Samuel Gee in 1882 and is a chronic functional gastrointestinal disorder of unknown etiology that is characterized by recurrent and episodes of rapid-fire vomiting between varying periods of completely normal health. The on-and-off stereotypical pattern of paroxysmic vomiting is pathognomonic [11].

The Rome IV diagnostic criteria for CVS include of the following criteria: (1) at least 2 periods of unremitting vomiting with or without retching, lasting hours to days within a 6-month period; (2) a return to the usual state of health that lasts weeks to months [12].

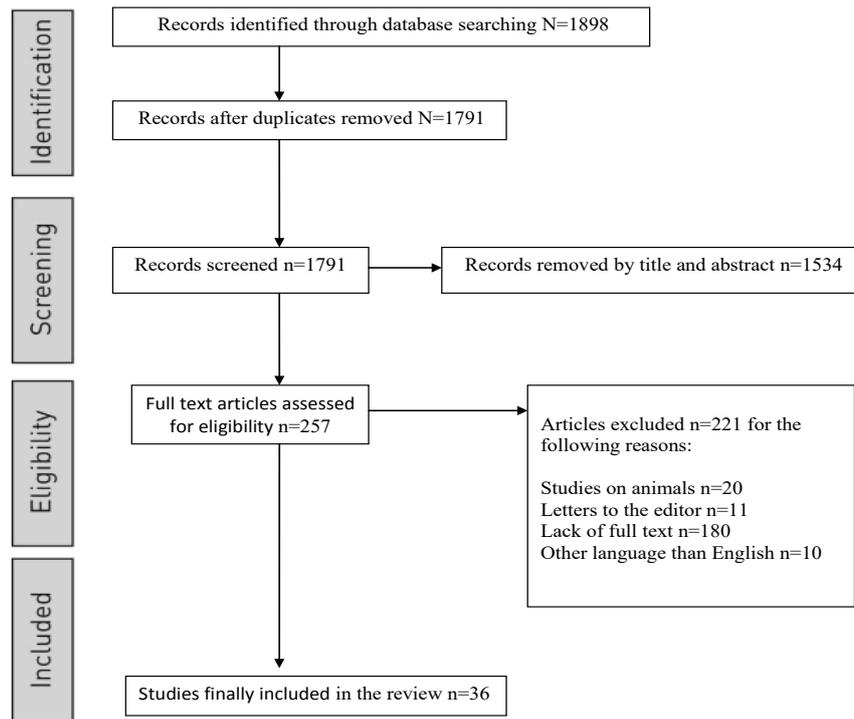


Fig. 2. Flow diagram for study selection.

The differential diagnostic between CNVS and CVS is made using temporal criteria, because CVS was described to have four temporal phases: 1) a pre-emetic period with nausea, pallor, diaphoresis; 2) intense emesis up to 30 episodes daily, often with associated epigastric or diffuse abdominal pain and/or diarrhea; 3) a recovery phase with gradual symptom resolution of nausea and vomiting; 4) interepisodic period without vomiting [9].

The true incidence and prevalence of CVS are unknown. Precise data about the epidemiology of CVS are available only for the population in Australia, where Cullen and MacDonald estimated the prevalence of CVS at 2.3% [13]. Initially, psychosocial factors were attributed to the pathogenesis of CVS, but the recent data show that mitochondrial DNA (mtDNA) mutations may be involved in the pathogenesis of CVS [14, 15]. Furthermore, 86% of children with CVS and neuromuscular disease had a history of migraines on the matrilineal side and two mtDNA polymorphisms (16519T and 3010A) are expressed with a high degree of frequency [14-16]. A study that included a small number of patients, found that adult-onset of CVS, unlike pediatric onset of CVS, was not associated with these polymorphisms, suggesting a degree of genetic distinction [16].

A study on 31 patients with CVS by Hikita et al. [17] showed that the median duration of the disease was 66 months and that 44% of the patients seen for follow-up, developed a severe migraine. The study also showed high serum levels of adrenocorticotrophic hormone and antidiuretic hormone in patients with CVS. Furthermore significant correlations between attack duration and antidiuretic hormone and adrenocorticotrophic hormone levels were described [17].

In conclusion, the pathogenesis of CVS is multifactorial. A major pitfall in the current medical literature describing CVS

is represented by the low number of subjects included in the majority of studies. Further studies are required to discover the exact mechanisms underlying the pathogenesis of this disorder.

Although patients are symptomatic only 10% of the time, CVS has a major economic impact and it is medically and socially disabling. More than a half of patients require intravenous (IV) fluids and the average annual cost of testing, treatment, and absenteeism is high. In adults, substantial morbidity is associated with CVS, perhaps because of lack of awareness and resultant delays in diagnosis. A study on 41 patients and 293 procedures performed by Fleisher et al. showed that 17 surgical procedures, including 10 cholecystectomies, appendectomies, laparotomies, pyloroplasties and a hysterectomy, were performed without any therapeutic benefit [18, 19]. Adults and children with CVS also have multiple emergency department consultations and day offs and the diagnosis is frequently mistaken [19]. Sleep deprivation has been described by Fleisher et al. as an important trigger for patients with CVS and the same author has described a 70% decrease in frequency of episodes only with lifestyle changes without pharmacological, psychological or surgical therapy [18, 19]. Contrary, a study performed by Li et al. [11] demonstrated that avoiding dietary triggers such as chocolate, cheese, and monosodium glutamate can prevent episodes without the use of drugs, emphasizing the role of diet in the pathogenesis and outcome of FGID.

Cannabinoid hyperemesis syndrome

Cannabis is the most frequently used illicit drug in the world, with more than 160 million users worldwide [20, 21]. In the United States, there are 2.4 million new users every year. The number of cannabis user has increased dramatically

as a consequence of the fast changing political landscape and laws that permit recreational medicinal use of cannabis [21].

Cannabinoid hyperemesis syndrome is characterized by significant nausea, vomiting, diffuse abdominal pain, and relief with hot showers [22]. The most important diagnostic criteria is chronic regular cannabis use. Furthermore, resolution of symptoms appears after stopping cannabis. Compulsive hot baths or showers are associated with symptom relief [22].

Patients follow an extensive evaluation in order to establish a correct diagnosis; frequently they perform unnecessary procedures including advanced imaging, endoscopy, expensive laboratory tests and repeatedly emergency department visits. The diagnosis is frequently mistaken and a delay in finding an appropriate treatment appears. The consequence is an increasing economic burden with no improvement of treatment. Complications of CHS include hospitalizations for severe arrhythmias, dehydration and electrolyte imbalance, ketonuria, mild leukocytosis [23]. If patients deny cannabis use or other illicit drugs but a clinical suspicion remains, a urine drug screen is recommended. Imagistic methods are not recommended because there are no specific radiological findings suggestive of the diagnosis.

Dysregulation of the endogenous cannabinoid system (ECS) is a physiologic regulator of gut motility and is involved in the reflex of emesis and is described as an important pathogenic mechanism in CHS [24-28].

Endogenous cannabinoid system is responsible for the complex effects of cannabis and includes the following components: ligands N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), their biosynthetic and degradative enzymes, and the cannabinoid receptors CB1 and CB2 [8, 24, 27, 28]. Other pathogenic mechanisms include accumulation of cannabinoid metabolites in the brain and fatty tissues inducing a toxic effect, desensitization and downregulation of CB1 receptors causing rebound vomiting and spasmodic pain and paradoxical and plastic changes in expression and downstream effects of cannabinoid receptors [8, 27, 28].

Patients presenting with emesis after a period of chronic cannabis use may have a genetic variation in their hepatic enzymes that results in an increase of the levels of cannabis metabolites, which explains the symptomatology [8, 24, 28].

If the cannabis administration is stopped, in most cases symptoms disappear. If the patients are resistant to the indication of cannabinoid abstinence, referral to an appropriate psychiatric dependency department is recommended.

Idiopathic gastroparesis

Gastroparesis (GP) is a chronic motility disorder characterized by delayed gastric emptying in the absence of organic modifications leading to mechanical obstruction [29]. It is frequently present in patients with diabetes, Parkinsonism and abdominal surgery affecting the vagus nerve. Rare causes include: mononucleosis, scleroderma, Ehlers-Danlos syndrome, chronic renal failure, hypochlorhydria, intestinal pseudoobstruction, eating disorders, mitochondrial disease, narcotic analgesic or anticholinergic medications, amyloidosis, heavy cigarette smoking, mesenteric ischemia and paraneoplastic syndrome [30-34].

Gastroparesis was first described among patients with diabetes along with typically end-organ complications such as nephropathy, retinopathy, and peripheral neuropathy [33].

Idiopathic GP is described after all other metabolic, endocrine, neurologic, rheumatologic, paraneoplastic, post-infectious and surgical causes of GP have been excluded [29-31].

The most common symptoms of IGP are represented by nausea (>90% of patients), vomiting (84% of patients), and early satiety (60% of patients). Rarely, postprandial fullness and upper abdominal pain appears, and weight loss, malnutrition, and dehydration appear only in severe cases [30-32]. In patients with mental disorders, such as depression or anxiety, higher anxiety/depression scores are correlated with the severity of the symptoms.

The dietary changes that can improve the symptomatology are: increasing the liquids ingestion rather than solids, consuming multiple low-fat small meals, and maintaining optimal glucose levels in diabetic patients. Male gender, gastrointestinal infections and the use of antidepressants, were proven to be predictors of symptom improvement by one study, and obesity, smoking, abdominal pain, gastroesophageal reflux disorder, severe depression were identified as predictors of no improvement [30-33].

A recent study demonstrated the importance of the genetic background in GP, showing that longer poly-GT that is repeating in the HMOX1 gene is more common in African Americans with GP and the symptomatology is more severe in subjects with longer alleles [34].

To diagnose GP one should assess gastric emptying. Among several techniques available, more frequently used are: scintigraphy, wireless motility capsule, and carbon13 breath testing. Scintigraphy of a solid phase meal is still the standard [35]. A new method used to increase standardization is the use of a wireless motility capsule, called SmartPill which is measuring pH, temperature, and pressure. It measures gastric emptying time calculating the duration from ingestion with a rise in pH from acidic antrum, until it enters the alkaline medium of duodenum [35].

In clinical practice, the "Gastroparesis Symptom Cardinal Index" is used for a correct diagnosis and treatment. It uses a scale of six levels of severity from "very severe" to "none" and it evaluates: nausea, retching, vomiting, stomach fullness, not able to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating, stomach or belly visibly larger [33-35].

Prokinetic medications (metoclopramide, erythromycin) and antiemetic medications are usually used as treatment. Metoclopramide can cause extrapyramidal symptoms and should be administered with caution to patients with anxiety or depression [36-38]. Furthermore, mirtazapine and other antidepressants may be an option by enhancing receptive relation and alleviating distress associated with gastroparesis [35-38]. Hypnotherapy is useful as reported by a recent systematic review [39].

Gastroparesis-like syndrome

Patients with GP with similar symptomatology but with normal gastric scintigraphy and non-delayed gastric emptying are defined as suffering from GLS.

There is still debate over the definition and the differences between GLS and IGP. Gastric emptying as diagnosed by nuclear scintigraphy may modify its clinical outcome in time and is considerable related to modifications by systemic processes (glycemic values, weight loss, etc) and medications [40].

Moreover, IGP and GLS patients included in studies are frequently heterogeneous, with similar symptoms, comorbidities, and response to treatment, complicating the protocol and the scientific outcome. Nevertheless, in the last decade, GLS is beginning to be recognized as a distinct pathological process.

The differential diagnosis between GLS and postprandial distress syndrome is made using the Rome IV Criteria and must include one or both of the following at least 3 days per week: 1) bothersome postprandial fullness (ie, severe enough to impact on usual activities); 2) bothersome early satiation (ie, severe enough to prevent finishing a regular-size meal); 3) no evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy); Criteria must be fulfilled for the last 3 months with symptom onset and at least 6 months before diagnosis [41].

The chemoreceptor trigger zone in the area postrema plays an essential role in the physiopathological process of emesis and is one of four principal areas that can induce emesis. Abdominal vagal afferents that identify potentially emetogenic substances in the lumen also terminate in this zone. Results from a wide variety of experiments show that the nucleus tractus solitarius connects to the emetic central pattern generator which is located in the retrofacial nucleus of the reticular formation playing a key role in the progression of various stimuli that will finally have the effect of emesis induction [37, 38, 40, 41]. It controls respiratory groups that coordinate the muscular movements involved in retching and vomiting. There is no isolated emesis center but fragments of unorganized neurons in the medulla that can be activated by vestibular, cortical, gastro-intestinal and metabolic factors.

Studies have demonstrated that significantly more fibrosis is present in the pylorus in GP patients, compared with patients with GLS, that demonstrates that fibrosis is a main pathogenic factor in the process of delayed gastric emptying in GP patients [40]. Furthermore, in a retrospective analysis, pyloroplasty in GP patients was associated with improvement in symptoms and improved gastric emptying in 83% of patients [42].

A recent study performed by Bashashati et al. [43] compared the histopathological features of antral and pyloric smooth muscle tissue in GP and GP-like syndrome. The result was that 17 out of 24 (70.8%) GP patients with pyloric biopsies had concomitant pyloric interstitial cells of Cajal (ICC) loss and severe fibrosis, while only one GLS patient had ICC loss [43]. Moreover, GP patients had a greater baseline total symptom score (TSS) compared to GP-like patients [43, 44]. These pathological findings clearly explain the pyloric dysfunction and delayed gastric emptying in GP.

Gastric electrical stimulation (GES) is a new form of therapy for both GP and GLS and is recommended for patients with refractory emesis at pharmacological agents. While the efficacy and benefits of GES in gastroparesis is extensively documented, the role of GES in GLS is not precisely reviewed.

A study performed by Singh et al. [46] analyzed the effects of temporary gastric electrical stimulation (tGES) in patients with GLS. Total symptom score and scintigraphic parameters were also analyzed. 551 patients suffering from symptoms of gastroparesis (emesis, nausea, bloating/distension, anorexia/early satiety, and abdominal pain) with negative endoscopy underwent gastric scintigraphy [46]. The following parameters were recorded: solid radio-nuclide gastric emptying, area under the gastric emptying curve and the total gastric emptying test. Patients were classified in three categories: delayed gastric emptying, normal gastric emptying, and rapid gastric emptying. Finally, from 551 patients in the larger cohort, 379 had implantation of tGES, symptoms and gastric emptying was compared pre and post tGES implantation [45, 46]. The results were that after tGES, the gastric retention after 2 hours decreased ($p < 0.01$) for the delayed patients and increased ($p < 0.001$) for normal and rapid patients [46]. Considerable improvement in vomiting, nausea, and total symptom scores in all 3 subgroups, was demonstrated ($p < 0.001$). Considering the recent data provided by studies of the neurophysiological mechanisms and pathogenesis of GP and GLS, the main recommendation for a research project for the future will be to determine which patients would benefit from the placement of a permanent gastric stimulator, which patients require surgery and which patients should be limited to pharmacological therapy.

DISCUSSION

Emesis is a frequent symptom in clinical medicine. However functional vomiting, associated with nausea, is difficult to diagnose and frustrating to treat. No therapeutically guidelines are available on CNVS, nor for GLS. There are guidelines for vomiting after chemotherapy or after surgery [47, 48].

Given the need of practitioners to be familiar with the entities of GBI presenting emesis, we reviewed the pertinent literature. The present review has identified articles, most of them prospective studies, about emesis in BGID during natural evolution or under therapy.

The pathophysiology behind emesis in DBGI is complex, with multiple and complex variables involved. Studies concentrating on histological changes in DBGI modify the basis of functional disorders paradigm and make more difficult the classification process of gastrointestinal disorders in organic and functional [35, 37, 43]. Furthermore, convincing data provided by the detailed analysis of genetic background of brain-gut disorders are changing the perspective of the psychosocial parameters as key determinants in the development long-term evolution of DBGI.

It is becoming obvious that precise mechanisms responsible for the development of different DBGI have to be further analyzed and compared in order to develop new pharmacological agents concentrating on the regulation of gastrointestinal motility.

Convincing evidence for the pathogenic mechanism implicated in the development of DBGI manifested with emesis is lacking. To date, IGP and CVS are the most frequently studied brain-gut disorders with emesis as the main symptom. Studies on CNVS and GLS, including case reports, are very limited.

Our review is limited by the small number of patients included in the studies.

CONCLUSIONS

Emesis is the Cinderella of DBGI. Contradictory results about the implication of the genetic background and the phenotypic parameters in its occurrence reflect the missing knowledge of its pathogenesis. The management of functional emesis may prove difficult at times.

Conflicts of interest: None to declare.

Authors' contributions: S.L.P. searched the literature, drafted and wrote the manuscript. G.I.G. literature search; L.D. suggested the methodology analyzed the results, and revised the manuscript; G.C. critically revised the manuscript; D.L.D. supervised the work and substantial contributions to the writing. All authors approved the final version of the manuscript.

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