Chronic Constipation

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KEYWORDS

• Constipation • Pathophysiology • Motility • Diagnostic testing
• Anorectal manometry • Laxatives • Secretagogues

KEY POINTS

- Chronic constipation is a disabling disorder affecting approximately 20% of the world's population. In outpatient clinics in the United States it is 1 of the 5 most commonly diagnosed gastrointestinal disorders.
- There are many etiologies for constipation and these can overlap. Constipation may be due to a combination of normal or slow transit, an evacuation disorder, or secondary to an underlying medical condition.
- Old and newer diagnostics are available to differentiate the causes of chronic constipation. Those most commonly used include radiopaque marker testing, anorectal manometry, balloon expulsion testing, defecography, and wireless motility capsule.
- Regularly used therapeutic classes include stool softeners, emollients, bulking substances, stimulant and osmotic agents, and the newest category of agents: the secretagogues.

CHRONIC CONSTIPATION

Introduction

Chronic idiopathic constipation (CIC) is one of the most common digestive complaints in the general population. This disorder affects approximately 20% of individuals, and is 1 of the 5 most common issues assessed by practicing gastroenterologists in the United States.[1,2] Data recently collected from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey recently identified CIC as the fourth most common gastrointestinal (GI) diagnosis made in emergency departments (EDs) between 2006 and 2012. This study found 800,000 visits representing

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a 60% increase over this time period. Combining ED, office, and hospital outpatient visits in 2010, CIC represented 3.7 million evaluations, ranking as the fourth most commonly diagnosed GI disorder in the United States.[3]

Although considered benign in most cases, CIC can result in chronic illness with potentially serious complications including fecal impaction, incontinence, hemorrhoids, anal fissures, bleeding, and in the most extreme cases colon perforation. These aside, the disorder alone is associated with significantly impaired quality of life.[4] Chronic constipation is most commonly associated with increasing age. There is also increased prevalence among women (median female-to-male ratio of 1:5:1) with women more likely to use laxatives and seek health care for their constipation. Although the exact etiologic mechanisms have yet to be elucidated, anatomic and hormonal differences (ie, elevations in serum progesterone) appear to play a role. This may also explain why some women experience increased rates or exacerbations of their symptoms with pregnancy and/or during hormonal fluctuations within their menstrual cycles. Other risk factors correlated with the development of CIC include decreased daily physical activity and/or low fiber intake, low socioeconomic status, and reduced education.[1]

Currently, CIC is defined via the Rome III criteria as documented later in this article.[5] However, updates to these are expected with the publication of the Rome IV criteria in 2016 (**Box 1**).

Etiology/Pathophysiology

The pathogenesis of CIC is complex; it has the potential to be derived from a singular entity or multiple overlapping etiologies (**Fig. 1**). Based on current schemata, chronic constipation is usually classified into 2 categories: idiopathic (or primary) and secondary constipation. The distinctions between the 2 types are important, as identification of etiology can help guide therapy.[6]

Secondary Constipation

Multiple biological, environmental, and pharmaceutical precipitants exist with the potential to cause CIC (**Fig. 2**). Pharmaceuticals are one of the most common contributors to the development of constipation. Major categories of secondary systemic

Box 1
Rome III diagnostic criteria for functional constipation

Infrequent loose stools

Insufficient criteria for a diagnosis of irritable bowel syndrome (IBS)

≥2 of the following symptoms present for ≥6 months

<3 bowel movements (BMs) per week

Lumpy or hard stools ≥25% BM

Straining ≥25% of BM

Sensation of incomplete evacuation ≥25% BM

Sensation of anorectal blockage ≥25% BM

Use of manual maneuvers to facilitate defecation ≥25% BM

Data from Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006;130:1480

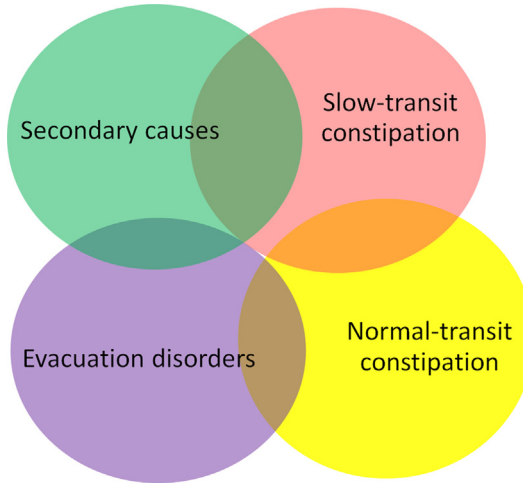

Fig. 1. Potential etiologies of CIC. (*Adapted from* Brenner DM, Chey WD. An evidence-based review of novel and emerging therapies for constipation in patients taking opioid analgesics. Am J Gastroenterol Suppl 2014;2:40; with permission.)

disorders include endocrinopathies (eg, diabetes, hypothyroidism), metabolic abnormalities (eg, hypercalcemia or hypocalcemia, hypokalemia), neuropathic or myopathic disorders (eg, scleroderma, multiple sclerosis, Parkinson disorder, amyotrophic lateral sclerosis), and mechanical or pseudo-obstructions.[6] An extensive list of potential causal factors is well described elsewhere in the clinical literature.[7]

Idiopathic Constipation

Normal transit

Normal transit constipation is usually defined as a subtype of CIC in which adults have adequate colonic transit rates. Individuals often complain of difficult evacuation,

Fig. 2. Potential causes of secondary constipation.

straining, the passage of hard stools, and abdominal discomfort. Most are subsequently diagnosed with irritable bowel syndrome.[8]

Slow transit

Slow transit constipation (STC) is most commonly characterized by infrequent defecation and blunted urge to defecate due to delayed transit of fecal material through the colon. These changes have been associated with impaired colonic propulsive motor activity, delayed emptying of the proximal colon, and an attenuated gastrocolic reflex. Immunohistochemical studies have revealed a paucity of interstitial cells of Cajal. Whether this a secondary consequence of CIC or the driving factor for the development of CIC has yet to be elucidated.[9]

Evacuation Disorders

This refers to difficulty or an inability to expel stool and is usually due to anatomic (ie, rectocele, enterocele, anal stenosis, excessive perineal descent, intussusception, rectal prolapse) or functional disorders of the anorectum. The most frequently identified of such disorders is dyssynergic defecation, which is known by many pseudonyms including pelvic floor dyssynergia, anismus, or obstructive defecation. All indicate a failure to coordinate abdominopelvic musculature leading to inadequate rectal propulsive forces, paradoxic anal sphincter and/or puborectalis muscle contraction, inadequate anal sphincter relaxation, or a combination thereof.[7]

CLINICAL EVALUATION

A meticulous history and physical examination are the most important elements of initial evaluation of patient with chronic constipation. Laboratory tests, endoscopic evaluation, and radiographic studies are not routinely recommended. These procedures should, however, be considered in patients with alarm features, such as hematochezia, weight loss, a family history of colon cancer or inflammatory bowel disease, anemia, positive fecal occult blood, or acute constipation in elderly. Further diagnostic workup is recommended for patients who fail conservative treatment and the etiology of their constipation remains unknown.[9]

History

A careful history focuses on the onset/duration of symptoms, bowel movement frequency, stool texture and caliber, straining, sensations of incomplete evacuation or mechanical obstruction, and the need for manual maneuvers to facilitate evacuation. However, no subjective symptom is sine qua none for a particular constipation subtype. The Bristol Stool Form Scale and symptoms diaries are useful adjunctive tools for defining fecal transit and overall bowel patterns.[10] A complete medical, surgical, dietary, and medication history are key to identifying secondary causes of constipation. Prior laxative use, doses, frequency, and response are important to help guide therapy.

Physical Examination

The most valuable components of a physical examination for chronic constipation include careful inspection of the perineum and the digital rectal examination. Inspection of the perineum is performed to identify fissures, hemorrhoids, excoriations, a gaping or patulous anus, or evidence of stool leakage. An assessment for appropriate perineal descent while a patient strains also should be observed. Identification of rectal prolapse may require the patient to strain in a squatting position. Palpation of the anal canal and rectum can identify rectal masses, strictures, hemorrhoids,

rectoceles, and rectal tenderness. If stool is palpated in the rectal vault, the consistency and any evidence of blood should be noted. Sphincter tone at rest, with squeeze, and bear down are defined as normal, weak, or increased. During bear down or simulating defecation, the examiner may assess abdominal push effort by placing the other hand on patient's abdomen. A lack of anal sphincter and puborectalis relaxation, paradoxic contraction of these muscles, or poor abdominal push efforts may suggest dyssynergia.[11]

Diagnostic Testing

Routine bloodwork, including a complete blood count, chemistry panel, and thyroid function test, are often routinely performed to evaluate for metabolic diseases. Colonoscopy is recommended in those who meet age-appropriate guidelines for colon cancer screening or in those with alarming symptoms, as previously mentioned. Routine radiographic evaluation by x-ray or barium enema has little utility when routinely obtained and should be discouraged. However, patients who have medication-refractory symptoms should be further evaluated and updated algorithms for the assessment of these individuals have been recently published by both the American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG).[12,13]

Physiologic Testing

Anorectal manometry

Anorectal manometry (ARM) in association with balloon expulsion testing (BET) is considered a first-line diagnostic in patients with medication-refractory CIC.[12,13] It is used to evaluate the functional performance of the pelvic floor musculature. A probe (usually high-resolution or high-definition) with circumferential pressure sensors along its length and a balloon at the tip is placed across the anal canal of a patient who is positioned in left later decubitus position. This probe can then be used to measure puborectalis and anal sphincter pressures at rest, with squeeze, during a cough maneuver, and attempted defecation, rectal sensation and compliance, the presence of the rectoanal inhibitory reflex, which is typically absent in patients with Hirschsprung and scleroderma.[14]

Rectal balloon expulsion test

The BET is another first-line diagnostic in the evaluation for dyssynergic defecation. The test is usually performed using a balloon filled with 50 mL water or air. However, some experts are advocating using a volume threshold consistent with a patient's desired urge to defecate. Although there are discrepancies and a lack of standardization regarding the amount of time considered appropriate for a positive study, most physicians agree that more than 5 minutes is abnormal, with many advocating a threshold of more than 1 minute.[7] This study is usually performed in conjunction with an ARM.

Radiopaque marker study

The radiopaque marker study (ROM) attempts to assess the rate of transit of stool through the colon to determine whether the etiology of constipation is transit related. Although many techniques are available, the simplest, the Hinton technique, uses a single capsule of 24 radiopaque markers. This is ingested on day 1 by the patient. An abdominal radiograph is obtained 120 hours later (day 6) and STC is indicated if there is retention of greater than 20% of markers. As up to 50% or patients with dyssynergic defecation may have comorbid slow transit, it is recommended to exclude dyssynergia before performing ROM testing.[14]

Defecography

Defecography is performed by injecting contrast material into the rectum and monitoring of defecation parameters via fluoroscopy. The study is useful for evaluating potential anatomic abnormalities causing CIC. Although not recommended as an initial diagnostic maneuver, it has benefits including testing in the natural-seated position. Findings suggestive of pelvic floor dysfunction, ineffective stool evacuation, and structural abnormalities (ie, rectoceles, rectal prolapse, or intussusception) can be identified on defecography. Patients with impaired mobility and embarrassment often find this examination difficult to tolerate. In addition, there is variation in quality of the test depending on operator and intraobserver bias. Recently, functional MRI has emerged as a tool to evaluate the anatomy and dynamics of the pelvic floor but this is performed in the left lateral decubitus position similar to ARM.[7]

Wireless motility capsule

Wireless motility capsule (WMC) is a newer technology used to assess regional and whole-gut transit times. Patients who have failed or become refractory to laxative therapy and other conservative measures are candidates for WMC testing. Given the high cost and similar clinical benefit as ROM, this test is not extensively performed, but saved in many instances for use in individuals with potential global dysmotility syndromes or to evaluate for concurrent upper gastrointestinal dysmotility in patients when a colectomy for isolated STC is being considered.[15]

Colonic manometry

Colonic manometry (CM) measures intraluminal colonic and rectal pressures to quantify colonic motor activity. In addition, CM attempts to identify complex contractile patterns in the colon at rest, during sleep, and with meals or other propagating stimuli. CM is predominately used when necessary to differentiate neuropathic from myopathic disorders. Currently, this diagnostic is relegated to large academic centers and used primarily for research purposes.[16]

Treatment

Multiple classes of agents are currently available for treating CIC: bulking agents, stimulant and osmotic laxatives, stool softeners, emollients, secretagogues, and serotonergic agents (**Table 1**). Each works via a specific mechanism of action. Given the array of currently available therapies and the availability of many of these agents as over-the-counter (OTC) therapeutics, it can be difficult for patients and physicians alike to choose first-line and second-line agents. In a recent survey of US gastroenterologists, 97% endorsed using an OTC therapy as a first-line agent, specifically recommending fiber (52%) and osmotic laxatives (40%) as their initial treatments of choice. Interestingly, if these failed, osmotic laxatives were used as the most common second-line intervention (46%), but there was a sharp decline in the use of fiber (6%) in favor of prescription secretagogues (24%).[17] Recent guidelines, including the ACG monograph on the treatment of CIC[18] and the AGA technical review on constipation,[7] have been congruous in their recommendations and appear to echo these general practice principles.

Bulking Agents

Dietary fiber supplements are carbohydrate polymers that are poorly digested in the small intestine; consequently, they are delivered almost unchanged to the colon where they bulk stool by drawing fluid into the intestinal lumen, and accelerate colon transit time. However, these agents can also undergo fermentation by colonic flora,

Table 1
Common chronic idiopathic constipation therapies

Medications	Important Information
Bulk laxatives	
Soluble: Psyllium Insoluble: Bran, methylcellulose, calcium polycarbophil	Increase stool bulk stimulating peristalsis
Stimulant laxatives	
Anthraquinones: (Senna/Casacara)	Stimulate intestinal secretion and motility. These may cause melanosis coli → No direct association to colon cancer or myenteric nerve damage proven
Diphenylmethane derivatives	
Bisacodyl	Hydrolyzed to active form by small intestine and colon enzymes
Sodium picosulfate	Hydrolyzed to active form by colon bacteria
Saline laxatives	
Mg hydroxide/Mg citrate	Hypermagnesemia can occur in renal failure and children
Sodium phosphate	Acute phosphate nephropathy can occur; black box warning
Osmotic laxatives	
Lactulose	Synthetic disaccharide consisting of galactose/fructose and resistant to degradation by disaccharidases but not bacteria. Gas/bloating common
Polyethylene glycol 3350	Organic polymer poorly absorbed and not metabolized by colonic bacteria; may cause less gas/bloating
Secretagogues	
Lubiprostone	Chloride ClC_2 agonist promoting luminal secretion and accelerated transit. May cause nausea (25%–33%)
Linaclotide	Guanylate Cyclase-C agonist promoting luminal secretion and accelerated transit. May cause diarrhea
Plecanatide	Guanylate Cyclase-C agonist currently completing Phase III clinical trials
Serotonergic agents	
Tegaserod	Withdrawn from US market due to small but significant increased risk of cardiovascular events
Prucalopride	Highly selective 5-HT_4 agonist approved for the treatment of chronic idiopathic constipation in Canada and Europe
Stool softeners	
Docusate sodium	Ionic detergent softens stool by lowering surface tension resulting in increased stool H_2O retention
Lubricants	
Mineral oil	Provides lubrication for the passage of stool.

generating hydrogen, methane, and carbon dioxide, which can increase gas and bloating. Fiber supplements can be soluble or insoluble in nature depending on their interactions with water. The most commonly used and tested fiber is the soluble fiber psyllium (ispaghula) derived from the seeds of the *Plantago ovata* plant. Insoluble

fibers include the natural supplement bran and the semisynthetic agents: methylcellulose and calcium polycarbophil.

Although high-quality studies on the overall effectiveness of fiber are sparse, data from a recent meta-analysis of 3 trials comparing psyllium with placebo (PBO) suggested beneficial effects from its use (number needed to treat [NNT] = 2; 95% confidence interval 1.6–3.0).[18] Furthermore, a recent systematic review identified 7 studies published over the past decade with 5 of 7 yielding beneficial effects in favor of fiber supplementation. However, these studies were small (enrolling 30–80 individuals), used variable fiber supplements and dosages, assessed different endpoints, and evaluated these findings over short durations.[19] Thus, longer more rigorously standardized trials are warranted. Currently, the ACG strongly endorses the use of fiber, particularly soluble fiber, for increasing stool frequency, but admits that this recommendation is based on low-quality evidence.[18]

Stimulant Laxatives

Stimulant laxatives exert their effect on the GI tract via induction of colonic peristalsis and/or fluid and electrolyte secretion. Although many are available, the data for the effectiveness of these therapeutics are sparse. To date, only 2 randomized, PBO-controlled trials have been completed: one using bisacodyl and the other liquid sodium picosulfate (SPS). Although different prodrugs, these molecules are activated in the small intestine to the same active molecule: bis-(p-hydroxyphenyl)-pyridyl-2-methane. In the first study, 267 individuals meeting Rome III criteria for CIC were randomized to receive 10 mg (18 gtts) of SPS or PBO in a 2:1 ratio for 4 weeks. At trial completion those receiving SPS experienced a significant increase in complete spontaneous bowel movements (CSBMs) compared with PBO (3.4 vs 1.7; $P<.0001$).[20] In the second study, 247 patients also meeting Rome III criteria were randomized to consume 10 mg bisacodyl or PBO. Four weeks later, patients receiving the bisacodyl also experienced a significant improvement in CSBMs compared with PBO (5.2 vs 1.9; $P<.0001$).[21] Unfortunately, their use can be limited by side effects including diarrhea and cramping with a recent meta-analysis yielding a number needed to harm of 3, which was equivalent to overall NNT of 3.[22] Stimulant laxatives are strongly recommended for the treatment of CIC with this recommendation based on moderate levels of evidence.[18]

Osmotic Laxatives

A mainstay of daily therapy, these agents function by retaining water in the intestinal lumen. Four major classes of osmotic agents current exist: polyethylene glycol (PEG)-based solutions, nonabsorbable carbohydrates, magnesium-containing solutions, and sodium phosphate–based products (see **Table 1**). Of these, PEG and lactulose have been most extensively studied. In the largest and longest laxative trial to date, 304 patients were randomized to receive PEG (n = 204) or PBO (n = 100) for 6 months. At completion of the study, individuals in the PEG cohort experienced a significant increase in bowel movements per week compared with PBO (7.9 vs 5.6; $P<.001$) and the percentage of individuals achieving a goal of 3 or more bowel movements per week was also significantly greater in favor of PEG (52% vs 11%; $P<.001$).[23] Multiple meta-analyses have also consistently yielded positive results favoring the use of osmotic agents. Ford and Suarez[22] recently pooled 5 studies comparing PEG and lactulose with PBO and identified a nonresponder rate of 37.2% compared with 68.9% of PBO (NNT = 3). Belsey and colleagues[24] analyzed 10 studies and found that PEG was superior to PBO and lactulose for increasing stool frequency. Furthermore, a recent Cochrane analysis of 10 clinical trials comparing PEG and lactulose revealed PEG

to be superior for improving stool frequency, stool texture, relieving abdominal pain, and reducing the need for additional laxative use.[25] Both PEG and lactulose are strongly recommended by the ACG for the treatment of CIC; however, the quality of evidence supporting the use of PEG is high, whereas for lactulose it is low.[18]

Secretagogues

Secretagogues, the newest class of agents, exert their effects by enhancing intestinal fluid secretion and accelerating small bowel and colonic transit. There are currently 2 commercially available agents in the class: the chloride channel activist lubiprostone and the guanylyl cyclase-C (GC-C) agonist linaclotide. Both are approved by the Food and Drug Administration (FDA) for the treatment of CIC. A second GC-C agonist, plecanatide, just completed phase III evaluation and a new drug application is currently being drafted to the FDA. The benefits of lubiprostone have been shown in 2 double-blind PBO-controlled trials randomizing 479 individuals with CIC. Patients received 24 μg lubiprostone twice daily or PBO for 4 weeks. In both studies a significantly higher percentage of subjects receiving lubiprostone experienced an increase in spontaneous bowel movements at the end of the first week of treatment (5.69 and 5.89 vs 3.46 and 3.99 in trials 1 and 2, respectively; $P<.05$), and these effects were maintained throughout all subsequent weeks of the study. Nausea was the most common adverse event affecting 21% to 32% of individuals.[26,27] Linaclotide has also been evaluated in 2 phase III trials enrolling 1272 individuals to either 145 mg or PBO for 12 weeks. The primary endpoint, the percentage of individuals experiencing 3 or more CSBMs per week plus an increase of at least 1 CSBM per week for 9 of 12 weeks of the study, was achieved by 18% of patients receiving linaclotide compared with 4.5% in the PBO arm. The most common adverse event was diarrhea, affecting 16% of those receiving linaclotide.[28] Both received strong recommendations from the ACG for treating CIC based on high levels of evidence[18] with NNT of 4 and 6 for lubiprostone and linaclotide, respectively.[22] Plecanatide is the first agent to be tested under the FDA's new guidance endpoint for CIC trials. To be considered an overall responder, individuals must have 3 or more CSBMs per week and an increase of at least 1 CSBM per week from baseline for 9 of 12 study weeks; however, now both endpoints must be met for at least 3 of the last 4 weeks of the trial. In these studies, 2683 individuals were enrolled to consume 3 or 6 mg of plecanatide or PBO once daily. At the end of 12 weeks, 20.5% and 19.75% of all test subjects in the 3-mg and 6-mg cohorts, respectively, achieved this endpoint compared with 11.5% in the PBO group ($P<.001$ for both comparisons to PBO). The most common adverse event was diarrhea, occurring in 4.55%, 5.00%, and 1.30% of those consuming 3 or 6 mg of the test drug and PBO, respectively.[29,30]

Serotonin Agonists

Serotonin (5-HT) plays a major role in the GI tract, influencing motility, secretion, and sensory functions, and although there are 7 major 5-HT receptor subtypes, the 5-HT_4 subtype has been most frequently targeted in this class. Tegaserod, a partial 5-HT_4 agonist, was the first in this class to be approved for the treatment of CIC but was withdrawn from the US market in March 2007, as postmarketing trials revealed the potential for increased cardiovascular events.[31] Currently, none of the drugs in this class are approved for the treatment of CIC in the United States; however, prucalopride, a highly selective 5-HT_4 agonist is approved for the treatment of CIC in Canada and Europe. A recent meta-analysis of 6 international trials compared the likelihood of response to prucalopride characterized as the percentage of individuals experiencing an average of 3 or more CSBMs over a period of 12 weeks. Twenty-eight percent of patients

receiving prucalopride compared with 13% of patients receiving PBO achieved this endpoint ($P<.001$; NNT = 6.8). The most common adverse events included headaches, nausea, and diarrhea.[32] Prucalopride has received a strong recommendation for improving CIC symptoms based on moderate levels of evidence.[18]

Miscellaneous Agents

Multiple therapeutics are currently being used to treat clinically refractive patients based on their mechanisms of action or anecdotal/case reports documenting their benefits. These include the anti-inflammatory agent colchicine and the synthetic prostaglandin E_1 molecule misoprostol. Both are known to induce diarrhea as a side effect, and thus may be beneficial in rare cases. Other common agents, such as the macrolide antibiotic erythromycin, which stimulates motilin receptors throughout the GI tract, are also under investigation. Early data suggested that erythromycin may be an effective intervention[33]; however, subsequent motility testing has revealed a lack of prokinetic effects in children and adolescents[34] and also a paucity of colokinetic activity in adults.[35] Each of these interventions is also associated with severe side-effect profiles including abortifacient properties (misoprostol) and an ability to prolong cardiac QT(c) intervals (erythromycin). Consequently, these drugs should be considered only in rare instances when other laxatives have failed and other causes for CIC (eg, dyssynergia) have been ruled out.

SUMMARY

Constipation is a common chronic disorder that can significantly impact an individual's quality of life. Despite advances in our therapeutic armamentarium, the rates of CIC in this country continue to rise. Much of this can be explained by currently identified precipitants. The diagnosis of CIC can be made using standard criteria and, once made, a determination of the underlying etiology/etiologies should be undertaken. In many instances, these will be gleaned from the history and physical examination with routine diagnostic studies unnecessary in the absence of alarming clinical signs or symptoms. Specialized diagnostic testing may be warranted after the failure of initial laxative trials.

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