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ABOUT COVER

AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pathophysiology* (*WJGP*, *World J Gastrointest Pathophysiol*) is to provide scholars and readers from various fields of gastrointestinal pathophysiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGP mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal pathophysiology and covering a wide range of topics including disorders of the esophagus, stomach and duodenum, small intestines, pancreas, biliary system, and liver.

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REVIEW

Electrical neuromodulation therapy for inflammatory bowel disease

Farah Yasmin, Abdul Moiz Sahito, Syeda Lamiya Mir, Govinda Khatri, Somina Shaikh, Ambresha Gul, Syed Adeel Hassan, Thoyaja Koritala, Salim Surani

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Farah Yasmin, Abdul Moiz Sahito, Syeda Lamiya Mir, Govinda Khatri, Somina Shaikh, Department of Medicine, Dow University of Health Sciences, Karachi 74200, Pakistan

Ambresha Gul, Department of Medicine, People's University of Medical and Health Sciences, Nawabshah 67480, Pakistan

Syed Adeel Hassan, Department of Medicine, University of Louisville, Louiseville, KY 40292, United States

Thoyaja Koritala, Department of Medicine, Mayo Clinic, Rochester, NY 55902, United States

Salim Surani, Department of Medicine, Texas A&M University, College Station, TX 77843, United States

Salim Surani, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55902, United States

Corresponding author: Salim Surani, FACP, FCCP, MD, MSc, Doctor, Professor, Department of Medicine, Texas A&M University, 00 Bizzell St, College Station, TX 77843, United States. srsurani@hotmail.com

Abstract

Inflammatory bowel disease (IBD) is an inflammatory disease of the gastrointestinal (GI) tract. It has financial and quality of life impact on patients. Although there has been a significant advancement in treatments, a considerable number of patients do not respond to it or have severe side effects. Therapeutic approaches such as electrical neuromodulation are being investigated to provide alternate options. Although bioelectric neuromodulation technology has evolved significantly in the last decade, sacral nerve stimulation (SNS) for fecal incontinence remains the only neuromodulation protocol commonly utilized use for GI disease. For IBD treatment, several electrical neuromodulation techniques have been studied, such as vagus NS, SNS, and tibial NS. Several animal and clinical experiments were conducted to study the effectiveness, with encouraging results. The precise underlying mechanisms of action for electrical neuromodulation are unclear, but this modality appears to be promising. Randomized control trials are required to investigate the efficacy of intrinsic processes. In this review, we will discuss the electrical modulation therapy for the IBD and the data pertaining to it.

Key Words: Inflammatory bowel disease; Sacral nerve stimulation; Vagus nerve stimulation; Tibial nerve stimulation; Electrical neuromodulation; Crohn's disease;

Ulcerative colitis; Neuromodulation

Core Tip: Inflammatory bowel disease (IBD) is an inflammatory disease of the gastrointestinal tract with no known available treatment. Electrical neuromodulation is the use of electric stimulation of nerves or brain regions as a therapeutic technique. Electrical neuromodulation therapy has been studied as a possible treatment regimen for IBD. There are several forms of neuromodulation that use various types of nerves, such as sacral nerve stimulation, vagal NS (VNS), and tibial NS. As indicated by many clinical investigations, VNS as a potential therapy for IBD has a lot of promise. More research is needed to assess the possibility of VNS as a viable cure for IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn's disease (CD). In these conditions, neutrophils and macrophages produce cytokines, proteolytic enzymes, and free radicals, leading to inflammation and ulceration of the intestinal lining. Both UC and CD share similar manifestations, including abdominal pain, diarrhea, weight loss, and hematochezia. Malnutrition, anemia, fatigue, fever, mouth ulcers, joint pain, and skin lesions, including erythema nodosum or pyoderma gangrenosum, are the common findings[1].

The exact etiology of IBD is unknown, but the altered immune system is suggested as a possible explanation. Risk factors include race, family history, ethnicity, cigarette smoking, and non-steroidal drugs. Colon cancer, skin infection, eye and joint infection, pharmaceutical side effects, and blood clots are all common complications of CD and UC[2].

Diagnostic procedures for IBD include blood work (for anemia and infection), endoscopic procedures (colonoscopy, flexible sigmoidoscopy, upper endoscopy, capsule endoscopy, and balloon aided enteroscopy), and imaging treatments (X-ray, computerized tomography scan, magnetic resonance imaging)[2].

The common medical treatment consists of antibiotics, corticosteroids, immune regulators, aminosalicylates, Janus kinase inhibitor (JAK), anti-tumor necrosis factor-alpha (Anti-TNF-α), anti-integrin, and anti-interleukin (IL) 12/IL23. Adverse reactions include itching, erythema, and delayed allergic reactions can be seen in patients due to these medication use[3]. Therefore, more effective, and safer therapeutic choices are needed. Nerves or brain structures electrical stimulation is being studied as an intervention in a growing number of conditions, including Parkinson's disease, arthritis, and depressive disorders. The idea that bioelectrical neuromodulation can be used to treat gastrointestinal (GI) disorders has piqued the interest of the medical community[4].

ELECTROMODULATION THERAPY FOR IBDS

The usage of electric stimulation of nerves or brain centers as a therapeutic tool is being tested in a wide variety of conditions as Parkinson's disease and schizophrenia. This approach is called neuromodulation or bioelectric neuromodulation, or electroceuticals[5]. GI tract is connected to the central nervous system *via* vagus and sacral nerve, providing disease-modifying bioelectric neuromodulation therapy opportunities[4]. Electrical neuromodulation (ENM) has been used effectively to treat variety of gastrointestinal disorders including GERD, dyspepsia, gastroparesis, fecal incontinence and constipation as shown in Figure 1. Neuromodulation may be central, as in thalamic stimulation or transmagnetic stimulation; spinally, as in spinal cord stimulation for ache and movement in spinal cord damage; vagal as regional, as in auricular stimulation for seizures; sacral, as in stimulation for genitourinary (GU)/GI dysfunction; and peripherally, as in electrified stimulation for GU/GI dysfunction peripherally, as in electroacupuncture; and enteric, as in gastric/GI electrical stimulation (GES)[6]. Sacral nerve stimulation (SNS) is the most effective neuromodulation protocol for GI disease that is currently in use[7]. Because of the dysregulation of brain-gut interactions in IBD, ENM can be

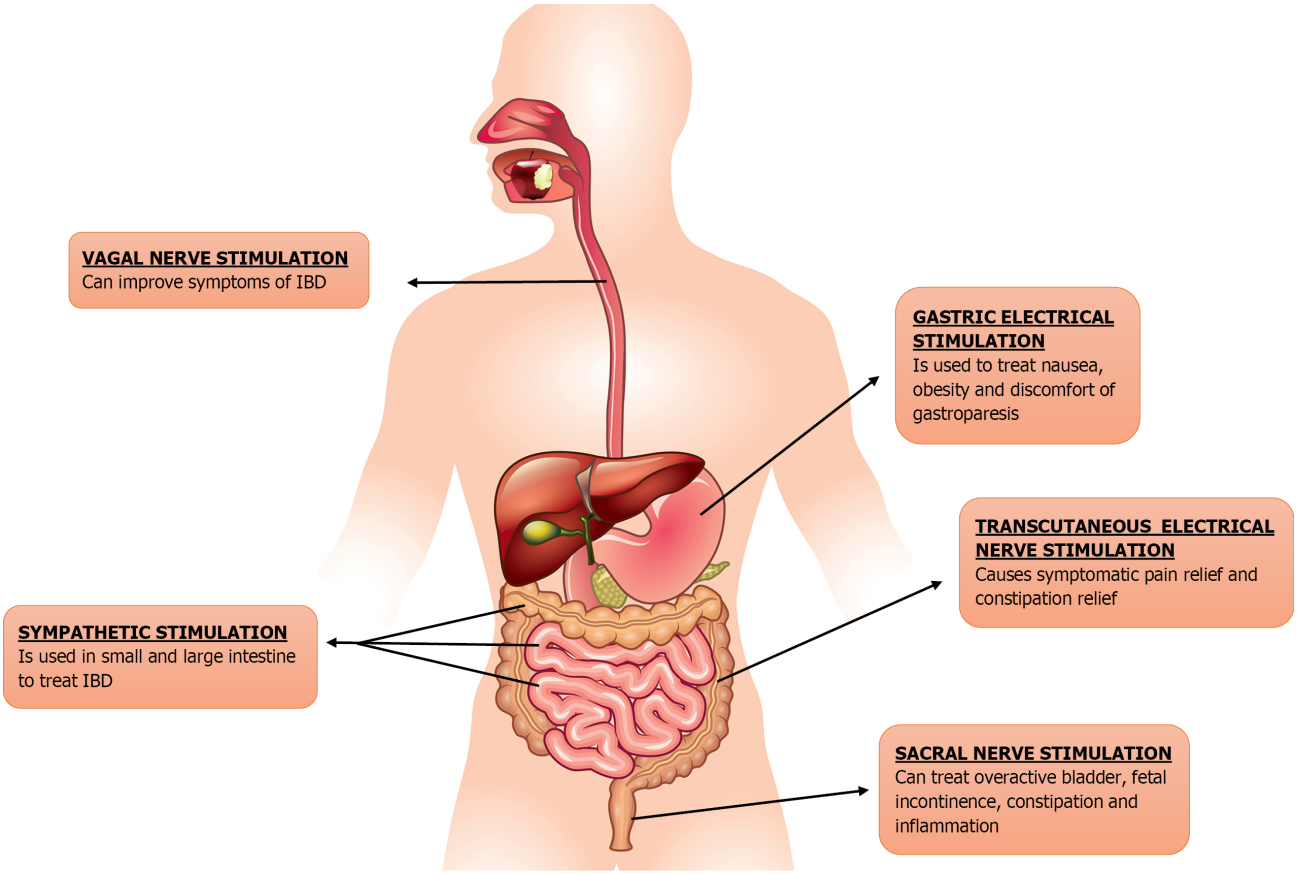

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Figure 1 Sites of bioelectric neuromodulation to improve gastro-intestinal symptoms. In animal research and experimental clinical settings, neuromodulation has been used to treat a ramification of gastrointestinal (GI) illnesses at numerous sites on neurons innervating the gastrointestinal tract. Some of the neuromodulation techniques such as transcutaneous electrical nerve stimulation, sympathetic stimulation, vagal nerve stimulation, and gastric electrical stimulation are mentioned in the figure above that relieve the symptoms related to inflammatory bowel disease. IBD: Inflammatory bowel disease.

considered as a treatment option[8]. Numerous electrical neuromodulation techniques for treating IBD, *i.e.*, we will be discussing vagus NS (VNS), SNS, and tibial NS (TNS), in this review.

INTERPLAY BETWEEN BRAIN-GUT AXIS/EXTRINSIC GI INNERVATION

The GI tract (GIT) has intrinsic (enteric nervous system) as well as extrinsic innervation (gut-brain axis). The gut-brain axis is bidirectional in nature, mediated through hormonal, neural, metabolic, and immunological responses. It carries different sensations such as GIT pressure changes, ischemia, poisons, bacterial infection, gastric acidity, and inflammation of the brain through afferent fibers, as demonstrated in Figure 2[9]. These fibers then carry information to the brain, which sends efferent signals to the gut and associated organs, causing toxic substances to be removed, decreasing acid production, increasing satiety, and nausea, to name a few. Recently, the gut microbiota is also included in the gut-brain axis[10], which links intestinal microbiota and the brain[11].

Accurate extrinsic innervation is crucial for the proper functioning of the gut as well as for the balanced emotional and psychological responses through dual connections between brain and gut[12]. Various researches have listed the effects of the brain on the gut or vice versa, signaling, *e.g.*, how depression and impaired brain functioning can increase an individual's vulnerability to IBD. Whereas other experimentations have shown the prevalence of psychic and anxiety-related disorders in IBD patients, these researches show a close interplay between the gut and the brain[8].

The complex pathway connects the central nervous system (CNS), sympathetic ganglia, enteric nervous system, and gastrointestinal effector tissues. The nucleus tractus solitarius receives the communications *via* the vagal afferents, while the thoracolumbar spinal cord receives the input *via* the spinal afferents. Cervical afferents also link the esophagus to the cervical spinal cord. Intestinal-fugal neurons that amplify from the intestine to the CNS are involved in certain afferent routes. To accurately understand the specifics of the extrinsic innervation in the form of the gut-brain axis, the various pathways through which the dual interaction between the gut and the brain takes place are described in Figure 2.

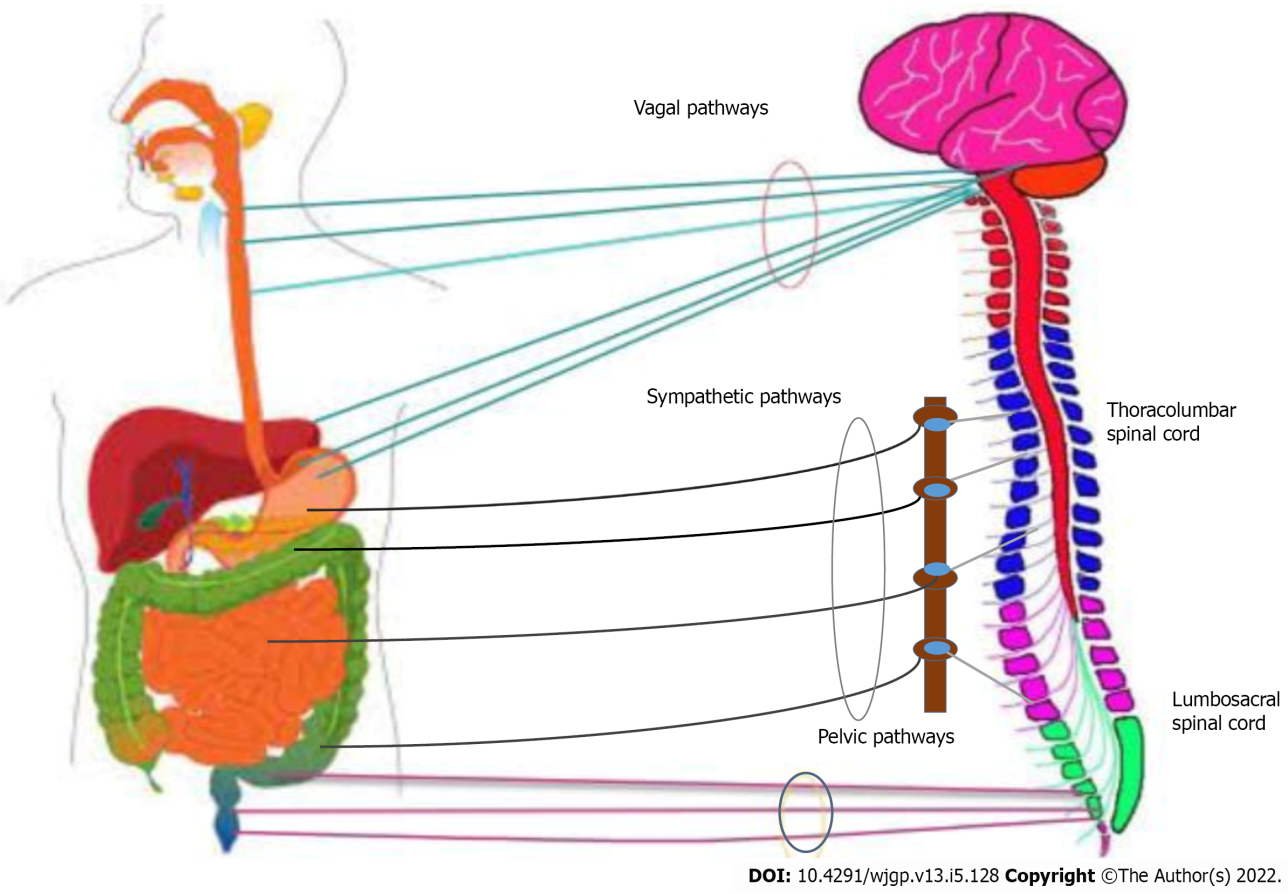

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Figure 2 Gastrointestinal tract's extrinsic innervation.

NEURAL CONTROL OF GUT INFLAMMATION

Influence of vagal pathway on gut inflammation

Preganglionic neurons of cranial nerve corticofugal fibers protrude from the medulla' dorsal motor nucleus of the vagus nerve and innervate the muscular and tissue layer layers of the gut, each within the lamina propria and also the muscularis externa of the viscus wall[13]. Food, antigens, potential pathogens, and symbiotic intestinal microbiota are always present in the gastrointestinal system, and some of them may present as risk factors for intestinal inflammation[14]. TNF-α, a cytokine, is released by activated macrophages, nerve fiber cells, and different tissue layer cells in response to the infective toxin and other harmful stimuli to cause inflammation[15,16]. Counter-regulatory mechanisms consist of capable immune cells and anti-inflammatory cytokines that inhibit inflammatory mediators' transfer into the circulation. As an anti-inflammatory mechanism, there is a fine relationship between neurological and immune system processes. The dorsal vagus complicated (DVC), which has the sensory nuclei of the solitary tract (NTS), the area postema (AP), and also the dorsal motor core of the cranial nerve (DMN), responds to higher current levels of TNF-α by increasing motor levels activity within the vagus nerve[17]. Two studies have shown that electrical cranial nerve stimulation will suppress inflammation in models of inflammation[18,19]. Furthermore, due to the lack of control on immunological mediating cells, the sub-diaphragmatic vagotomy increases inflammation in the gut. The brain can monitor immunological states and detect peripheral inflammation through two mechanisms.

Neural pathway

Stimulation of the vagus nerve is triggered directly or indirectly by cytokines discharged by nerve fiber cells, macrophages, and different vagus-associated immune cells and indirectly by chemoreceptors[20]. Visceral afferent vagus fibers within the neural structure nodosum principally end in the DVC of the medulla oblongata. DVC includes NTS, the dorsal motor nucleus of the vagus (DMV), and also the post-mammary region (AP)[21]. DMN is a critical region for the formation of preganglionic vagus efferent fibers. The majority of sensory vagal input is received by the NTS[22]. The paraventricular nucleus (PVN) of hypothalamus, receives signals from the NTS. PVN causes the production and release of corticotropin-releasing hormones (CRH), which is an important chemical on the hypothalamus-pituitary-adrenocortical (HPA) axis (described below)[23].

Humoral pathway

Circulating cytokines in the humoral route interact directly with areas of the brain involved in anti-inflammatory response. Circulatory IL-1 and TNF can move across the blood-brain barrier through a saturated transport mechanism to get into the CSF and interstitial space of the brain and spinal cord, where they can directly stimulate the brain to produce an anti-inflammatory reaction[24]. Circumventricular organs that lack regular blood-brain barrier protection uses cytokine-to-brain transmission. Postrema is the most well-known circumventricular organ[23].

Followings are a few pathways that are included in the neural control of gut inflammation.

HPA axis pathway

The HPA axis is composed of three major components (the hypothalamus, the anterior and posterior pituitary gland, and the adrenal cortex). Steinlein[25] demonstrated the role of vagal afferents in the neuro-immune axis in the control of the HPA axis. According to L E Goehler and co-workers, peripheral administration of lipopolysaccharides (LPS), a pro-inflammatory cytokine that stimulates vagal afferents *via* IL-1 receptors, induces the production of IL-1, a pro-inflammatory cytokine[26]. The vagal nerve is susceptible to peripheral pro-inflammatory cytokines generated by macrophages and other immune cells, such as IL-1, IL-6, and TNF-α[27]. Vagal afferent receptors (IL-1 beta) convey information to the parvo-cellular zone of the paraventricular nucleus of the hypothalamus (PVH) around corticotrophin-releasing-factor (CRF)-containing neurons. These CRF neurons subsequently drive the hypophysis to release the adreno-corticotrophin hormone, which stimulates the adrenal glands to release glucocorticoids, reducing peripheral inflammation[27]. Glucocorticoids affect the inflammatory response by suppressing immune cell release of pro-inflammatory cytokines, as well as inhibiting vasodilation and vascular permeability caused by inflammation. The brain can influence the activity of functional intestinal effector cells such as immune cells, smooth muscle cells, epithelial cells, interstitial cells of Cajal, enteric neurons, and enterochromaffin cells through neuronal and hormonal communication lines [24]. These cells, on the other hand, are influenced by the gut microbiome. The internal organ microbiota encompasses a vital influence on the intestinal axis, not solely through native interaction with intestinal cells conjointly with the enteric systema nervosum, but also through direct effects on the system and metabolic processes[28]. Emerging evidence supports the function of gut bacteria in anxiety and depressive-like behavior[29].

Cholinergic anti-inflammatory pathway (ach axis)

Acetylcholine is a crucial neurochemical and neuromodulator within the brain, mediates neuronal transmission in sympathetic and parasympathetic neurons, and acts as a primary neurotransmitter in parasympathetic/pneumogastric neural structure corticoefferent neurons[23]. This neurotransmitter acts through two varieties of receptors: muscarinic (metabotropic) and nicotinic (ionotropic)[30,31]. The seven component of the nicotinic acetylcholine receptor is displayed on phagocytes[32]. TNF production from human macrophages used by endotoxins is considerably reduced by acetylcholine through a post-transcriptional mechanism and is concentration-dependent. The authors demonstrated the connection of a bungarotox-insensitive vasoconstrictor receptor in suppressing cytokine production in vitro by neurotransmitter mistreatment specific muscarinic and nicotinic agonists and antagonists[23]. Apart from TNF, acetylcholine suppresses alternative endotoxin-inducible pro-inflammatory proteins reminiscent of IL-1, IL-6, and IL-18 through a post-transcriptional mechanism. However, acetylcholine has no effect on the discharge of the anti-inflammatory cytokine IL-10 from endotoxin-stimulated macrophages[32]. Nicotinic acetylcholine receptors are a ligand-gated pentameric ion channel family. The HPA axis (afferent vagal Fibers) activates the cholinergic anti-inflammatory pathway. Proinflammatory cytokines discharged throughout the immunologic response will activate vagal receptive signals, resulting in direct or indirect activation (via the core of the neurons of the solitary tract NTS) of the vagal efferents in the DMN. As a result, the sensory vagal afferents and motor vagus efferents produce an inflammatory reflex that constantly monitors and modifies the inflammatory condition in the periphery[33]. Since the tetravalent guanyl hydrazone CNI1493 induces the activation of the vagus and, by activating the cholinergic anti-inflammatory signal pathway, confers anti-inflammatory effects in each native and general model of inflammation, it's going to be attainable to activate the cholinergic anti-inflammatory pathway (with centrally active substances)[34].

Vagal sympathetic pathway

The celiac, superior mesenteric, and inferior mesenteric ganglia contain the cell bodies of the bulk of postganglionic sympathetic neurons that innervate the gastrointestinal tract[35]. In gut noradrenaline (NA) is the primary neurotransmitter released from sympathetic postganglionic nerve terminals; however, ATP and neuropeptide Y (NPY) can also engage in sympathetic neurotransmission within the GI tract[36,37]. The vagal afferent Fibers terminate in the NTS, which ultimately activates the central autonomic network (CAN). The sympathetic outlet is operated by 5 CAN brain regions (the paraventricular nucleus of the neural structure HPV, the noradrenergic cluster A5, the area of the caudal raphe, the rostral ventrolateral medulla, and ventromedial medulla)[38]. By increasing sympathetic outflow, the vagal nerve can generate a non-direct anti-inflammatory reaction. Abe *et al*[39] explained

the role of the C1 adrenergic cluster. They concluded that these neurons are concerned with protecting the result of stress in reperfusion injuries because of nephritic anemia *via* a sympathetic pathway. They conjointly mentioned how activation of vagal afferents in mice twenty-four hours before injury considerably reduced acute excretory organ inflammation and plasma levels of TNF-α[30]. Tyrosine hydroxylase is found in the lamina propria, the submucosa, the ganglia of the nerve plexus, and lymph follicles (Peyer' plaques)[40]. Adrenergic receptors of diverse types are expressed by macrophages. In vitro, beta receptors mediate the anti-inflammatory effects of agonists on macrophages derived from the intestine[41]. Although sympathetic nerves decrease gut inflammation, persistent nerve stimulation should be avoided as it can promote stasis and aggravate bacterial growth in Crohn's illness[4].

Vagal splenic pathway

Through an association between the VN and the splenic nerve, the Vago-splenic pathway works collectively[42]. In general inflammatory conditions, the spleen is a crucial supply of inflammatory cytokines, and excision considerably reduces circulating TNFα levels in mouse endotoxemia[43]. Tracey *et al* identified the vagal splenic route, finding that VNS caused the celiac ganglion to produce acetylcholine (Ach), which subsequently adhered to the c7nAChR of the splenic neve to release norepinephrine (NE) in the spleen[24]. Following that, it binds to beta two adrenergic receptors of splenic lymphocytes, which produces acetylcholine, which will act on the α c7nAChR of splenic macrophages limiting release of TNF, resulting in an anti-inflammatory impact[44]. According to Martelli *et al*[45], there is also a non-nervous relationship between the vagus and splenic sympathetic nerves. In another article, Martelli *et al*[46] noted how the sympathetic nerve, not the vagal nerve, is the efferent mediator of the cholinergic anti-inflammatory pathway (splenic nerve).

CAPSAICIN-SENSITIVE AFFERENTS AND INFLAMMATION REGULATION

Electrical and physiological stimulation of receptive neurons, particularly afferent nerves of the digestive tract, generates the release of transmitters at their peripheral ends, most often tachykinin and the amide (CGRP) linked to the calcitonin gene[47]. CGRP serves a number of purposes *via* serving as a modulator, transmitter, and hormone. CGRP-containing nerve Fibers are numerous surrounding blood vessels, particularly arterioles, suggesting that they may have a physiologic role in regulating blood flow to the gastric mucosa[48]. Capsaicin-sensitive afferent Fibers conduct protective anti-inflammatory activities in the gastrointestinal tract by releasing peptides from their peripheral ends[49-52]. Sensory inputs innervating the stomach generate CGRP, which reduces mucosal damage and improves mesenteric and mucosal blood flow in stomachic ulcer models in rats and mice[50,51]. Once administered at the time of injury, capsaicin promotes the discharge of neuropeptides and reduces the extent of ethanolin-induced gastric injury in rats[49,52]. This impact is operated by the discharge of CGRP from receptive nerve endings before their degeneration, which happens hours or days after the capsaicin injection. Numerous studies have shown that hCGRP (837), a fraction of human CGRP lacking the cyclic loop at the amino terminus of native CGRP, inhibits the action of exogenous CGRP[53,54].

VNS FOR INTESTINAL BOWEL DISEASE

VNS is a unique therapeutic method for chronic TNF-mediated inflammatory illnesses in the framework of bioelectronic medicine, with the objective of employing tiny stimulators to provide electrical nerve signals for therapeutic, rather than pharmaceutical, purposes[55-57]. VNS is already used to treat depression and epilepsy which is resistant to drugs[58]. There is currently no recognized curative medicine for IBD. Current medicines reduce disease activity, and when therapy is stopped, the condition recurs. TNF is one of the most significant cytokines in IBD, and anti-TNF medicines have transformed the therapy of the disease[59]. New compounds are available that target pro-inflammatory cytokines such as IL-12, IL-23, anti-integrin, and anti-JAK therapies[60,61]. In the case of treatment failure or an IBD consequence (perforation, abscess, stenosis), surgery is an option, although the disease reappears after the procedure. While anti-TNF medications are effective in IBD, there is a 20%-30% initial non-response rate, and the yearly chance of anti-TNF reactivity is 13% per patient year for infliximab and 20% per patient year for adalimumab[62-64]. This lack of secondary response is attributable to I the formation of autoantibodies, particularly for infliximab but also, to a lesser extent, for adalimumab, or (ii) secondary failure due to insufficient dose[65,66]. As a result of the risk of adverse effects and the requirement for ongoing therapy for these disorders, patients are increasingly hesitant to begin and maintain these treatments once they are in remission. The non-compliance rate is 30%-50% [67,68]. Therefore, targeted therapy for pro-inflammatory cytokines such as TNF-alpha and others using CAP could be extremely helpful with fewer side effects, no compliance issues, and cheaper than biologics (*i.e.*, anti TNF-alpha). In this case, targeting the VN's anti-inflammatory characteristics might be of interest. VNS, particularly as a non-drug therapy, has the potential to be employed as an

alternative to conventional biological therapies. A number of animal and clinical research have been undertaken in recent years to investigate the efficacy of VNS in the treatment of IBD (Supplementary Table 1).

Animal evidence

Vagotomy has been found in several studies to enhance the disease activity index (DAI), gross and pro-inflammatory cytokine levels in mice[69-71]. To replicate UC, Chen and colleagues employed dextran sodium sulphate (DSS) colitis in mice. They observed that VNS eased cerebral cortical microinfarcts induced by a two-photon laser and reduced DSS colitis. This neuroprotection was linked to decreased blood-brain barrier permeability and inflammatory processes[72].

Human evidence

Indirect data suggests that a vagal anti-inflammatory action plays a role in IBD. Vagal activity has been demonstrated to be inversely associated with inflammatory markers in healthy and cardiac patients as evaluated by HRV spectral analysis[73]. VNS might be an attractive method for the treatment of IBD based on pre-clinical results in rats with colitis and two recent clinical pilot trials targeting two distinct categories of patients with active CD, either ignorant of anti-TNF on inclusion or resistant to biologics [74].

LABORATORY AND CLINICAL STUDIES

Animal studies

Miceli and Jacobson[75] published the first data on the anti-inflammatory effects of VN in digestive inflammation. Colitis in rats with 2,4,6 trinitrobenzenesulfonic acid (TNBS) improved with early treatment of anticholinesterase medications such as neostigmine, which does not cross the blood-brain barrier, or physostigmine. This impact was more pronounced with physostigmine, indicating a dominating central mechanism. In mice, vagotomy aggravated experimental colitis, indicating that NV serves a protective function[76]. It was demonstrated that in the non-vagotomized watchful rat, 3 h per day for five consecutive days, low-frequency VNS (5 Hz) led in an improvement in TNBS colitis in rats [31] VNS inhibited weight loss and inflammatory indicators.

An improvement in a multivariate measure of colitis was also observed as an anti-inflammatory impact (which includes body mass, temperature, and motor function, macroscopic area of the lesions, histological and biological parameters such as myeloperoxidase activity, cytokines, and mRNAs related to cytokines)[77]. Sun *et al*[32] showed that chronic VNS increased the clinical activity index, the histological scores, the biological inflammation due to myeloperoxidase activity, the iNOS, TNF, and IL-6 Levels among rats with colitis, and the inflammatory response induced by LPS in cells of the human epithelial colorectal adenocarcinoma (Caco2) by ACh *in vitro*. In 2000, Kevin Tracey's team first described CAP[78,79]. They found that there is an inflammatory reflex in which proinflammatory cytokines stimulate vagus afferents, which activate vagus efferents, causing the production of these cytokines by tissue macrophages, mainly TNF, but also other pro-inflammatory cytokines such as IL-6. IL-1b, but not IL-10, an anti-inflammatory cytokine VN has anti-inflammatory effects because it inhibits pro-inflammatory cytokines.

Human studies

Decreased vagus activity was observed to be related to systemic inflammatory markers in both IC and CD patients[80,81]. VNS improved several inflammatory markers in rats' small intestines, including fecal quality, inflammatory processes, and leukocyte infiltration. Furthermore, considerable cardiac and respiratory changes happened with supra-threshold cervical VNS, while abdominal VNS caused alterations. Due to the lack of side effects and effectiveness in reducing inflammation, abdominal VNS appears to be a viable alternative to cervical VNS. This evidence supports the application of this novel peripheral nerve network for abdominal VNS as a potential therapy for IBD like CD[82]. A pilot study on VNS was carried out for the first time in patients with moderate to severe celiac disease as an alternative to drug anti-TNF therapy or in untreated patients in a translational approach from the laboratory to the bedside[56]. A VNS device and electrode were implanted in nine patients. At the time of implantation, two patients had failed immunosuppressive drugs (azathioprine), while the other seven received no treatment[56]. ENV was carried out on a continuous basis over a period of one year. In April 2012, the first patient was implanted, and then the last in March 2016.

Due to increasing condition, two patients were removed from the trial after three months of neurostimulation: The first had ileocecal resection but elected to continue neurostimulation until the end of the study due to an early good response and rejection of pharmaceutical therapy. The second patient took infliximab and azathioprine and continued to use an active VNS. Six patients were in remission owing to neurostimulation alone after one year of follow-up, while the seventh was in relapse. In April 2012, the first patient to get the implant was in remission from azathioprine in ileal CD with a history of ileocecal resection[56]. In conclusion, five out of seven patients who received the one-year VNS attained

clinical improvement (CDAI 150), and all gained the CDAI70 response (CDAI decreased 70 points from baseline). Similarly, the Endoscopic CD Severity Score (CDEIS) decreased from 60% to 100% in five patients. Other than complaints caused by the output current/intensity of the device, no adverse events were observed[56]. In patients with UC decrease activity has been linked with autonomic function[83].

Devices and methods

Currently, the generally used VNS therapeutic equipment is invasive and implantable. The VNS Therapy System consists of an implanted pulse generator, a bipolar VNS electrode, a small handheld device, programming software, a programming stick, and hand magnets. VNS is traditionally used to treat epilepsy and depression, as well as in the two pilot studies in patients with CD.

It is invasive, generally performed by a neurosurgeon who is experienced in the surgery, and lasts 1 h with minimal side effects. Noninvasive (n) VNS may be beneficial in certain patients who are afraid to have surgery in a vasculo-nervous location, such as the vein or the external carotid artery, which are close to the VN. Furthermore, if the device is removed, the electrode wrapped around the VN is normally kept in place, although some writers have removed it without causing significant nerve and artery damage[84]. Anesthesia is necessary for the operation, which requires two small incisions. The bipolar lead is looped around the left cervical VN and the pulse generator is positioned in the top-left chest. Physicians program the stimulator with a small handheld device, programming software, and a programming stick. After implantation, patients are given a wearable magnet to manipulate the stimulation on their own. The left vagus, which is more intimately linked to cardiovascular activities, is considered more suitable than the right cervical vagus. In the treatment of epilepsy, right-sided VNS has been observed in numerous patients[85-87]. Right-sided VNS appears to be as effective as, if not more successful than, left VNS[88]. Gadgets stimulating the VN on the cervical degree or on the auricular degree were produced (Figure 3). Certainly, the cymbal concha of the external ear is innervated by means of a sensory auricular branch of the VN that sends projection inside the NTS in cats and human beings[89-91]. These noninvasive devices have not been associated with any significant major side effects. In comparison to invasive VNS, n-VNS has the disadvantage of low compliance, which is a major concern in the treatment of IBD. Indeed, 30%-40% of IBD patients fail to take their medicine[92]. One can wonder if the same problem arises with these noninvasive devices. Furthermore, in the case of the Gamma core device, the repeatability of the placement of the discs in contact with the VN is unknown. Finally, ta-VNS was less efficient than VNS in decreasing the LPS-induced serum cytokine (TNF, IL-1, and IL-6) response in a septic shock animal[93].

Mechanism of VNS

An unexpected receptor mechanism underpins the anti-inflammatory effect of the Vagus nerve. In comparison to many "classical" physiological activities, which might be managed with the aid of metabotropic mAChRs, the anti-inflammatory effects of the Vagus nerve are mediated *via* ionotropic nicotinic acetylcholine receptors (nAChRs)[94]. The frequency of stimulation for VN activation is critical to the function of various therapies[95-100]. A couple of studies have indicated that mAChRs, especially the M1 mAChR, play a role in this regulation in endotoxemia, inflammatory bowel disorder (colitis), hemorrhagic shock, and other illnesses[101,102-104].

Increased cholinergic transmission in the brain with centrally acting acetylcholinesterase inhibitors, particularly galantamine, leads to inhibition of unusual inflammatory responses generated by vagus nerve impulses in mice models of endotoxemia, colitis, and lupus[105-107]. The most recent work, which used targeted optogenetic stimulation and sophisticated pharmacological methods, discovered that forebrain signal transduction and M1 mAChR play a unique role in the modulation of peripheral inflammatory responses in endotoxemia mice *via* vagus nerve transduction[108]. VNS blocks splenic TNF, which has been identified as a primary contributor to systemic TNF. It is critical to understand how the vagus nerve regulates cytokines in the spleen. The vagus nerve innervates the celiac ganglia and the superior mesenteric ganglion, which have been shown to provide neurons to the splenic nerve [101].

SNS

The sacral nerves are divided into five pairs. Each contains an afferent and efferent component, allowing for effective interaction between the lower GIT and the nervous system. The activity of the lower GIT (descending colon, rectum), sexual organs, and urinary bladder is modulated by the parasympathetic component of sacral nerves. The principal somatic nerve of the sacral plexus is the pudendal nerve (S2-S4). It is both sensory and motor. The external anal sphincter, which is under our conscious control, receives sensory and motor innervation from it. It also gives sensation to the external genitalia, the skin around the anal area, the anal canal, the perineum, and motor innervation to the external urethral sphincter.

SNS, also known as "sacral neuromodulation", is a relatively new and promising treatment option. SNS uses an implanted device that stimulates the S3 nerve root and offers a wide range of applications

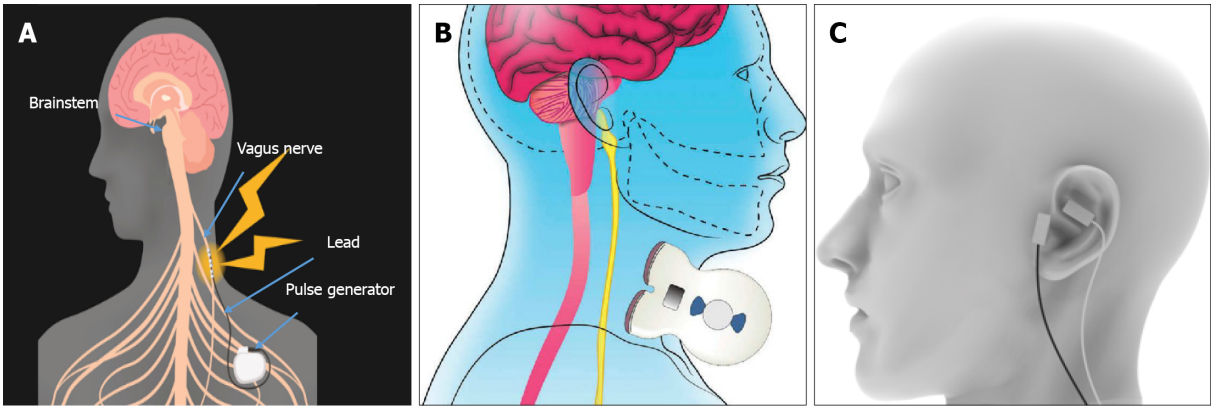

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Figure 3 Vagus nerve stimulation. A: Direct vagus nerve stimulation; B and C: Noninvasive vagus nerve stimulation; transcutaneous cervical vagus nerve stimulation (VNS) (B); transcutaneous auricular VNS (C).

in conditions such as urgency urinary incontinence, pelvic pain, detrusor stimulation with transurethral approach, FI, *etc*. Following are some applications of SNS in relation to IBD[3].

SACRAL NEUROMODULATION FOR INFLAMMATION AND INTESTINAL BARRIER IN IBD

Experimental and clinical evidence from several studies signifies the potential of SNS as a treatment option for IBD Patients who have received SNS had less severe mucosal lesions than those who have not received SNS. SNS also improves the recovery of enema caused by trinitrobenzene sulfonic acid (TNBS enema). With elevated TNF1 and trypsin levels, SNS also increases the number of mucosal neutrophils. SNS also stopped TNBS-induced inflammatory factors, including IL-4 and IL-1, from rising. All of these variables indicate that sacral neuromodulation is beneficial in restoring the intestinal barrier following mucosa injury[109]. In IBD, SNS has a significant anti-inflammatory impact. SNS enhanced the spinal afferent-vagal efferent pathway and improved autonomic function by increased vagal efferent activity. SNS also causes anti-inflammatory effects due to the SNS-mediated release of Ach[110]. In a study using the TNBS rat model, sacral neuromodulation lowered the level of pro-inflammatory cytokines and improved colonic inflammation[111].

SACRAL NEUROMODULATION IN FECAL INCONTINENCY

The inability to regulate bowel movements, which can range from modest rectum leaks to total bowel control, is known as FI. Viability of sacral neuromodulations as a treatment option for FI is tremendous. Many studies have demonstrated that FI responds positively to SNS. SNS has proven to be a reliable method for dealing with FI in children[112]. Clinical trials have also shown that SNS can help with FI [113]. Another extensive approach conveys the benefits of SNS in patients with neuropathic FI[114].

OTHER METHODS OF NEUROMODULATION

Other than SNS and VNS, other neuromodulation methods to treat IBD are TNS and Spinal Cord Stimulation (SCS). The sensory, motor and autonomic fibers in the tibial nerve make it a mixed nerve. It is caused by the L4-S3 nerves, which feed the colorectum, bladder, and pelvic floor. TNS uses electrical impulses to treat bladder and pelvic floor issues. TNS is classified into two types: Percutaneous TNS (PTNS) and transcutaneous TNS (TCTNS) (TTNS). The former makes use of a needle electrode, whilst the latter makes use of a sticky electrode[3]. PTNS is a minimally invasive method that has been demonstrated to be beneficial in treating overactive bladder, FI, and pelvic discomfort. Having few side effects is highly convenient, but it is limited by the necessity that patients visit the clinic weekly to obtain the series of treatments[115].

The actual mechanism of TNS is uncertain however it appears to involve excitation of afferent pathways to the sacral spinal cord as well as regulation of efferent nerves[116]. Retrospective research looked at 183 individuals with refractory overactive bladder (OAB) who had 30-min PTNS sessions for 12 wk during nine years. There was a significant improvement in micturition frequency, nocturia, and urge incontinence episodes in the PTNS group, with the impact obvious by week 10 of therapy. With a

wide range of PTNS times, 61.5 percent of subjects self-proclaimed > 50% improvement in signs and symptoms, raising the subjective accomplishment percentages[117]. For a 12-wk treatment period, a recent randomized research of forty women with nocturia of weekly TTNS periods compared pelvic floor muscle training and behavioral therapy. Both medicines improved sleep quality by reducing the number of times people awoke to pee (45 percent reduced by 1 in both groups)[118]. A spinal cord stimulator (SCS) is surgically implanted under the skin and delivers a weak electrical current to the spinal cord. Current from a pulse generator is carried to the spinal cords' nerve fibers by thin wires. When the SCS is activated, it stimulates the nerves in the area where a person is feeling pain. The pain signal is altered and masked by electrical impulses, prohibiting it from going to the brain[119].

For more than a half-century, spinal cord stimulation (SCS) has been used to treat chronic pain. Several studies have demonstrated that SCS can help with stomach discomfort[120]. Randomized trial has shown that SCS can lessen diarrhea and pain pain in persons with irritable bowel syndrome[121]. Although it has been quite successful, some people might experience device-related challenges such as pain at the implantation site or subsequent infections. But it doesn't cause any serious complications like paralysis or hemorrhage in the epidural space[122,123].

CONCLUSION

The digestive system's broad and approachable interaction with the CNS, the predominance of IBD, and the lack of effective treatment options make it an appealing target for bioelectrical neuromodulation therapy for digestive system innervation. A wide range of gastrointestinal problems has been treated with various degrees of success. This approach has been tried with different degrees of effectiveness in a range of gastrointestinal diseases. SNS for faecal incontinence has become a popular bio-electric therapy for gastrointestinal disorders. The development of bioelectrical digestive system neuromodulation medicines requires investigation. The advancement of our understanding of the multiple roles of the mixed nerve components, such as vagus nerves and sympathetic routes to the intestines, should allow us to take IBS treatment to a new level.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Farah Yasmin https://orcid.org/0000-0002-5264-6140; Abdul Moiz Sahito 0000-0001-7748-3440; Syeda Lamiya Mir 0000-0001-9327-4390; Govinda Khatri 0000-0002-7233-753X; Somina Shaikh 0000-0002-9943-9907; Ambresha Gul 0000-0002-0618-1397; Syed Adeel Hassan 0000-0002-8484-0319; Thoyaja Koritala 0000-0002-1020-9882; Salim Surani 0000-0001-7105-4266.

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REVIEW

Epilepsy and the gut: Perpetrator or victim?

Mohammed Al-Beltagi, Nermin Kamal Saeed

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Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31527, Algharbia, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medica City, Arabian Gulf University, Manama 26671, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 26612, Bahrain

Nermin Kamal Saeed, Department of Microbiology, Irish Royal College of Surgeon, Busaiteen 15503, Muharraq, Bahrain

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, Al Bahr Streat, Tanta 31527, Algharbia, Egypt. mbelrem@hotmail.com

Abstract

The brain and the gut are linked together with a complex, bi-path link known as the gut-brain axis through the central and enteric nervous systems. So, the brain directly affects and controls the gut through various neurocrine and endocrine processes, and the gut impacts the brain *via* different mechanisms. Epilepsy is a central nervous system (CNS) disorder with abnormal brain activity, causing repeated seizures due to a transient excessive or synchronous alteration in the brain's electrical activity. Due to the strong relationship between the enteric and the CNS, gastrointestinal dysfunction may increase the risk of epilepsy. Meanwhile, about 2.5% of patients with epilepsy were misdiagnosed as having gastrointestinal disorders, especially in children below the age of one year. Gut dysbiosis also has a significant role in epileptogenesis. Epilepsy, in turn, affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of medications on the gut and the gut microbiota. Epilepsy with abdominal pain, a type of temporal lobe epilepsy, is an uncommon cause of abdominal pain. Epilepsy also can present with postictal states with gastrointestinal manifestations such as postictal hypersalivation, hyperphagia, or compulsive water drinking. At the same time, antiseizure medications have many gastrointestinal side effects. On the other hand, some antiseizure medications may improve some gastrointestinal diseases. Many gut manipulations were used successfully to manage epilepsy. Prebiotics, probiotics, synbiotics, postbiotics, a ketogenic diet, fecal microbiota transplantation, and

vagus nerve stimulation were used successfully to treat some patients with epilepsy. Other manipulations, such as omental transposition, still need more studies. This narrative review will discuss the different ways the gut and epilepsy affect each other.

Key Words: Epilepsy; Epilepsy with abdominal pain; Gut; Gastrointestinal diseases; Gut-brain-microbiota axis; Abdominal aura; Ketogenic diet; Abdominal migraine

Core Tip: The brain and the gut have an intense but complex interaction through a strong relationship between the enteric and the central nervous systems. Epilepsy and the gut may affect each other in diverse ways. About 2.5% of patients with epilepsy are misdiagnosed as gastrointestinal disorders, especially at an early age. Gut dysbiosis also has a significant role in epileptogenesis. Epilepsy affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of antiseizure medications on the gut and the gut microbiota. Simultaneously, many gut manipulations successfully managed some cases of epilepsy.

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INTRODUCTION

The human body organs and systems interact with each other in harmony. However, the interaction between the brain and the gut is overly complex, forming a two-way link known as the gut-brain axis through the central and the enteric nervous system. The enteric nervous system is the most crucial autonomic nervous system component. It has common structural and functional similarities with the brain, consequently named the second brain, forming 90%-95% of total body serotonin[1]. It is uniquely prepared with intrinsic microcircuits to orchestrate the gastrointestinal functions independent of the central nervous system (CNS) control[2]. The brain directly affects the stomach and intestines and controls the gut through various neurocrine and endocrine processes[3].

On the other hand, the gut impacts the brain *via* different mechanisms, including neuropeptide and neurotransmitter release such as leptin and serotonin, vagus nerve activation, immune signaling through controlling the release of secretory IgA, affecting the integrity of mucous membrane barrier through Zonulin protein, and local production of short-chain fatty acids such as butyrate by gut microbiota[4]. The gut-brain axis explains the effects of the emotional and cognitive centers of the brain and its control over peripheral intestinal functions. It also describes how a chronic painful abdominal condition such as irritable bowel syndrome (IBS) can affect the cognitive and psychological function of the body[5]. Many neurological disorders, including hereditary, metabolic, infectious, vascular, inflammatory, and metabolic diseases, may affect the brain and gastrointestinal tract. Consequently, the clinical neurological or gastrointestinal findings may assist in confirming the diagnosis or reducing the differential diagnosis[6]. This review sheds some light on the relationship between epilepsy, a common neurological disorder, and its effects on the abdomen and vice versa.

EPILEPSY AND SEIZURE DISORDERS IN GASTROINTESTINAL DISORDERS

Epilepsy is a CNS disorder with abnormal brain epileptic activity, causing repeated seizures or periods of sudden abnormal motor or sensory behavior and sometimes impaired or even loss of consciousness due to a transient excessive or synchronous alteration in the brain's electrical activity. Any part of the brain can be affected by epileptic activity, especially the mesial part of the temporal lobes[7]. Epilepsy is a common neurological condition, affecting about 5%-10% of the population at a particular time of their life and about 0.5%-1.0% of children. It can affect any age or sex and all races[8].

According to the etiology, there are four main types of epilepsy, idiopathic, symptomatic, provoked, and cryptogenic, resulting from genetic, structural/metabolic, immunological, infectious, or unknown causes. Idiopathic epilepsy is pure epilepsy resulting from a single gene disorder or complex inheritance. Symptomatic epilepsy has predominately genetic or developmental causation such as childhood epilepsy syndromes, progressive myoclonic epilepsies, neurocutaneous syndromes, other single-gene

neurologic disorders, chromosomal disorders, developmental cerebral structure anomalies, perinatal and infantile causes, cerebral trauma, tumor, or infection, cerebrovascular disorders, cerebral immunologic disorders, or degenerative brain diseases. Provoked epilepsy could arise from provocation factors like fever or menses or reflex epilepsy such as photosensitive or reading epilepsies. Cryptogenic epilepsies are "unknown" and more common in adults than in the pediatric age[9,10]. Due to the strong relationship between the enteric nervous system and the CNS is always single and never be multiple, gastrointestinal dysfunction can be seen in neurological disorders, and neurological dysfunction can be seen in gastrointestinal disorders[11]. About 2.5% of patients with epilepsy were misdiagnosed with gastrointestinal disorders, especially in children below the age of one year[12].

Gastroesophageal reflux and gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a common childhood disorder. It can simulate epileptic seizures and may be misdiagnosed as epilepsy. Sandifer Syndrome is a distinct clinical entity presented with GER, irritability, and abnormal head and body movements with spasmodic contractions of the neck. It may appear as paroxysms with abnormal neurobehavior like crying, irritability, torticollis, head/eye version, and extensor spasm of the neck with dystonic posturing. These paroxysms may simulate epilepsy and can be misdiagnosed with specific types of epilepsy, particularly infantile spasms [13].

On the other hand, epilepsy can be missed as GERD. Sweetman *et al*[14] reported a gelastic seizure due to hypothalamic hamartomas misdiagnosed as GERD[14]. Eating epilepsy is a type of feeding-related reflex focal epilepsy. It may be misdiagnosed as GERD, especially in very young infants[15]. Eating epilepsy should be considered if the history, clinical examination, and investigations for GER and apparent life-threatening events are absent[16].

Meanwhile, GERD is a common comorbidity in children with neurological problems such as cerebral palsy, frequently complicated with epilepsy. Early-onset neurological disease, abnormal electroencephalogram (EEG), and the presence of mitochondrial disorder are significant risk factors for severe GERD [17]. The presence of GERD in such patients may jeopardize their management and mimic refractory seizures[18]. Asymptomatic gastroesophageal reflux can induce laryngospasm during sleep. This nocturnal laryngospasm causes non-rapid eye movement parasomnias, which clinically simulate sleep-related hypermotor epilepsy. Video-EEG can differentiate between the two conditions[19]. The nocturnal choking sensation is a scary condition that may complicate insular epilepsy, nocturnal laryngospasm, and gastroesophageal reflux[20]. Acid reflux can induce obstructive laryngospasm and subsequent respiratory arrest, a probable mechanism of sudden unexpected death in epileptic patients. Proper GERD management and antiseizure medication significantly improve the prognosis[21].

Peptic ulcer

Peptic ulcers are up to eight times more prevalent in patients with epilepsy than in the general population[22]. At the same time, epilepsy can be misdiagnosed as a peptic ulcer, as reported by Magon [23]. At the same time, a perforated peptic ulcer may provoke or complicate a generalized tonic-clonic seizure. Consequently, we should carefully consider the vital signs during seizure episodes. Omeprazole is a proton pump inhibitor effectively used to treat peptic ulcers. It has effective anticonvulsant activity through carbonic anhydrase inhibition but with rapid tolerance[24].

Celiac disease

Celiac disease is a well-known systemic autoimmune disease characterized by gluten-induced autoimmune intestinal villous atrophy, malabsorption, and various systemic and gastrointestinal symptoms. The older the patient with celiac disease is, the more the prevalence of systemic symptoms not related to the gastrointestinal tract, including neurological symptoms[25]. About 10% of patients with celiac disease develop neurological complications, including seizures. At the same time, about 0.78% to 9.10% of patients with epilepsy develop celiac disease[26,27]. The exact mechanism of neurological manifestations is poorly understood, probably related to immune mechanisms. This hypothesis is advocated by the presence of anti-Purkinje cells and anti-ganglioside antibodies in patients with celiac disease who developed neurological manifestations[28]. Another possible hypothesis is neurological damage due to deficiencies of the neurotrophic and neuroprotective vitamins (*e.g.*, vitamin D, vitamin E, thiamine, and vitamin B12) resulting from the malabsorption associated with celiac disease[29]. The prevalence of drug-resistant epilepsy is more common in children who have celiac disease as a comorbidity. Most patients with celiac disease and epilepsy have been cured with adherence to a gluten-free diet. Adherence to a gluten-free diet and adequate antiseizure medications can also reduce the seizure frequency and severity in patients with celiac disease and drug-resistant epilepsy[30].

Gut dysbiosis

Gut dysbiosis strongly relates to autoimmune diseases, which are closely linked with epilepsy, suggesting an association between epilepsy and gut dysbiosis[3]. Huang *et al*[31] showed that mild gastroenteritis precedes the development of benign infantile convulsions. This temporal relation links

the infection-induced gut dysbiosis with epileptogenesis[31]. Şafak *et al*[32] found a significant increase in Fusobacteria prevalence in patients with epilepsy (10.6%) but not in the healthy control. This considerable shift and drift in the intestinal microbiota and the subsequent gut dysbiosis may be present in certain epilepsy types[32]. Meanwhile, the gut microbiome differs in patients with drug-resistant epilepsy (*e.g.*, *Cronobacter, Bacteroides, Bifidobacterium,* and *Erysipelatoclostridium*) from patients with drug-sensitive epilepsy with an abnormally increased richness of rare flora. On the other hand, patients with drug-sensitive epilepsy have a gut microbiome composition like the healthy controls, enforcing the evidence of the effects of gut dysbiosis in the development of epilepsy and drug-resistant epilepsy[33, 34].

IBS

IBS is a constellation of symptoms occurring together, such as repeated abdominal pain and changes in bowel habits, such as diarrhea, constipation, or both. It affects about 7%-21% of the population[35]. IBS is associated with increasing the incidence of epilepsy, particularly temporal lobe epilepsy. A large population-based cohort study by Chen *et al*[36] showed that IBS increased the epilepsy risk with a cumulative incidence of epilepsy of 2.54/1000 person-years *vs* 1.86/1000 person-years in the cohort without IBS with an adjusted hazard ratio of 1.30[36]. Studies also showed that the incidence of IBS increases five times in patients with epilepsy than in controls[37]. There is also an increased incidence of functional gastrointestinal disorders, including IBS, in children with epilepsy than in matching controls [38]. Epilepsy with abdominal pain could also be misdiagnosed as IBS[39]. The cumulative data from these studies showed the bidirectional link between IBS and epilepsy. The exact cause of this increase in epilepsy risk is not known. It is probably related to the shared pathophysiological mechanisms and risk factors such as disturbed brain-gut axis, microbiota imbalance of the gastrointestinal tract, increased incidence of dietary allergies, neuroimmune interactions, and mucosal inflammatory mediator deregulation in the gastrointestinal tract[40-42]. Patients with epilepsy with IBS as a comorbidity have an increased rate of depressive and anxiety disorders[43]. If IBS is present in patients with drug-resistant epilepsy, most of the seizures occur during the period of altered bowel movements[44].

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are chronic autoimmune and immune-mediated inflammatory disorders affecting the digestive system with gastrointestinal and systemic manifestations, including the central and peripheral nervous systems. IBDs include ulcerative colitis, Crohn's disease, and unclassified IBD[45]. Neurological complications occur in 0.25% to 47.50% of patients with IBDs. Seizures of all types, including status epilepticus, can be observed during the clinical course of IBDs, especially in severe cases[46]. Many underlying mechanisms explain the occurrence of seizures in IBDs. These mechanisms include autoimmune-mediated neuroinflammation, gut dysbiosis with brain-gut-microbiota axis dysfunction, the associated nutritional deficiencies, especially thiamine and vitamin B12, increased incidence of infections, arterial and venous thromboembolism, and possible side effects of medications especially sulfasalazine, metronidazole, steroids, tumor necrosis factor-α inhibitors, and anti-integrin antibodies[47]. Seizures in patients with IBDs indicate the need to rule out a cranial thromboembolic event[48].

Gastrointestinal disorders in children with autism

Gastrointestinal disorders occur in 46%-84% of children with autism. The most common gastrointestinal problems observed in children with autism are motility disorders such as chronic constipation or diarrhea, nausea, vomiting, gastroesophageal reflux or disease, chronic flatulence, abdominal discomfort, ulcers, inflammatory bowel disease, colitis, food allergies or intolerance, and failure to thrive. The severity of autism strongly correlates positively with gastrointestinal symptoms[49]. Meanwhile, abnormal EEG is present in 60% of children with autism (compared to 6%-7% of typically developed children), while epilepsy is present in 10% to 30% of children with autism. Children with autism have a high rate of celiac disease and gut dysbiosis, which increases the incidence of epilepsy [50].

Situation-related seizures (Convulsions associated with gastrointestinal infections CwG)

Gastrointestinal infections were first reported to cause epileptiform activity development by Japanese researcher Morooka in 1982 and were called "situation-related seizures"[51]. It occurred in a previously healthy child who developed nonfebrile convulsions following mild gastroenteritis and mild dehydration for 1–5 d without apparent acid intoxication or electrolyte imbalance. It usually occurs during the winter, mainly by the rotavirus, which can reach the brain and cause encephalitis, cerebropathy, or convulsions[52]. The convulsions may present as single or multiple attacks of generalized tonic-clonic or focal seizure with characteristic normal interictal EEG, normal electrolytes, serum glucose, and cerebrospinal fluid. Stool analysis may test positive for rotavirus, norovirus, adenovirus, sapovirus, and coxsackievirus. It occurs in young children with an immature nervous system, like febrile convulsions[53]. Unfortunately, the prevalence of this type of convulsion is on the rise and has not been affected by the introduction of the rotavirus vaccination[54]. The etiology and pathophysiology are not yet thoroughly explained. However, it could be related to direct microbial invasion of the CNS

due to the indirect effects of specific mediators triggered by gastrointestinal infections[55]. This type of seizure has a favorable prognosis with infrequent relapse and typically normal development without the need for long-term antiseizure therapy[56].

EFFECTS OF EPILEPSY ON THE GUT

As the brain has a bidirectional relationship with the gut, neurological disorders may impact the gastrointestinal tract. Examples of this impact include the occurrence of sialorrhea, anorexia, dysphagia, gastroparesis, and motility disorders such as diarrhea, intestinal pseudo-obstruction, constipation, and fecal incontinence[57]. Hence, epilepsy, in turn, affects the gastrointestinal tract in different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of medications on the gut and the gut microbiota.

Abdominal aura

An 'aura' is subjective warning feelings, experiences, movements, or events (*e.g.*, specific memory, music, song, or swirling colors) some people with epilepsy may experience, usually before or at the onset of a tonic-clonic seizure. Auras occur in about 70% of patients with generalized epilepsy[58]. Auras arise due to the activation of a functional cortex by aberrant, unilateral, focal, and short neuronal discharge[59]. It is a form of an aware focal seizure that develops into another type of seizure. It usually occurs at the seizure onset before impairment or loss of consciousness and is usually memorized afterward. We should differentiate auras from the premonitory or prodromal sensations, which occur at least 30 min before the seizures[60]. There are different forms of auras depending on the epileptogenic zone. Auras could be visual, auditory, olfactory, gustatory, somatosensory, psychic, autonomic, or even sexual. Hence, auras are accurate anatomical markers of the epileptogenic zone[61]. However, auras could be multiple, as reported in 6% of patients with epilepsy. Multiple auras are associated with multifocal epilepsy or activation of a neural network that involves more than one functional region. The presence of aura has an essential role in diagnosing, localization, and classification of epilepsy. Epileptic aura could assist in differentiating partial from generalized seizures[62].

Gustatory aura or gustatory hallucination epilepsy are a type of simple partial seizures. They are characterized by taste sensations, including sweet, bitter, acidic, salty, or metallic tastes, as the first clinical manifestation of the seizure. It is one of the parietal, temporal, or temporoparietal seizure manifestations and often evolves into complex partial seizures[59]. It occurs in the form of a sudden taste sensation of short duration, primarily seconds, that usually follow or is accompanied by the olfactory hallucination that resembles the perceived taste in the absence of an actual stimulus of the sensation. Both gustatory and olfactory auras are often linked together and are difficult to differentiate [63]. Gustatory auras arise from the mesial temporal region, particularly the left side, and are a manifestation of mesial temporal sclerosis or tumors[64].

An epigastric aura (visceral aura) is a somatosensory (*e.g.*, pain) aura that typically demonstrates an increasing epigastric sensation. It may appear as visceral sensations (*e.g.*, abdominal discomfort), visceromotor symptoms (*e.g.*, vomiting, borborygmi, or tachycardia), or vegetative symptoms (*e.g.*, blushing or sweating). Epigastric aura occurs due to abnormal neuronal activation and discharges in the sensory cortex representing the abdominal viscera[65]. This type of aura is frequently seen in migraine or epilepsy. Epigastric auras are the most prevalent aura in medial temporal lobe epilepsy. It also may have an insular origin[66]. The presence, type, and severity of epigastric aura and other forms of autonomic manifestations depend on the seizure onset location and timing, propagation pathway, lateralization, and the persistence of interictal autonomic dysfunction. The presence of a severe autonomic aura can expect the occurrence of sudden death[67].

Abdominal skin temperature in focal epilepsy

Thermographic studies showed that the abdominal wall has colder spots and areas in patients with focal-onset epilepsy than in controls. It could be related to the visceral-somatic and somatic-visceral neurological interactions[68]. We can use infrared thermography mapping and thermochromic/thermo-sensitive silicone to locate the irritative epileptogenic areas in patients with focal epilepsy. Their accuracy and safety are like electrocorticography. This thermographic localization of the epileptogenic activity can be used to locate the irritative zones in neurosurgery, particularly epilepsy surgery[69].

Epilepsy with abdominal pain (abdominal epilepsy)

Abdominal pain is one of the most frequent complaints, especially in pediatric age. It may result from a wide range of causes, both intra- and extra-abdominal. Systemic causes of abdominal pain may include hereditary, infectious, inflammatory, metabolic diseases, and neurologic disorders[70]. Many neurologic diseases can cause abdominal pain. For example, abdominal migraine, epilepsy, peripheral neuropathy, or even cerebral tumors can present with abdominal pain[71,72]. Occasionally the cause of the abdominal pain is ill-defined, making the diagnosis of abdominal pain without evident abdominal abnormality a puzzle for most physicians.

Epilepsy with abdominal pain is an uncommon condition of abdominal pain. It is a type of temporal lobe epilepsy that usually presents with abdominal auras and is characterized by recurrent episodic paroxysms of abdominal and periumbilical pain with various abdominal symptoms (*e.g.*, nausea and vomiting) accompanied or followed by disturbed brain functions. Epilepsy with abdominal pain usually occurs in childhood, but it is also reported in adults[73]. The characteristic postictal manifestations (such as lethargy, drowsiness, headache, blindness, paraesthesia, or even convulsions) help to differentiate it from the abdominal migraine[74].

The exact mechanism of epilepsy with abdominal pain is not fully understood but could be related to abnormal neuronal activation of the temporal lobe involving the amygdala. Amygdala then serves as a signal conductor to the gut through direct projections to the dorsal motor part of the vagus nerve nucleus. The vagus nerve then transmits the electrical activity to the target organs causing different gastrointestinal symptoms, especially abdominal pain (Figure 1)[75]. It is usually idiopathic; however, it may manifest temporal lobe lesions such as prematurity, febrile seizures, neuronal migration defects, cortical malformations, arterio-venous malformations, neuroendocrine dysfunction, mesial temporal lobe sclerosis, gliotic damage resulting from encephalitis, or brain tumors such as dysembryoplastic neuroepithelial tumors, benign tumors, cerebral astrocytoma, or gliomas[76,77].

Epilepsy with abdominal pain has a characteristic tetrad[78]: (1) Paroxysmal gastrointestinal and autonomic complaints (abdominal pain, vomiting, nausea, flushing, palpitation, and stuttering) of unapparent cause; (2) CNS disturbance symptoms (*e.g.*, alteration of mental status, headache, dizziness, and convulsions); (3) Abnormal EEG findings characteristic of epileptic activity; and (4) Improvement of the symptoms with antiseizure medications.

The diagnosis of epilepsy with abdominal pain is essentially clinical. To properly diagnose epilepsy with abdominal pain, we should rule out organic causes in the gastrointestinal tract and the nervous system. Other causes of recurrent abdominal pain should also be ruled out, such as porphyria, familial Mediterranean fever, abdominal migraine, and cyclic vomiting[79]. Describing the abdominal attacks by emphasizing the presence or absence of aura and postictal events may help reach the diagnosis. Complete physical, abdominal, and neurological examinations should be performed in suspected patients. Serum prolactin could increase within 20 min of the attack in epilepsy with abdominal pain. The sample should be taken within two hours. Presumably, the prolactin release is due to the propagation of epileptic activity from the temporal lobe spreading to the hypothalamic-pituitary axis. High serum prolactin could help to differentiate epilepsy with abdominal pain from psychogenic or functional causes of abdominal pain[80]. The presence of abnormal epileptogenic activity by EEG accompanying the pain paroxysm or between the attack confirms the diagnosis. Computed tomography or magnetic resonance imaging of the brain may be needed to rule out neurologic diseases or tumors. Other laboratory tests to rule out the gastrointestinal causes of abdominal pain are tailored according to the clinical finding. Abdominal ultrasound could also help[77].

Epilepsy and migraine are frequent comorbid conditions and shared genetic susceptibility[81]. Abdominal migraine has many shared features with epilepsy with abdominal pain: Auras, abdominal pain, nausea, vomiting, and headache. So, when a patient with epilepsy with abdominal pain presents with a headache, it will be challenging to differentiate it from abdominal migraine (Table 1). The duration of the symptoms could help in diagnosis, as headache is usually prolonged in abdominal migraine rather than in abdominal epilepsy. Postictal manifestations, abnormal EEG, and high postictal serum prolactin could help confirm epilepsy with abdominal pain[79]. Treatment of epilepsy with abdominal pain with antiseizure medications is usually successful, with very few relapse rates. There are no current recommendations on the type of antiseizure medications, but many studies recommend using oxcarbazepine[82].

Postictal abdominal manifestations

Postictal states are transient brain conditions following seizures (most common complex partial and tonic-clonic seizures), manifested as neurological deficits (confusion, weakness, memory impairment, and headache) with/without psychiatric manifestations of variable severity and duration, frequently associated with EEG slowing or suppression, and persist for minutes to days[83]. The duration of these symptoms usually corresponds to the intensity and duration of the ictal period. The mechanism of postictal states is related to robust cortical inhibitory mechanisms that try to inhibit and terminate the seizures, producing changes in membrane receptors and alteration of neurotransmitter release together with cerebrovascular changes, contributing to the development of these postictal events. Postictal event type depends on the type of epilepsy, the location of the epileptogenic activity, and the severity of the seizure[84,85]. Sometimes it is challenging to differentiate between ictal and postictal events, especially in nonconvulsive seizures[86]. The EEG and magnetic resonance imaging brain changes usually relate to the postictal manifestations with characteristic slowing and temporary signal increases[87].

Postictal hypersalivation is rare but occurs entirely in seizures of mesial origin in temporal lobe epilepsy, mainly from the left side[88]. Hypersalivation reflects a purposeful response to hypersecretion following regaining consciousness after a complex partial seizure. It is prevalent in patients with temporal lobe epilepsy, especially mesial temporal lobe epilepsy[89]. This postictal event is more common in females than males supporting the sex differences in epilepsy[90]. Postictal hyperphagia and compulsive water drinking were reported in a few case reports in patients with secondary epilepsy due

Table 1 Differences between epilepsy with abdominal pain and abdominal migraine

Parameter	Epilepsy with abdominal pain	Abdominal migraine
Age	Mainly pediatric age (4-9 yr), scarce in adults	It starts in childhood (3-10 yr with a peak at 7), though it may occur in adults
Sex	More in males during childhood, more in females in adulthood	More in females
Prevalence	Very rare	More common affect 2% to 4% of children
Etiology	Focal partial temporal lobe epilepsy due to idiopathic or secondary causes	Food allergy, Mitochondrial DNA mutation (cytopathy), Corticotropin-releasing factors abnormalities, Endogenous prostaglandin release
Family history		Strong family history of migraine
Duration of episodes	Usually 10-30 min, 4–5 times/month	Usually, more than an hour (3-4 h), at least twice/6 mo
Aura	May present	May present
Headache if present	Short duration	Long duration
Consciousness	May be altered	Not affected
Postictal tiredness or confusion	May present	absent
EEG	Abnormal epileptogenic electrical activity of focal temporal epilepsy	Usually, normal
Postictal serum Prolactin	Usually, high	Usually normal, it may be high, especially in females
Prevention	Prevention and treatment of the cause in secondary cases and sleep hygiene in idiopathic cases	Good sleep hygiene, hydration, stress reduction, and avoiding dietary triggers
Prophylaxis therapy	Antiseizure medications	Amyltryptine, propranolol, cryoheptadine, pizotifen

EEG: Electroencephalogram.

to temporal lobe lesions. It showed a dramatic response to carbamazepine[91]. It was also reported in secondary epilepsy due to frontal lobe lesions[92]. Remick *et al*[93] described three patients who experienced postictal hyperphagia[93].

Effects of antiseizure medications on the gastrointestinal tract

Antiseizure medications generally have a narrow therapeutic window with many adverse effects, especially on the gastrointestinal tract. According to the reporting method, the prevalence of the antiseizure side effects ranges between 10%-90% of the patients[94]. Over the last one and half centuries, the adverse effects of antiseizure medications remain the primary cause of treatment failure. About 10%-30% of the patients with epilepsy did not tolerate these side effects and stopped the drugs, especially with polytherapy[95]. Gastrointestinal side effects were observed in many antiseizure medications. Table 2 summarizes the common gastrointestinal side effects of the commonly used antiseizure medications.

On the other side, some antiseizure medications can improve some gastrointestinal manifestations. For example, gabapentin can improve functional dyspepsia, which is resistant to other conventional therapies[96]. Gabapentin also decreases rectal mechanosensitivity and enhances rectal compliance in patients suffering from diarrhea-predominant IBS[97]. Another interesting finding by Liu *et al*[98] is the ability of valproate to prevent peritoneal adhesion following abdominal injury through chymase inhibition[98]. Valproate also decreased intestinal inflammation in inflammatory bowel disease[99].

Meanwhile, Patel and Patel[100] showed that sodium valproate could experimentally inhibit the proliferation of carcinogenic cells in colon cancer associated with diabetes mellitus[100]. As valproate is a GABA agonist, it can modulate gastrointestinal motility and the anal sphincter. Valproate can normalize the activity of the human lower esophageal sphincter and reduces the number of reflux episodes in health and GERD[101]. Phenobarbital is effective and safe for preventing prenatal and treating postnatal hyperbilirubinemia through its effects on the hepatic enzymatic elimination of bilirubin[102,103].

ABDOMINAL MANIPULATIONS TO MANAGE EPILEPSY

As the gut-brain axis has a bidirectional effect on both gut and brain, modulation of the gut microbiota

Table 2 Common gastrointestinal side effects of antiseizure medications[122-129]

Antiseizure medications	Common gastrointestinal side effects
Carbamazepine	Dry mouth, mouth sores, glossitis, loss of appetite, dysphagia, nausea, vomiting, hurt burn, gastritis, stomach/abdominal pain, constipation, diarrhea, abnormal liver functions, cholestatic and/or hepatocellular jaundice, hepatitis; hepatic failure (very rare), and pancreatitis (rare), eosinophilic colitis
Ethosuximide	Anorexia, nausea, vomiting, gastric pain, diarrhea, gastric and intestinal atony with decreased peristaltic activity
Phenobarbital	Diarrhea, sore throat, swelling of the tongue/throat, nausea, vomiting, constipation, dysphagia, and heartburn. As it is a cytochrome P450 hepatic enzyme inducer, it can cause abnormal hepatic function, hepatitis, liver damage, cholestasis, toxic hepatitis, and jaundice
Phenytoin	Changes in taste sensation, gingival overgrowth, sore throat, mouth ulcers, diarrhea, nausea, vomiting, constipation, dysphagia, heartburn, idiosyncratic hepatotoxicity (< 1% of the patients), reduced gastrointestinal absorption of calcium, reduced hepatic synthesis of 25-hydroxycholecalciferol, cause a relative vitamin K deficiency
Valproate	Diarrhea, nausea, vomiting, constipation, dysphagia, gastritis with heartburn, several distinctive forms of acute and chronic liver injury, and vitamin D deficiency
Gabapentin	Vomiting, constipation, gastritis, pancreatitis
Topiramate	Taste perversion, anorexia, nausea, abdominal pain, indigestion, diarrhea, constipation
Lamotrigine	Dry mouth, nausea, vomiting, gastritis, diarrhea, or constipation

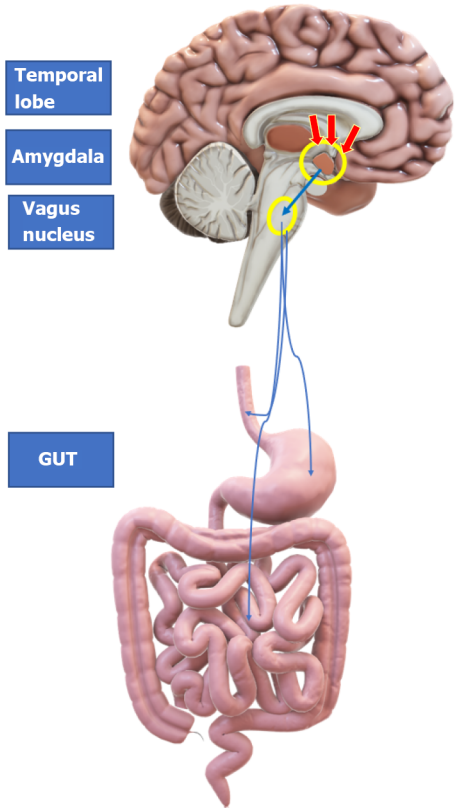

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Figure 1 Mechanism of epilepsy with abdominal pain.

could positively impact managing diverse types of epilepsy. The gut microbiota may influence brain functions in several ways, including the CNS, the hypothalamic-pituitary-adrenal axis, immune and inflammation modulation, and neuromodulators. Therefore, gut microbiota modulation could exert a beneficial role in epilepsy management. Prebiotics, probiotics, synbiotics, postbiotics, a ketogenic diet, and fecal microbiota transplantation are probable methods to treat epilepsy *via* modulation of the microbiota-gut-brain axis[104]. Probiotics are living organisms able to provide the host with health benefits when supplied in an appropriate dose. At the same time, prebiotics is selective nutritious substrates for specific types of host microorganisms to confer health benefits to the host. Synbiotics are a mixture of both pre- and probiotics. Postbiotics are the metabolic end products of the probiotic

organisms that can confer health benefits to the host[105].

Gómez-Eguílaz *et al*[106] found a reduction in seizure frequency by 50% in about 28.9% of patients with drug-resistant epilepsy when supplied with a probiotic mixture as adjuvant therapy for four months. This effect persisted for another 4 mo after probiotic discontinuation in 78.9% of those who showed improvement[106]. The gut microbiota can modulate brain activity by the peripheral production of GABA, metabolizing serotonin precursors, and modulating brain-derived neurotrophic factors that correlate with epilepsy severity. The bacterial production of short-chain fatty acids, which have anti-inflammatory effects, is another factor explaining the probiotic effects in treating epilepsy. Gut microbiota also modulates the endocannabinoid system with its inflammatory suppressor effects on seizure events[107]. At the same time, some gut microbiota strains can metabolize anticonvulsants affecting their antiseizure effect. For example, the gut microbiota can metabolize the antiseizure zonisamide into pharmacologically inactive 2-sulfamoyl-acetyl-phenol[108]. Fecal microbiota transplantation is a promising approach to reconstructing the gut microbiota. It is successfully used to treat various diseases, including neurological disorders. He *et al*[109] successfully treated a girl with long-term Crohn's disease and epilepsy for 17 years with fecal microbiota transplantation, which could prevent seizure relapse during 20 mo of follow-up[109]. However, we need more time to have a valuable experience with the efficacy of fecal microbiota transplantation in treating epilepsy.

The ketogenic diet is an old modality used to treat drug-resistant epilepsy and metabolic diseases since 1920. Though the precise mode of action is not well known, its activity could be related to modifying the gut microbiota composition and function. The gut microbiota modification causes alteration of beta-hydroxybutyrate levels and elevates the hippocampal GABA compared to the glutamate content[110]. In addition, the ketogenic diet modification of the gut microbiota reduces the alpha diversity and increases proposed beneficial bacteria like *Akkermansia muciniphila* and *Parabacteroides spp*. This microbiota modulation changes the colonic luminal metabolome, with a decrease in gamma-glutamyl amino acids and an increase in the brain GABA/glutamate content by reducing the blood gamma-glutamyl amino acids[111]. A ketogenic diet also alters neuronal metabolism by reducing cerebrospinal fluid glucose levels, increasing ketone bodies, and reducing cortical hyperexcitability with reduced seizure frequency[112]. Ketone bodies such as acetoacetate exerted a broad-spectrum anticonvulsant effect through modulation of neurotransmitter release and modification of ATP-sensitive potassium channels[113]. Additionally, ketone bodies have a direct inhibitory influence on the vesicular glutamate transport[114].

Vagus nerve stimulation was approved by the Food and Drug Administration in 1997 as adjuvant treatment in patients with multidrug resistant epilepsy who are not fit for epilepsy surgery. The vagus nerve is a vital brain-gut axis component and plays an essential role in inflammation modulation, intestinal homeostasis maintenance, food intake, satiety regulation, and energy homeostasis[115]. Vagus nerve stimulation leads to electrical energy discharge into a wide brain area, disturbing the unusual brain activity that produces seizures[116]. At the same time, vagal stimulation has anti-inflammatory properties affecting the gastrointestinal tract through hypothalamic-pituitary-adrenal axis activation and vasovagal reflex-induced cortisol release, which has an anti-tumor necrosis factor effect[117]. Consequently, vagus nerve stimulation can be used to treat multidrug resistant epilepsy and at the same time can treat gut inflammatory disorders such as IBD, which at the same time is a risk factor to increase the incidence of epilepsy[118].

Omentum is a large double peritoneal flat sheet of fatty tissue that hangs from the greater and the lesser gastric curvature to float on the intraperitoneal organs, including large and small intestines. It has many functions: Fat storage, immune regulation, neovascularization, tissue regeneration, and healing. Omental transposition or graft was used in various surgeries, including abdominal, cardiac, thoracic, orthopedic, plastic, vascular, urogenital, gynecological, and neurosurgeries[119]. Omental transposition on the brain surface enhances neoangiogenesis by generating plentiful new vessel connections between the omentum and the brain, which induces healing of neural injury by increasing the cerebral blood flow and the available oxygen to the neural tissues, releasing omental neurotransmitters, such as acetylcholine, dopamine, and noradrenaline. It also releases neurotrophic factors such as gangliosides and nerve growth factors that help to restore neurologic functions[120]. Rafael *et al*[121] used omental transplantation to treat two patients with uncontrolled temporal lobe epilepsy. They transplanted the omental tissues directly upon the epileptic focus on the left temporal lobe and the anterior perforated space. One patient showed complete recovery, while the other showed about 85% improvement in seizure frequency and severity[121]. However, there are few reported cases, and there is a need for long-term follow-up to have a better experience with omental transplantation to treat epilepsy.

CONCLUSION

There is a strong interaction between the gut and the brain. This interaction forms the typical gut-brain axis. Consequently, gastrointestinal dysfunction can be seen in neurological disorders, and neurological dysfunction can be seen in gastrointestinal disorders. There is an increase in epilepsy incidence in various gastrointestinal diseases. On the other hand, epilepsy, in turn, affects the gastrointestinal tract in

different forms, such as abdominal aura, epilepsy with abdominal pain, and the adverse effects of antiseizure medications on the gut and the gut microbiota. Various gut manipulations could help manage epilepsy, such as gut microbiota modification, fecal microbiota transplantation, ketogenic diet, vagus nerve stimulation, and omentum transplant. Understanding the strong relationship between epilepsy and the gut could help alleviate epileptic and gastrointestinal disorders.

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Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207.

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MINIREVIEWS

Influence of the COVID-19 pandemic in the gastrointestinal oncology setting: An overview

Breno Bittencourt de Brito, Hanna Santos Marques, Filipe Antônio França da Silva, Maria Luísa Cordeiro Santos, Glauber Rocha Lima Araújo, Lara de Araujo Valente, Fabrício Freire de Melo

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Breno Bittencourt de Brito, Filipe Antônio França da Silva, Maria Luísa Cordeiro Santos, Glauber Rocha Lima Araújo, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45029-094, Bahia, Brazil

Hanna Santos Marques, Lara de Araujo Valente, Campus Vitória da Conquista, Universidade Estadual do Sudoeste da Bahia, Vitória da Conquista 45055-380, Bahia, Brazil

Fabrício Freire de Melo, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45029-094, Brazil

Corresponding author: Fabrício Freire de Melo, MSc, PhD, Postdoc, Professor, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Rua Hormindo Barros, 58, Quadra 17, Lote 58, Vitória da Conquista 45029-094, Bahia, Brazil. freiremeloufba@gmail.com

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been impacting healthcare in various ways worldwide and cancer patients are greatly affected by the coronavirus disease 2019 (COVID-19) pandemic. The reorganization of the health facilities in order to supply the high demand resulting from the aforementioned infection as well as the social isolation measures led to impairments for the diagnosis and follow-up of patients with gastrointestinal cancers, which has had an impact on the prognosis of the oncologic patients. In that context, health authorities and organizations have elaborated new guidelines with specific recommendations for the management of individuals with gastrointestinal neoplasms during the pandemic. Of note, oncologic populations seem to be more susceptible to unfavorable outcomes when exposed to SARS-CoV-2 infection and some interactions involving virus, tumor, host immune system and anticancer therapies are probably related to the poorer prognosis observed in those COVID-19 patients. Moreover, vaccination stands out as the main prevention method against severe SARS-CoV-2 infection and some particularities have been observed regarding the seroconversion of vaccinated oncologic patients including those with gastrointestinal malignancies. In this minireview, we gather updated information regarding the influence of the pandemic in the diagnosis of gastrointestinal neoplasms, new recommendations for the management of gastrointestinal cancer patients, the occurrence of SARS-CoV-2 infection in those individuals and the scenario of the vaccination against

the virus in that population.

Key Words: Gastrointestinal cancer; COVID-19; Treatment; Diagnosis; Vaccination; Pandemic

Core Tip: The coronavirus disease 2019 pandemic has impacted the care of patients with serious chronic conditions such as cancer. In this minireview, we gather updated information regarding the influence of the pandemic in the diagnosis of gastrointestinal neoplasms, new recommendations for the management of gastrointestinal cancer patients, the occurrence of severe acute respiratory syndrome coronavirus 2 infection in those individuals and the scenario of the vaccination against the virus in that population.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak emerged in 2019 which soon spread worldwide becoming a pandemic[1]. Coronavirus disease 2019 (COVID-19) infection is one of the greatest threats to global public health and by March 2022 the World Health Organization had already identified 464809377 confirmed cases and 6062536 deaths[2]. The course of the disease ranges from asymptomatic to fatal infection and its clinical presentation is mainly characterized by respiratory symptoms such as cough and dyspnea but it can also affect other systems leading to cardiac, gastrointestinal, renal, neurological, cutaneous and hematological disorders[3]. Severe COVID-19 primarily affects patients with comorbidities including individuals with cancer who are often immunocompromised[4]. Gastrointestinal neoplasms including colorectal, gastric, liver, esophageal and pancreatic cancers are relatively frequent and some of them are among the malignancies that kill the most in the world, such as gastric and colorectal cancers[5]. In the context of the new coronavirus pandemic, tumors that affect the gastrointestinal tract are the most common malignancies among patients infected with COVID-19 in various investigations[6]. Disturbingly, SARS-Cov-2 infection in oncologic patients is linked to higher rates of intensive care unit (ICU) admission, greater need for mechanical ventilation and increased propensity to death[7-9].

The clinical practice of oncologists and the routine of cancer patients were significantly affected by the effects of the COVID-19 pandemic[10]. The measures adopted to prevent the spread of the disease and the overload of health services around the world impacted the diagnosis of some malignancies, especially those that require invasive procedures such as colorectal and gastric cancers[11]. In addition, cancer health care including oncologic surgeries, visits to the health system, outpatient consultations and anti-cancer therapies were negatively affected by experiencing delays or interruptions during treatment[12]. Finally, vaccination is the main available strategy to prevent the SARS-CoV-2 infection. However, studies have highlighted particularities involving the effectiveness of the available immunizers in the oncologic population[13-15].

This minireview focuses on addressing the key challenges faced by oncologists and patients with gastrointestinal malignancies in face of the changes that follow the aforementioned pandemic. The aim is to highlight the main aspects discussed in the current scientific evidence regarding diagnosis, treatment, vaccination and infection prevention among patients with gastrointestinal cancer in that context.

METHODS

In order to review the repercussions of SARS-CoV-2 infection in patients with gastrointestinal cancer, a search was performed for relevant articles published in English in the National Library of Medicine (PubMed) database until March 5, 2022. In this sense, two researchers acted independently using the following descriptors: COVID-19; SARS-CoV-2 in combination with Gastrointestinal cancer; Gastric cancer; Esophageal cancer; Colorectal Cancer; Treatment; Cancer diagnosis; Vaccination. The selection of studies was made by screening the titles and abstracts of articles. We included studies that evaluated

outpatients and inpatients with confirmed SARS-CoV-2 infection who had cancer, outpatients and inpatients with confirmed SARS-CoV-2 infection who had gastrointestinal cancer, prospective, retrospective, cross-sectional studies, systematic reviews and narratives.

IMPACTS OF THE COVID-19 PANDEMIC OVER GASTROINTESTINAL CANCER DIAGNOSIS

Healthcare systems around the world have been broadly impacted by the COVID-19 pandemic. Many health facilities had to be reorganized in order to uphold the high demand for medical assistance imposed by the aforementioned disease[16]. Financial, structural and personal resources have been redirected to supply the unexpected consequences that follow such an unprecedented health problem [17]. Other issues also impaired the access of populations to healthcare providers including the burden of the pandemic over the economy as well as the difficulties and fears faced by populations to reach healthcare centers in the presence of lockdowns and other measures for contagion containment[18]. In addition, the interruption of nonurgent medical procedures, including diagnostic tests, in order to avoid viral dissemination, was another trouble in that setting[19]. Unfortunately, these changes undoubtedly prejudiced the proper assistance and early diagnosis of serious chronic conditions such as gastrointestinal malignancies.

A population-based study performed by Maringe *et al*[20] in England aimed at estimating the influence of the pandemic over cancer deaths due to delays in diagnosis in that country, gathering 24975 individuals with colorectal cancer and 6744 persons with esophageal malignancy. They estimated an increase of about 15.3%-16.6% in the number of colorectal cancer-related deaths and an enhancement of 5.8%-6.0% in esophageal cancer-associated deaths within the first 5 years after diagnosis. Another study carried out with the Chilean population estimated the impact of the COVID-19 outbreak on the diagnosis and survival of breast, cervix, colorectal, prostate and stomach cancers. The results predicted a larger percentage of individuals diagnosed with cancer at advanced stages between 2020 and 2022 which leads to a lower 5-year net survival. They previsied 3542 extra deaths from 2022 to 2030 (95% UI 2236–4816) associated with these cancers, led by colorectal cancer, which accounts for 1389 excess deaths (95% UI 364–2567), whereas stomach cancer will probably be the cause of 6.0% of those additional deaths[21].

In addition, an investigation performed in an academic health center in New York (United States) compared the number of diagnostic and resection specimens for the detection of gastrointestinal malignancies during the years 2018, 2019 and 2020. They included 949 patients, gathering 1028 pathology samples, and observed a reduction of 57% in the number of samples in 2020 compared to the preceding year ($P < 0.01$). Moreover, a drop in the number of colorectal cancer specimens from older patients was found when pre- and post-COVID-19 periods were compared ($P < 0.01$)[22]. Alarmingly, a retrospective Japanese study evaluated 5167 patients (4218 before the pandemic and 949 diagnosed with gastrointestinal cancer during the pandemic) and observed that during the pandemic period there was a significant decrease in diagnoses of stage 0 colorectal cancers ($P = 0.008$, stage I ($P = 0.003$) and stage II (0.01) and an increase in diagnoses in stage III malignancies ($P < 0.001$)[11]. These data evidence the repercussions of the pandemic on the diagnosis of gastrointestinal cancers as well as the impact of the delay for diagnosis on the prognosis of oncologic patients. Interestingly, a study with 298 patients carried out in an Italian hospital observed a lower number of elective colorectal cancer screening colonoscopies, but a higher detection of colorectal cancer cases during the pandemic[23]. They found five cases (8%) of the malignancy among individuals ($n = 60$) evaluated from March 9 to May 4, 2020 (lockdown group), and only 3 cases (1%) among the patients ($n = 238$) who underwent the diagnostic assessment in the same period of 2019 (control group, $P < 0.01$). Moreover, the prevalence of patients with more high-risk factors for the disease, such as a familiar positive history and significant symptoms (*e.g.*, rectal bleeding), was higher in the lockdown group. These results suggest that the presence of meaningful risk factors for colorectal cancer probably made patients prioritize the diagnosis of the disease despite the risk of acquiring SARS-CoV-2 infection.

TREATMENT OF GASTROINTESTINAL CANCER PATIENTS DURING THE PANDEMIC

Since the World Health Organization declared the SARS-CoV-2 outbreak a pandemic, the impacts of the infectious disease on cancer treatment have become a major concern around the world. Patient protection and continuity of treatment became challenging factors within that context in which social isolation and reduced displacement were the main measures to be taken.

In Europe, one of the first continents that became the epicenter of transmission, health authorities and governments decided to postpone consultations for patients with gastric cancer or carry them out remotely, treatment plans were reformulated and many clinical trials on gastrointestinal malignancies had their development impaired. In Italy and the United Kingdom (UK), for example, some health units

were designated for the exclusive care of patients with COVID-19 and others to assist individuals without the infection, and even so it is estimated that more than 200000 weekly exams were unable to be performed in the UK[24].

In a Japanese cross-sectional study carried out with 61 patients undergoing treatment for gastrointestinal cancer, it was observed that the pandemic caused a reduction in the number of exits and more caution regarding the prevention of infections ($P < 0.001$) as well as an increase in the occurrence of anxiety and insomnia in those patients during treatment ($P < 0.01$). Of note, most patients do not wish to change their treatment plans as recommended by guidelines developed during the pandemics[25] and this may be due to the fear and insecurity in face of the chance of having a worse prognosis because of a decrease in the frequency of care measures. Another American study that compared 25666 patients being treated for gastrointestinal cancer in 2020 and 23530 patients followed up in 2019, observed that there were statistically significant decreases in the number of radiotherapies and surgeries in patients with gastrointestinal neoplasms[26]. Sozutek *et al*[27] recently observed a reduction of about 70% in the volume of cases of colorectal cancer at an academic center during the pandemic. This study also showed that there was a lower proportion of cancer resections ($P = 0.01$), with a decrease of about 15% in the number of colorectal cancer surgical therapies ($P = 0.04$)[22]. These results indicate that the pandemic, indeed, has had negative impacts on the treatment of patients with various gastrointestinal malignancies.

The international survey in question focused on the preoperative screening of asymptomatic patients aiming to elucidate the current global situation of surgical practice under the COVID-19 pandemic. A total of 936 centers in 71 countries completed the survey; the survey respondents were a total of 1173 surgeons who represented the centers' surgical departments. Results show that the majority of them (73.8 per cent) performed preoperative COVID-19 testing exclusively based on symptoms or suspicious radiologic findings, but only 22.8 per cent of the overall centers performed routine screening by chest-computer tomography (CT) scan. To test every surgical patient for COVID-19 was a guideline recommended in barely 17 per cent of the centers. Results also show that 27.5 percent of the centers reported asymptomatic COVID-19 patients who tested positive postoperatively; most centers (81.9 per cent), only then, changed testing policies and preventive measures in surgical practice[28].

The surgeon's personal feelings were also investigated in the survey; in total, 1124 surgeons replied to the questions. When asked about the personal fear of getting sick or infecting others, the respondents overall reported a relatively high score of 37 ± 13, 1 point meaning "never" and 5 points meaning "always". Just over 50 per cent of the surgeon's said to be satisfied with the hospital's preventive measures, agreeing that their centers were taking enough preventive measures to avoid in-hospital transmission. The survey clarified the current surgeons' fear of getting infected was particularly associated with shortage of gloves, gown, hand sanitizer and medical masks. That, in addition to experiencing in-hospital infection, which was reported in 31.5% of the overall centers and the majority of these centers failed to trace it. Social support for the surgeons' fear and secure working environment with enough personal protective equipment (PPE) supply have shown to be unwarranted[29].

Despite all the risks involved in performing surgical procedures during the pandemic, a 60-d observational study of 177 patients with gastrointestinal cancer observed that there was no SARS-CoV-2 infection in any staff member or patient who underwent tumor resection during the study period. They concluded that even in a hospital that takes care of patients with COVID-19, if there are adequate prevention measures for both the patients and the medical staff, the procedure can be performed safely, thus optimizing the treatment of these patients[27]. It is important to point out that, unfortunately, this was not the reality of most underdeveloped countries which had little availability of adequate infrastructure and resources for the implementation of proper preventive methods to avoid SARS-CoV-2 contagion and had to postpone many surgical procedures due to the high chance of infection in a hospital environment[30].

While a guideline for clinicians published by the World Health Organization states that patients who have confirmed COVID-19 infection should be assessed for holding anticancer therapy until they are deemed medically clear, it is unquestionable that surgery and adjuvant therapies cannot always be postponed; emergency surgery is still recommended in certain diagnoses[31]. Studies show that patients who underwent chemotherapy or surgery in the past month before diagnosis with COVID-19 had a higher risk of severe clinical events than those not receiving chemotherapy or surgery. Therefore, the necessity of any interventional procedure must be balanced against the increased risk during a pandemic and should be evaluated on a case-by-case basis[9,32]. The potential benefit of chemotherapy remains unchanged during a pandemic, but the risk of harm would be increased to a degree that cannot be quantified. Undoubtedly, cancer patients need to be made aware that myelosuppressive treatment could carry greater risk during a pandemic so they may well make an informed choice[31,33]. Moreover, it is clear that an intentional postponement of adjuvant chemotherapy or elective surgery for stable cancer should be considered for patients with acute SARS-CoV-2 or other infections[32].

However, delays for surgery or curative adjuvant chemotherapy can only be considered within acceptable periods for each disease. While some cases can be postponed indefinitely, the majority of them are associated with progressive diseases that will continue to advance at variable disease-specific rates. For instance, while some asymptomatic breast cancer tumors can be followed up until the pandemic is more controlled or over, chemotherapies against stage III colorectal cancers can only be

safely delayed up to 8 wk post -surgery, but more than 12 wk of delay is not recommended, being associated with worse outcomes[34,35].

To spare this group of patients the possibly irreparable consequences of delayed treatment in this uncertain pandemic setting, it is imperative that each hospital should review its own facilities and provide these patients with treatment when possible. During the COVID-19 pandemic, one of the points to be considered when making the decision for surgery in cancer patients is the current condition of the hospital. Operating rooms are high-risk areas for contact contamination through airway or possible splash; to avoid the risk is it a demand that they should be very well-designed to deal with this type of high contamination risk situation; a minimum number of people should enter and leave patient rooms for all types of work and procedures. The widespread use of hand washing, antiseptic procedures and PPE should be ensured by the hospital and usage rules should be strictly followed. In cases of required emergency surgery for a patient with both cancer and ongoing SARS-CoV-2 infection, it has to previously be defined in detail the operational, perioperative and postoperative management including prevention and control measures for the medical staff, operating rooms and surgical tools as well as the protection of the wards, healthcare personnel and other patients. Hospital resources should be evaluated with a multidisciplinary approach and a personalized treatment protocol should be developed for each patient[36-38].

Considerations for gastric and esophageal cancer

Upper gastrointestinal tract (esophageal and gastric) malignancies rank among the ten most common malignancies worldwide while gastric cancer still remains one of the leading causes of cancer-associated deaths. The incidence of upper GI malignancies varies widely and regions with high COVID-19 incidence such as, China, Japan, Central, and South America, also represent areas with the highest occurrence of esophageal and non-cardiac gastric cancer[39].

With regard to the treatment of these malignancies, the Society of Surgical Oncology affirms that most upper gastrointestinal tract cancer surgeries are not elective. If there are inadequate resources to manage potential complications then surgery may need to be delayed or, if necessary, referred to centers with resources to perform the procedure. Discussion of cases remains critical to assert priorities, resources, and personalized treatment plans based on the hospital, patient and tumor specificities. However, a few organ-specific approaches are determined: cT1a lesions amenable to endoscopic resection may preferentially undergo endoscopic management where resources are available; cT1b cancers should be resected; cT2 or higher and node-positive tumors should be treated with neoadjuvant systemic therapy. Given the concerns regarding laparoscopic surgery in COVID-19 patients, since the SARS-CoV-2 may be present in the smoke caused by the cautery devices, consideration may be given to proceeding straight to neoadjuvant treatment in COVID-19 positive patients.

Patients completing neoadjuvant chemotherapy may stay on chemotherapy if responding to and tolerating treatment. If patients are not responding to systemic treatment, resection and/or referral may be considered. Patients with gastric outlet obstruction or hemorrhage should be treated with endoscopic measures to allow for enteral nutrition or control of bleeding; proceed to surgery if these measures fail. In less biologically aggressive cancers, such as gastrointestinal stromal tumors - unless symptomatic or bleeding - surgery may be considered for short-term deferral[40].

Considerations for colorectal cancer

Guidelines have been published by several associations based on the experience gained from colorectal cancer patients in China and Italy, during the pandemic, reciting recommendations to protect both patients undergoing cancer treatments and healthcare professionals. These guidelines all converge to a general direction: It is critical to postpone elective surgery as much as possible but to perform emergency surgery provided that general measures are taken. The Society of American Gastrointestinal and Endoscopic Surgeons published similar guidelines recommending that surgical intervention should be performed in cancer patients who are likely to progress or who require emergency intervention. The situation is not all that simple with regard to colorectal cancers. It is accepted that surgery should be performed in life-threatening conditions such as cancer patients with perforating, obstructing, actively bleeding tumors or septic patients, but other conditions might require further consideration such as looking into the status of the patient, the stage of the tumor, the risk of the surgical procedure and the condition of the respective hospital[41]. Asymptomatic stage I-II patients can have their elective colon cancer surgery deferred for 30 d and have a new decision made at the end of this period; they will not be affected unfavorably by the deferral up to approximately 6 wk. However, the need for a further deferral at the end of the 60-d-period warrants radiological staging for decision making in those patients. In asymptomatic stage III colon cancer patients, deferral longer than 30 d should involve discussing a plan of neoadjuvant chemotherapy. In asymptomatic stage IV colon cancer patients, guidelines recommend initiating chemotherapy and planning surgery depending on the radiological response after three courses of chemotherapy[42]. Figure 1 summarizes the recommended approach to colon cancer in the context of COVID-19.

Rectal surgery can wait no longer than 60 d between the diagnosis and the treatment or the rate of survival will be considerably lower. In a stage I asymptomatic rectal cancer, a 30-d deferral might not affect the oncological outcomes. At the end of the 30-d delay, depending on the patient's symptoms,

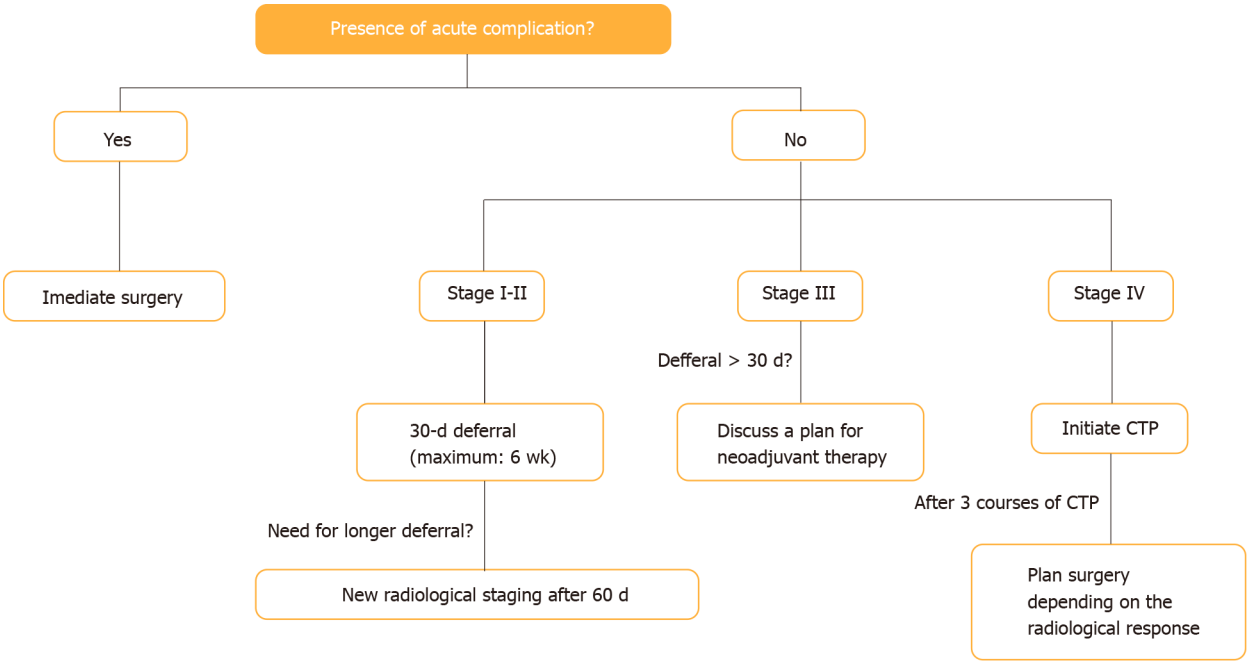

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Figure 1 Summarizes the recommended approach to colon cancer in the context of coronavirus disease 2019. CTP: Chemotherapy.

treatment can be deferred for another month but radiological staging is necessary to make any new decisions. In stage II-III rectal cancers, radiotherapy should be administered; its response should be evaluated in the 8th week after radiotherapy. If there is a regression with radiotherapy, surgery could wait for a period of up to 12 or even 16 wk while the patient is closely monitored. If, however, results show no regression at the 8th week with radiotherapy, the decision for surgery can be made depending on the infrastructure of the hospital[43].

Symptomatic rectal cancer patients, usually between the stages II-IV, should make the decision for the treatment depending on the severity of symptoms and findings and their effect on the quality of life. Radiology staging is necessary; patients who are symptomatic but can wait, should, preferably, defer the surgery as described for asymptomatic stage I, II and III. As for patients who have been diagnosed with malignant polyps, it is appropriate to postpone prophylactic surgeries. Whichever the decision regards the patient's treatment, it is necessary to choose protocols that will minimize the patient's hospitalization for both surgery, radiotherapy and chemotherapy procedures. It is peremptory that all the staff should be careful and follow the protocols during the preoperative and postoperative period to prevent infection for themselves and all other patients hospitalized[36].

An issue that should not be forgotten is the fact that because of the aforementioned higher risk of viral transmission in laparoscopic surgeries, open surgeries are the most suitable for COVID-19 patients. If the surgery has to be performed laparoscopically, fixed pressure insufflators, a closed-circuit smoke absorption system, a negative pressure operating room and a carbon dioxide filter should be used to discharge the smoke to reduce the aerosol effects of insufflation. On the other hand, laparoscopic surgery is associated with earlier recovery and discharge and might benefit individuals who are not currently infected with the virus. In summary, minimally invasive surgery, ideally, should not be used in cases known to be infected with SARS-CoV-2 and should only be used after all necessary precautions have been taken[40].

SARS-COV-2 INFECTION AMONG PATIENTS WITH GASTROINTESTINAL CANCER

The current scientific evidence indicates that individuals with cancer might be more susceptible to a severe course of infection with SARS-CoV-2[44]. The greater likelihood of severe development is probably explained by the immunosuppression that often accompanies malignancies and oncological therapies[45]. However, data on the repercussions of SARS-Cov-2 infection in cancer patients are still being developed with the possibility of inconsistencies regarding the conclusions on the subject[46]. In addition, most studies address various types of neoplasms with a focus on lung and blood cancer, with limited information on gastrointestinal malignancies. In a case-control analysis with 73.4 million cancer patients, including colorectal cancer, the authors concluded that cancer carriers are at increased risk of SARS-CoV-2 infection and that the occurrence of the infection is associated with higher rates of hospitalization and mortality in that population. It confirms the occurrence of worse outcomes among infected

oncologic patients and, interestingly, these findings were especially substantial among African Americans[4].

Furthermore, two meta-analyses had similar conclusions regarding COVID-19 infection in cancer patients. The first included 38 studies and 7094 patients with COVID-19, with a pooled cancer prevalence of 2.3%, and demonstrated that cancer significantly contributed to the occurrence of severe course and death in SARS-CoV-2 infections. The second covered a total of 110 studies with a combined prevalence of cancer as a comorbidity of 2.6% in hospitalized patients with COVID-19 and indicated that the risk of mortality is about five times higher among oncologic patients when compared to non-elderly SARS-CoV-2-infected individuals without comorbidities[44]. One of the first cohorts on the subject evaluated characteristics and clinical outcomes of 105 individuals with gastrointestinal cancer and COVID-19 and 536 non-oncologic SARS-CoV-2-positive patients. Their findings revealed that patients with COVID-19 and gastrointestinal cancer had worse outcomes regarding mortality, ICU admissions, the prevalence of at least one severe or critical symptom and the need for invasive mechanical ventilation when compared to the non-oncologic patients[47]. In addition, a retrospective study with 52 oncologic COVID-19 patients found that some complications such as liver injury (36.5%), acute respiratory distress syndrome (17.3%), sepsis (15.4%), myocardial injury (15.4%), renal failure (7.7%) and multiple organ dysfunction syndrome (5.8%) are common in cancer patients infected with SARS-Cov-2 and, therefore, these individuals may be more prone to more severe outcomes[45].

A study looked at COVID-19-related clinical symptoms, survival rate and risk of infection among cancer patients, including colon cancer and gastric cancer, and the results suggested that thrombocytopenia, anemia and diarrhea are symptoms that increase independently the risk of death in oncologic patients with COVID-19[48]. Another study portrayed gastrointestinal manifestations in 36 cancer patients, of whom 8 had gastrointestinal cancer. Their results concluded that the most prevalent gastrointestinal symptoms in the hospitalized patients were anorexia (52%), diarrhea (39%) and vomiting (35%) and that elevations in hepatic transaminases were associated with a higher occurrence of gastrointestinal symptoms[49].

From an immunological point of view, viral infections and neoplasms are associated with high levels of proteins that activate the T cell-mediated response leading to inflammation which may play important roles in cancer progression[50]. In this sense, some signaling pathways can be affected by both COVID-19 infection and cancer, influencing the expression of type-I IFN and androgen receptor as well as the activation of immune checkpoint signaling pathways, and alterations at these points of the immune response have the potential to lead to the development of a cytokine storm that is closely associated with acute respiratory distress syndrome, organ failure and death in severe COVID-19[51]. Furthermore, ACE2 receptors are highly consumed in SARS-CoV-2 infection due to their ability to assist the virus in cell entry[52]. For this reason, there is a decrease in the availability of those receptors and, as a consequence, important functions played by these receptors may be compromised[52]. In this context, low ACE2 activity has the potential to contribute to severe inflammation and is related to some types of gastrointestinal malignancies such as gallbladder cancer and pancreatic ductal adenocarcinoma[53,54]. Another well-established issue in cancer patients is the immunosuppression caused by the depletion of leukocytes and the use of glucocorticoids in addition to other oncological therapies that compromise the ability of the immune system to respond to viral infections such as SARS-CoV-2 infection, leading to a course of more serious illness[55].

Despite what has been discussed so far, some studies present results that contrast with the conclusions that associate cancer with worse COVID-19 infection outcomes. A prospective cohort that included 9842 patients found that the incidence and severity of clinical presentation of COVID-19 infection in cancer patients are not significantly different from those observed in the general population [46]. In agreement with the aforementioned results, in an observational study gathering 78 cancer patients positive for SARS-Cov-2, only one developed the severe form of the disease and only three developed symptoms[56].

VACCINATION AGAINST COVID-19 IN GASTROINTESTINAL CANCER PATIENTS

During the new coronavirus pandemic, as soon as vaccination schemes were implemented, certain priority groups were identified, taking into account the epidemiological data obtained so far. In this sense, cancer patients were considered as a priority group, mainly, the worst prognosis of the disease among these individuals including a higher mortality rate. In this context, institutions such as the Asian Oncology Society, the European Society for Medical Oncology and the National Comprehensive Cancer Network recommended that cancer patients be a priority thus including individuals undergoing treatment or about to undergo treatment and those who underwent treatment for at least 6 mo[51,57].

However, despite the priority for vaccination, little is known about the immune response of these individuals after the application of the immunizer. It is necessary to take into account that cancer patients, including those with gastrointestinal involvement, have conditions linked to the disease and to the treatments adopted that can compromise the effective response to the vaccine. In this context, chemotherapy, by causing bone marrow suppression can cause thrombocytopenia and neutropenia. In

addition, radiotherapy, because it is capable of damaging the DNA of cells, including lymphocytes, is also capable of causing lymphopenia. Associated with this, therapies that use corticosteroids and other immunosuppressive elements can further compromise the full functioning of the immune system of individuals undergoing cancer therapy and directly influences the immune response to vaccination. In addition, the initial clinical trials did not include individuals with cancer and the literature addressing the relationship between the vaccine and cancer patients is scarce[58].

Thus, given the need to better understand the immune response to the vaccine in cancer patients, some studies were carried out bringing results with the ability to directly influence the care provided to this group. However, studies focusing exclusively on patients with gastrointestinal involvement seem to have not yet been performed.

Among the parameters adopted by the studies to analyze the immune response to vaccines, anti-Spike (anti-S) IgG antibodies were the most used. Thus, the Coronavirus Disease 2019 Antiviral Response in a Pan-tumor Immune Monitoring (CAPTURE) trial, which included 585 participants, including 87 with gastrointestinal cancer (19%), evaluated individuals immunized with the BNT162b2 (Pfizer–BioNTech) or AZD1222 vaccines (Oxford–AstraZeneca) and found 85% seroconversion after the application of two doses of the immunizer in the general group of patients with solid cancer. In addition, they reported that older age is related to a lower titer of neutralizing antibodies[59].

In this context, studies evaluating seroconversion after the application of the CORONAVAC vaccine were also carried out. In this sense, Yasin *et al*[60] defined an IgG level ≥ 50 AU/mL as seropositive in a study that included 776 cancer patients, including 174 (22.4%) with gastrointestinal involvement, and 715 non-cancer volunteers. The seropositivity rate and antibody level were significantly lower in individuals with cancer when compared to the control group ($P < 0.001$). In this context, the seropositivity rate was 85.2%, with a mean antibody titer of 363.9 AU/mL in the patient group and 97.5%, with a mean antibody titer of 656.5 AU/mL in the control group. In addition, as the CAPTURE study pointed out, age was a factor associated with a lower rate of seropositivity ($P < 0.001$). The study also pointed to ongoing chemotherapy in the group of cancer patients ($P = 0.038$) as a factor capable of negatively influencing seropositivity rates, the opposite was pointed out by the Vaccination Against COVID in Cancer (VOICE) and CAPTURE trials[61]. Table 1 summarizes the seroconversion rates of the immunizers among oncologic patients.

Another important point is linked to the increase in antibody titers that were observed after the application of the second dose. Thus, it is noted that only one dose of the immunizer provides immunity much lower than that which can be obtained with the application of two doses[62]. In this context, Becerril-Gaitan *et al*[57] reported that cancer patients with an incomplete vaccination schedule, when compared to individuals in the control group without cancer, had a 55% reduced probability of reaching anti-S IgG titers above the stipulated threshold (RR 0.45; CI95% 0.35-0.58). For those with a complete vaccination schedule, the reduced probability was 31% (RR 0.69; 95%CI 0.56-0.84).

Given the above, although individuals with cancer reach acceptable seroconversion rates, despite being reduced compared to the "healthy" population, studies indicate that the application of booster doses is indicated for individuals with compromised immunity[63,64]. Thus, in August 2021, the Food and Drug Administration (FDA) authorized the application of the booster dose to immunosuppressed individuals[13]. In this context, Ligumsky *et al*[14] when analyzing the response of 72 cancer patients and 144 "healthy" individuals (control group) to the booster dose of the BNT162b2 vaccine (Pfizer–BioNTech), they initially observed that before the application of the third dose, 20 cancer patients (28%) and two in the control group (1%) were seronegative. However, after the application of the booster dose, only three cancer patients and none of the control group remained seronegative. In addition, when comparing the absolute concentration of anti-SARS-CoV-2 S IgG antibodies, they observed that there was a significant increase in levels in both groups ($P < 0.0001$). In this context, studies also point out that the application of the booster dose can guarantee a better response to variants of concern such as Delta and Omicron[15].

Therefore, it is evident that cancer patients have a less pronounced immune response to vaccination, even with the application of the third dose, when compared to "healthy" individuals in the control group, although satisfactory in most individuals. In addition, it is noted that the application of the booster dose is capable of guaranteeing greater seroconversion in this group and therefore should be encouraged. Finally, more studies are needed to better understand the immune response of cancer patients to currently available vaccines, given that these individuals are subject to variables related to cancer and to the different treatments that can be applied which influence immunity in different ways.

Adverse effects associated with vaccination against COVID-19

Another factor that should be taken into account are the adverse events that may occur as a result of vaccination. In this sense, studies were carried out to analyze the acceptance of cancer patients to immunization. In one of these studies, which involved the participation of 364 cancer patients, when asked if they would take the vaccine as soon as it became available, 41.8% answered "yes", 37.6% answered they were "not sure", and 20.6% answered who would not get the vaccine. Among the factors that encourage cancer patients to be vaccinated are the fear of getting sick, trust in the recommendations of health professionals and the desire to contribute to herd immunity. As for those who expressed doubt or refusal of the vaccine, fear and concern about possible adverse effects were present in 24.5% of the

Table 1 Seroconversion of immunizers in oncologic patients

Immunizer	Ref.	Cancer patients, *n*	% GIC	Seroconversion, %
BNT162b2 (Pfizer–BioNTech), OR, AZD1222 (Oxford–AstraZeneca)	Fendler *et al*[59]	585	19	85
CORONAVAC	Yasin *et al*[60]	776	22.4	85.2

GIC: Gastrointestinal cancer.

participants[65].

In this sense, studies suggest that, as in the general population, cancer patients tend to have mild to moderate effects. Thus, a study that included 291 participants immunized with BNT162b2 reported adverse events following immunization in 14.78% of subjects. These include local reactions, pyrexia, fatigue, headache and chills. Furthermore, the risk of developing these events was higher in women (P = 0.001) and young patients (P = 0.009). Another study, which evaluated the BNT162b2 vaccine in 326 participants diagnosed with cancer, reported similar results, without any serious reaction[66,67].

However, despite the majority of events being mild or moderate, the possibility of serious complications exists. Thus, there are case reports that associate certain events with vaccination. In this context, Chong *et al*[68] reported severe thrombocytopenia 3 d after the application of the first dose of the Moderna vaccine and Brage *et al*[69] reported fulminant myocarditis after receiving the third dose of the Moderna vaccine. In this context, it is evident that serious adverse events can occur, but most patients have mild or moderate events. However, more studies are needed to better clarify the effects presented and understand the possible interactions between the different types of anti-cancer treatment and the epidemiological factors of each individual with the development of mild, moderate or severe reactions.

Nevertheless, it is still the role of health professionals to inform their patients about the risks and benefits of vaccination helping them to make effective decisions.

CONCLUSION

The COVID-19 pandemic has been negatively impacting the diagnosis, treatment and prognosis of gastrointestinal cancer. Although most studies indicate that having cancer, in general, implies a greater risk of severe COVID-19, it is an ongoing pandemic with still limited studies and only a few investigations are specific for neoplasms from the gastrointestinal tract. The immunosuppression caused by cancer and its related therapies probably make the patient more vulnerable to infections; however, the measures adopted to avoid the contagion in this population can also impair anticancer therapies. Therefore, it is essential that research on the subject continues to evolve towards a better understanding of how the pandemic caused by the new coronavirus interferes with the context of gastrointestinal cancer in order to improve the approach to cancer patients and solve remaining challenges in that context.

FOOTNOTES

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Country/Territory of origin: Brazil

ORCID number: Breno Bittencourt de Brito 0000-0002-1831-7909; Hanna Santos Marques 0000-0001-5741-1570; Filipe Antônio França da Silva 0000-0002-0550-1109; Maria Luísa Cordeiro Santos 0000-0001-7078-9789; Glauber Rocha Lima Araújo 0000-0002-5195-3632; Fabrício Freire de Melo 0000-0002-5680-2753.

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MINIREVIEWS

COVID-19 in patients with gastrointestinal stromal tumors: Recommendations for management and vaccination

Violeta Snegarova, Dimitrina Miteva, Milena Gulinac, Monika Peshevska-Sekulovska, Hristiana Batselova, Tsvetelina Velikova

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Violeta Snegarova, Clinic of Internal Diseases, Naval Hospital – Varna, Military Medical Academy, Medical Faculty, Medical University, Varna 9000, Bulgaria

Dimitrina Miteva, Faculty of Biology, Department of Genetics, Sofia University "St. Kliment Ohridski", Sofia 1164, Bulgaria

Milena Gulinac, Department of General and Clinical Pathology, Medical Faculty, Medical University of Plovdiv, Plovdiv 4000, Bulgaria

Monika Peshevska-Sekulovska, Department of Gastroenterology, University Hospital Lozenetz, Sofia 1407, Bulgaria

Monika Peshevska-Sekulovska, Tsvetelina Velikova, Medical Faculty, Sofia University St. Kliment Ohridski, Sofia 1407, Others, Bulgaria

Hristiana Batselova, Department of Epidemiology and Disaster Medicine, Medical University, Plovdiv, University Hospital "St George", Plovdiv 6000, Bulgaria

Tsvetelina Velikova, Department of Clinical Immunology, University Hospital Lozenetz, Sofia 1407, Bulgaria

Corresponding author: Tsvetelina Velikova, MD, PhD, Assistant Professor, Chief Doctor, Department of Clinical Immunology, University Hospital Lozenetz, Kozyak 1 Street, Sofia 1407, Bulgaria. tsvelikova@medfac.mu-sofia.bg

Abstract

The coronavirus disease 2019 (COVID-19) pandemic profoundly affected the management and treatment of patients with malignancies. Based on the progress reported in the literature, we reviewed the recommendations for treatment and vaccination in patients with gastrointestinal stromal tumor (GIST) during COVID-19. We focus on whether there is a risk and what could be the possible effects of vaccinating patients with GIST/cancer. Since the situation is quickly changing, and the health services have been severely disrupted, the diagnosis, treatment and recommendations for vaccination of these patients against COVID-19 are still not updated. The approval of vaccines in the pandemic gave hope that we would soon be able to return to a more normal life. However, the oncology community needs to adapt and provide the most effective treatment and care models for patients with rare cancer, such as GIST. Collecting data on the impact of

vaccination in patients with GIST/cancer also will be beneficial in expanding knowledge about the future planning of treatment strategies and optimizing care in the event of a subsequent pandemic.

Key Words: Gastrointestinal stromal tumor; GIST; Cancer; COVID-19 vaccination; efficacy; Treatment strategy; Side effects

Core Tip: Even under normal operating conditions, appropriate monitoring and treating patients with gastrointestinal stromal tumors (GISTs) require complex decision-making. Given the growing number of deaths worldwide and the failure of many countries to control the pandemic, vaccination against COVID-19 in these patients must be accelerated. The data show no significant difference in the efficacy of vaccines for the GIST population compared to that of other cancers. Vaccination between cycles of therapy and after waiting periods for patients with stem cell transplantation and immunoglobulin therapy can be used to reduce the risks while protecting patients from risk groups.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in China at the end of 2019 and coronavirus disease 2019 (COVID-19) are considered risk factors for severe outcomes in cancer patients[1]. Statistics indicate that by March 13, 2022, there have been > 6 million deaths caused by COVID-19 worldwide, and the number of confirmed cases recorded is > 455 million[2].

In line with this, according to a number of reports, diseases such as diabetes, hypertension, cardiovascular diseases, respiratory diseases, and cancer are associated with an increased risk of fatality in patients diagnosed with COVID-19[3]. In addition, an international study involving 1035 patients with COVID-19 who have concomitant cancer showed that these patients had a higher risk of hospitalization and need for intensive care and mechanical ventilation, regardless of the type of malignancy and antitumor therapy[4].

Patients with malignant diseases represent a heterogeneous group. Therefore, it remains to be determined which factors related to tumor type and treatment increase the risk of infection with COVID-19 and adverse outcomes[5]. According to a study that aimed to identify the risk factors of severe COVID-19 infection in patients with malignancy, the administration of antitumor treatment (chemotherapy, radiotherapy, targeted therapy or immunotherapy) within 14 d of diagnosis significantly increases the risk[6].

To assist health care facilities and minimize the negative effects of the pandemic associated with COVID-19 in patients with malignancies, the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN) and other organizations have developed recommendations for patient categorization based on the Ontario Health Cancer Care criteria[7].

Gastrointestinal tumors are a relatively new tumor group that has emerged in recent decades from other mesenchymal tumors in this field, mainly neurinomas and leiomyomas, thanks to the achievements of modern medicine in molecular biology and pharmacotherapy. Therefore, the justification for a separate tumor form merits an in-depth multidisciplinary study. Furthermore, it represents a model for successfully applying targeted therapy in treating solid tumors[8].

Gastrointestinal stromal tumors (GISTs) are rare neoplasms of the gastrointestinal tract associated with high rates of malignant transformation. They represent 1%–2% of all gastrointestinal neoplasms [9]. The mean age at diagnosis is 58 years, with most patients being between the ages of 40 and 80 years [10].

Although the risk of SARS-CoV-2 infection is not increased in GIST patients, they may experience other consequences during the COVID-19 pandemic, such as delay in treatment, delayed surgery or long waiting period for elective surgery, a heavy burden on medical resources, and the need for emergency surgery[11]. Additionally, neoadjuvant imatinib is routinely used to shrink locally advanced GISTs and if there is a danger of positive margins, unresectable, or borderline resectable tumors[12]. Imatinib may be a beneficial alternative to minimize the possibility of tumors developing in

intermediate or high-risk cancers bearing imatinib-sensitive mutations that would otherwise be excised during a time of limited access to surgical therapy[12]. Even if imatinib is generally well tolerated, patients may develop adverse effects such as myelosuppression (grade 3 in up to one-fifth of all patients), which might be concerning if the patient becomes infected with SARS-CoV-2[13]. Finally, initial watchful waiting would not rule out the possibility of starting imatinib if the tumor progressed.

The term GIST was introduced by Mazur and Clarck in 1983 for a group of nonepithelial mesenchymal tumors of the gastrointestinal tract (most often leiomyomas, leiomyosarcomas and neurinomas), which differ from the eponymous tumors in other areas of the body in their immunohistochemical characteristics[14]. It is now commonly accepted that GISTs derive from so-called pacemaker cells in the intestinal tract – the interstitial cells of Cajal or similar stem cells[15]. Cajal cells are intermediates of gastrointestinal autonomic nervous system cells and smooth muscle cells and regulate the motility and autonomic nerve conduction and function activity. They are positive for Kit and Kit-ligand (stem cell marker), localized around the myenteric plexus and in the stratum muscularis propria along the entire gastrointestinal tract. Cajal cells can either be or include a subclass of multipotent, stem-like cells that can differentiate into smooth muscle cells if the Kit signaling pathway is disrupted[16]. In most cases, GISTs are specifically Kit (CD117) positive or caused by mutations in *Kit* or *PDGFRA* genes, and are the primary mesenchymal tumors of the gastrointestinal tract with characteristic histological features[17].

In the 1990s, GIST were found to express CD34 antigen, which has been identified as a distinguishing feature of neurinomas and leiomyomas. However, in a new study phase, GISTs were found to have standard immunohistochemical and ultrastructural features with Cajal interstitial cells or related stem cells, as stated above. For this reason, studying Kit (CD117) expression in tumor cells is the best immunostaining method for identifying GIST[14,18-20].

GISTs have malignant and insufficiently predictable biology and behavior, even with benign histological features. Morphologically, GISTs vary from spindle cell tumors to epithelioid and pleomorphic tumors. GISTs have approximately the same distribution in both sexes. Most are localized in the stomach (50%–60%) and the small intestine (30%). Esophageal, colorectal and rectal GISTs are rare (3%)[21].

The diagnosis of GIST is based on pathomorphological evidence by histological examination of biopsy material, and when taking a biopsy, the recommendations of NCCN. The NCCN organized a multidisciplinary panel composed of experts in surgery, pathology, medical oncology and molecular diagnostics to discuss the optimal approach for the care of patients with GIST at all stages of the disease [22,23].

SEARCH STRATEGY

We performed a modified form of a narrative review where a search through scientific databases combined solid evidence from studies on vaccine effectiveness and safety in patients with gastrointestinal tumors and GISTs. The first literature search was carried out in Medline (PubMed) and Scopus bibliographic databases. Both MeSH and relevant free-text terms were used, as follows: (COVID-19 OR SARS-CoV-2) AND (GIST OR gastrointestinal stromal tumor) AND (vaccine* OR mRNA). Our search was confined to articles published up to April 2022. Finally, references of retrieved publications were further hand-searched for supplements.

Official recommendations for COVID-19 vaccination in patients with GIST

Up to date, no specific and official recommendations are included in the ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up for GIST (2022)[24]. However, ESMO statements on vaccination against COVID-19 in people with cancer conclude that all the approved COVID-19 vaccines could be administered to patients with cancer taking into account their effectiveness and safety, according to the official international recommendations[25]. Furthermore, ESMO has confirmed that the mass vaccination program is a crucial strategy for protecting against severe infection. This also stands for vulnerable patients, such as cancer patients, who take advantage of the most preferable benefit–risk ratio[25]. Since some patients with cancer, especially those with active malignancies, may experience a greater risk of severe SARS-CoV-2 infection, ESMO recommends COVID-19 vaccination. Despite reduced effectiveness for specific subgroups of cancer patients, the protection is still meaningful, and vaccination is strongly advised. Patients with hematological malignancies, particularly those undergoing cytotoxic chemotherapy, anti-CD20, CAR-T cell, or stem-cell-transplant-based treatments, are also among these populations.

Effectiveness and safety of COVID-19 vaccines in patients with GIST

Prior to the COVID-19 pandemic, there was little evidence of the humoral and cellular immune responses to antiviral vaccination in cancer patients. Additionally, this primarily addressed the influenza vaccination[26,27]. Despite a general exclusion of cancer patients from the major clinical studies of COVID-19 and COVID-19 vaccination, subsequent results repeatedly proved the effectiveness

and safety of SARS-CoV-2 immunization in these patients. Overall, after complete COVID-19 immunization, persons with cancer have clinically significant seroconversion rates[28-32]. Although the efficiency of mRNA and adenoviral vector vaccines appears almost identical[30], there is a lack of comparative effectiveness data, particularly in cancer patients. Notably, when only one dose of an mRNA vaccine is delivered, the incidence of seroconversion is much reduced, emphasizing the necessity of vaccination completion and, eventually, booster for cancer patients[33,34].

However, there are not enough data from studies for COVID-19 vaccination in patients with GIST. There have been a few studies[30,35-39] that mainly recruited patients with gastrointestinal tumors, some with GIST, as summarized in Table 1. Thakkar *et al*[30] and Suenaga *et al*[35] demonstrated that even on chemotherapy, patients with gastrointestinal tumors tolerated COVID-19 vaccines well. Additionally, the effectiveness was assessed as adequate for SARS-CoV-2 infection protection. This observation was also valid for immunocompromised patients due to cancer treatment[36-38]. Given the scientific and logistical challenges in identifying cancer patients with weak or decreasing immunity, the global strategy of a booster dosage vaccination should be investigated for cancer patients. However, until better quality information on booster dosage benefits becomes available, international recommendations considering the risk of poor COVID-19 outcomes in cancer patients, vaccine availability/access, immunization progress, and the pandemic burden should be followed.

Are there any risks for vaccination of patients with GIST/cancer

The most significant driver for public health protection is the availability and equal access to COVID-19 immunization, with conformity to international criteria to be encouraged and supported. Therefore, vaccination plans have been established worldwide to prioritize vaccine delivery in various groups, including cancer patients. On the other hand, cancer patients do not constitute a homogenous group. And GISTs are among the rare cancer types.

In general, cancer patients can be divided into three groups: patients with active disease undergoing treatment, patients with chronic illness following specific therapy, and patients in the survival phase. Vaccination is essential to protect all of these patient groups[25]. If we translate this knowledge to the patients with GIST, we can assume that COVID-19 vaccination is strongly advised for them.

However, despite increasing compliance rates and existing evidence/data, 10%–20% of patients remain skeptical about the COVID-19 vaccine. These patients are at a higher risk of developing severe COVID-19 illness. In addition, they are a more likely source of SARS-CoV-2 transmission to other, more sensitive cancer patients[25]. It is critical to reinforce trust, education, and easy, transparent communication with those patients and their relatives based on the accumulated knowledge and better understanding of their concerns and hesitancy. In addition, communication of available data on vaccine safety and efficacy to people with cancer should also include assuring them that COVID-19 vaccines will not interfere with their cancer treatment[40]. Furthermore, there is no indication that COVID-19 immunizations substantially influence anticancer medication's efficacy or safety profile, such as cytotoxic chemotherapy, immune checkpoint inhibitors, or targeted therapies. Thus, COVID-19 vaccination is strongly advised[25]. More data on the preference for a specific type of vaccine and potential unusual interactions of SARS-CoV-2 vaccines with antineoplastic therapy should be collected by in-trial, post-trial, and registry monitoring.

Suppose an anticancer medication is urgently required for disease control. It is advised that suitable medication be implemented first, followed by COVID-19 immunization, as soon as the patient is clinically stable and significant symptoms are under control. To minimize misattribution of any short-term reactions/side effects, providers may consider administering anticancer medication and COVID-19 vaccinations on different days[41].

Therefore, since we do not have studies on the effectiveness and safety of COVID-19 vaccination for patients with GISTs, we have to rely on the official recommendations for patients with cancer generally. The data for rare diseases usually accumulate slowly. To protect patients from a "double jeopardy", informed consent and collaborative decision-making should be the rule when discussing the advantages and risks of COVID-19 immunization and SARS-CoV-2 infection.

CONCLUSION

Before the COVID-19 pandemic, most vaccination research with cancer patients was conducted for vaccines against hepatitis B, influenza and other infections. However, as the immune response is reduced in those patients, the risk of severe COVID-19 should be noted. Therefore, patients have to receive complete vaccination and booster doses to acquire higher levels of protection. This is also valid for patients with GIST. COVID-19 vaccination could be administered to patients who are even on therapy if some vaccine components are not contraindicated. The data show no significant difference in the efficacy of vaccines for the GIST/cancer population compared to other cancers. Oncologists have extensive experience in vaccinating cancer patients who are being treated, so they can effectively help save their patients' lives.

Table 1 Studies of COVID-19 vaccination in patients with gastrointestinal tumors

Ref.	Type of study	Type of COVID-19 vaccine	Participants	Efficacy/effectiveness	Adverse effects
Suenega *et al* [35], 2022	Retrospective observational study	mPNA (BNT162b2 or mRNA-1273)	Gastrointestinal cancer patients, *n* = 52	BNT162b2 (approximately 95%), mRNA-1273 (approximately 94%)	82.2% had adverse events: Injection site pain (approximately 67%), fatigue (approximately 12%), fever (approximately 6%), headache (approximately 4%), gastrointestinal problems (approximately 4%), redness (approximately 2%), insomnia (approximately 2%); no vaccine-related deaths
Fendler *et al* [36], 2022	Retrospective observational study	BNT162b2; mRNA-1273	115	mRNA vaccines (against omicron approximately 75%) (against delta approximately 79%); against omicron increased from 47.8% to 88.9% following a third vaccine dose	Injection site pain (approximately 63%), local swelling (9%), muscle pain (34%), fatigue (34%), headache (16%), fever (10%), chills (10%) and gastrointestinal events (10%); no vaccine-related deaths
Thakkar *et al* [30], 2021	Retrospective study	BNT162b2, mRNA-1273, Ad26.COV2.S	27 (14%) from 200 are with GIST	BNT162b2 (95%), mRNA-1273 (94%), Ad26.COV2.S (85%)	Sore arm (20%–37%), fatigue (5%–16%), muscle ache (5%–17%), fatigue (1%–5%), rash (1%–3%), redness (approximately 2%), other (1%–5%); no vaccine-related deaths
Embi *et al* [37], 2021	Observational study	BNT162b2; mRNA-1273	20 101 immunocompromised patients	BNT162b2 (71%), mRNA-1273 (81%)	Sore arm (20%–47%), fever (10%), fatigue (1%–5%), other (1%–5%); no vaccine-related deaths
Karacin *et al* [38], 2021	Prospective observational study	CoronaVac vaccine	47	Sero-response rate 63.8%	Pain at the injection site (4.2%), fever (2.1%), fatigue (4.2%–10.5%), headache (2.1%), and myalgia (2.1%), There were no serious side effects or toxic deaths
Ariamanesh *et al*[39], 2022	Prospective study	BBIBP-CorV	364 (32 patients with gastrointestinal tumors)	Sero-response rate 86.9%	Injection site pain, fever, fatigue, headache

FOOTNOTES

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Country/Territory of origin: Bulgaria

ORCID number: Violeta Snegarova 0000-0003-0754-6439; Dimitrina Miteva 0000-0002-5931-2426; Milena Gulinac 0000-0001-7970-9378; Monika Peshevska-Sekulovska 0000-0002-8468-0132; Hristiana Batselova 0000-0002-6201-848X; Tsvetelina Velikova 0000-0002-0593-1272.

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