Chronic Constipation: Gastroenterohepatologist's Approach

Tomica Milosavljevic^a Dusan D. Popovic^{b, c} Dragana Danilo Mijac^{b, c}
Tamara Milovanovic^{b, c} Slobodan Krstic^{c, d} Miodrag N. Krstic^{b, c}

^aGeneral Hospital "Euromedik", Belgrade, Serbia; ^bClinic for Gastroenterohepatology, University Clinical Centre of Serbia, Belgrade, Serbia; ^cSchool of Medicine, University of Belgrade, Belgrade, Serbia; ^dEmergency Centre, University Clinical Centre of Serbia, Belgrade, Serbia

Keywords

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Abstract

Background: Constipation is a common problem in gastroenterological practice. The prevalence of constipation is about 16%. Constipation can be primary or secondary. **Summary:** The diagnostic and therapeutic approach to patients with constipation begins with a detailed history and physical examination. In selected cases, the use of additional diagnostic procedures is very important. This includes the use of laboratory, endoscopic, and radiological examinations, as well as advanced physiological testing (anorectal manometry, balloon expulsion test, colonic transit studies, and defecography). Constipation therapy can be both nonoperative and operative. Nonoperative therapy includes the application of a lifestyle measures, pharmacotherapy and biofeedback therapy. **Key Messages:** Two key things when taking a medical history and physical examination are to rule out the existence of alarm symptoms/signs and to rule out secondary constipation (primarily drug-induced). Therapy begins with lifestyle modification, and in case of failure, bulk or osmotic laxatives are used. In case of failure, the use of lubipro-

stone is indicated, as well as linaclotide. Surgical treatment of constipation is reserved for cases of refractory constipation, with delayed intestinal transit.

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Introduction

Constipation is a common problem in gastroenterological practice. Constipation is most often defined as infrequent and/or difficult bowel emptying, often accompanied by straining or a feeling of incomplete emptying [1–3]. However, an ideal, concise definition of constipation does not exist.

The prevalence of constipation is about 16%, varies in the range of 0.7–79.0%, and is higher in women [1, 4, 5]. The frequency of constipation increases with age so that its prevalence is as high as 33% in people aged 60–110 [1]. Notwithstanding this fact, constipation cannot be considered a normal consequence of aging [5].

The reason for the wide variation in the prevalence of chronic constipation is multifactorial. Different criteria for chronic constipation have been used in different studies. In addition, the structure of patients in different studies is different, primarily in terms of age, gender, comor-

bidity, and use of drugs. All of these factors can affect the prevalence of constipation. Since studies have been conducted in culturally diverse settings, cross-cultural constipation factors must also be considered [6]. Namely, in different cultures, there are different dietary habits, different tolerance of health problems, as well as different individual factors (genetics, microbiome, environmental hygiene, cytokines, and the nervous system) [6].

Primary and Secondary Constipation

Depending on the cause, constipation can be primary or secondary. Primary constipation can be divided into 3 types [7] as follows:

- Constipation with normal transit time
- Constipation with delayed transit time
- Anorectal dysfunction

Constipation with normal transit time most often occurs as functional constipation [7]. Functional constipation, together with irritable bowel syndrome, forms a group of functional bowel disorders [3]. Although the symptomatology of these 2 forms overlaps, the key differential diagnostic symptom is pain. Namely, in irritable bowel syndrome, in addition to constipation, abdominal pain is also present, more often than once a week [2]. The pain decreases after bowel movements or flatulence. In functional constipation, in addition to infrequent and difficult emptying, tension, and a feeling of incomplete evacuation are often present [2–4].

The diagnosis of functional bowel disorders is made on the basis of the Rome criteria [3, 8]. Based on Rome IV criteria, functional constipation is characterized by the presence of 2 or more of the following symptoms, for more than one-fourth (25%) of defecations [3, 8]:

- Straining
- Lumpy or hard stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction/blockage
- Manual maneuvers to facilitate evacuation
- Fewer than 3 spontaneous bowel movements per week

In addition to the abovementioned symptoms, it is necessary that loose stools are rarely present without the use of laxatives and that the criteria for IBS are not met [3, 8]. In addition, these criteria must be met for the last 3 months, with the onset of symptoms being at least 6 months before diagnosis [3, 8]. It is important to note that meeting the criteria for IBS does not exclude the existence of fecal evacuation disorder and slow transit constipation [4].

Table 1. Risk factors for constipation

Age
Female gender
Depression
Inactivity
Low calorie intake
Low income and low educational status
Side effects of certain medications
Physical and sexual abuse

Constipation with a delayed transit time is characterized by a slow passage of contents through the intestines and may be a consequence of disorders of the myenteric plexus and neurotransmission [7]. Anorectal dysfunction occurs as a consequence of dysfunction of the pelvic floor and sphincter muscles [5, 7]. Based on the World Health Organization guidelines [5], risk factors for constipation are shown in Table 1. Protective factors are physical activity and a diet rich in fiber [5].

Secondary constipation occurs as a consequence of other diseases and conditions. Disorders that can lead to constipation can be intrainestinal or extraintestinal. The reason for constipation can be mechanical obstruction, anorectal diseases, myopathies, neuropathies, endocrinopathies, metabolic disorders, low-fiber diet, immobility, psychiatric disorders, etc. [4, 5]. The use of some drugs (antidepressants, antiepileptics, antipsychotics, calcium channel blockers, antispasmodics, etc.) can also be a common cause of secondary constipation [5, 7]. Knowledge of the causes of secondary constipation is necessary for differential diagnosis.

Diagnosis

History and Physical Examination

The diagnostic approach to patients with constipation begins with a detailed history and physical examination [9]. It is necessary to take the anamnesis data on frequency of bowel emptying, stool consistency, associated symptoms/signs, dietary habits, etc. In order to more objectively assess constipation and monitor the effects of therapy, it is useful to use validated scales and questionnaires (e.g., Bristol stool chart, obstruction defecation score, quality of life assessment questionnaires, etc.) [9].

Two key things when taking a medical history and physical examination are to rule out the existence of alarm symptoms/signs and to rule out secondary constipation (primarily drug-induced). Alarm symptoms/signs often occur as a consequence of serious, organic diseases and require prompt and detailed gastroenterological examination. Alarm symptoms/signs are age >50 years, anemia, gastrointestinal bleeding, significant weight loss, palpable masses in the abdomen and rectum, new-onset constipation, family history positive for colorectal cancer and inflammatory bowel disease, etc. [10].

A detailed physical examination is indispensable in approaching patients with constipation. Examination of the abdomen should be used to assess painful sensitivity, organomegaly, palpable abdominal masses, and peristalsis. Examination of other organ systems is important in excluding secondary constipation.

Anorectal examination is important especially in a patient with symptoms/signs of anorectal disease and can be very useful in determining the cause of constipation. Symptoms of anorectal diseases occur in functional or organic disorders of this region. Symptoms of functional disorders occur due to dyssynergic activation of the pelvic floor muscles, sphincters, and rectum. Symptoms of organic anorectal diseases occur in the presence of organic substrate (inflammation, tumors, anal fissures, hemorrhoids, etc.). Anorectal diseases are manifested as a feeling of incomplete or obstructive defecation, urgency of defecation, changes in stool caliber, perianal pain, appearance of blood and mucus in the stool, etc. Inspection of the perianal region can determine the presence of scars, efflorescence, anal tags, warts, the presence of blood and pus, hemorrhoids, abscess, fistula, anal asymmetry, etc. Inspection during the defecation attempts may indicate rectal prolapse. Palpation assesses the tone of the anal sphincter, the presence of masses in the anal canal and rectum, the presence of fissures, etc. [11]. Determination of anal tone during pressing and squeezing by rectal examination is a useful method for proving synergy in patients with constipation, which directs further physiological testing [11, 12].

Advanced Physiological Tests

In patients who do not respond to the initial treatment of constipation, the use of advanced physiological testing is useful. These methods are primarily useful for the assessment of anorectal disorders, which cause constipation. Advanced physiological tests include:

- Anorectal manometry
- Balloon expulsion test
- Colonic transit studies

- Defecography (fluoroscopic/magnetic resonance imaging [MRI])

Anorectal manometry, based on the measurement of pressure changes during defecation attempts, enables quantification of functions of the internal and external anal sphincter, rectal sensation, anorectal reflex, and rectal compliance [11]. In patients with dyssynergic defecation, 4 patterns of the disorder can be registered manometrically [1, 13] which are as follows:

- Pattern 1 is characterized by a paradoxical increase in pressure and intrarectal pressure ≥ 45 mm Hg
- Pattern 2 is characterized by the inability to produce sufficient expulsive power, without an increase in intrarectal pressure and with a paradoxical increase in residual intra-anal pressure
- Pattern 3 is characterized by sufficient expulsive power but with insufficient reduction of intra-anal pressure (<20%)
- Pattern 4 is characterized by the inability to achieve adequate expulsive power, with no increase in intrarectal pressure and the absence/insufficient reduction of intra-anal pressure

The balloon expulsion test is performed using a balloon filled with water (usually 50 mL) [11]. If patients are able to evacuate the balloon, the diagnosis of dyssynergia is unlikely, with a sensitivity of 88% and a specificity of 89% [11, 14].

Colonic transit studies are performed using radiopaque markers [11, 15]. Laxative use should be discontinued at least 3 days before examination [15]. Abdominal radiography is used to assess the elimination of markers after 4 days. If retention of >20% of markers is present, 4 days, delayed transit is present [15].

Defecography is an additional diagnostic method that is important in diagnosing defecation dysfunction. Defecation dysfunction occurs in 20–81% of patients with chronic constipation [16]. Defecography can be performed using classical fluoroscopy or MRI. The advantage of MRI defecography is that in addition to showing the structure and function of the anorectum and pelvic floor, it also enables the visualization of the surrounding structures (organs and muscles) [16]. MRI defecography avoids exposure to ionizing radiation.

Therapy

Constipation therapy can be both nonoperative and operative [9]. The vast majority of patients are treated with nonoperative methods. Operative therapy of consti-

pation is very rarely indicated in strictly selected cases. Nonoperative therapy includes the application of lifestyle measures, pharmacotherapy, and biofeedback therapy.

Lifestyle Measures

Lifestyle measures include sufficient fiber intake (20–30 g/day), adequate fluid intake (1.5–2 L/day), physical activity, and avoidance of food and medications that cause constipation [3, 17]. If there is no success on the lifestyle measures, pharmacotherapy is indicated. For the treatment of constipation, the following can be used: bulk-forming agents, osmotic laxatives, stimulant laxatives, secretory laxatives, prokinetics, emollients, and lubricants [17].

Bulk-Forming Agents

Bulk-forming agents increase the volume and reduce the consistency of the stool. Treatment of constipation usually begins with these preparations. The most commonly used are *Plantago ovata* and methylcellulose. Compared with placebo, soluble fiber led to improvements in global symptoms, straining, pain on defecation, stool consistency, and stool frequency [18]. The use of *P. ovata* in patients with idiopathic chronic constipation or constipation after proctological interventions leads to improved bowel emptying, improved stool consistency, and reduced pain, as well as feelings of incomplete emptying [19].

Osmotic Laxatives

Osmotic laxatives are nonabsorbable molecules and ions, which osmotically draw water into the intestinal lumen. These laxatives increase stool volume, reduce its consistency, and improve peristalsis [17]. Osmotic laxatives are polyethylene glycol (PEG), lactulose, sorbitol, mannitol, magnesium citrate, magnesium hydroxide, magnesium sulfate, sodium sulfate, etc. Osmotic laxatives are comparatively easy to use and inexpensive.

Lactulose and PEG are recommended for the treatment of chronic constipation, with PEG being preferred [17]. This group of drugs can be used as the first-line therapy for chronic constipation [1].

Although lactulose and PEG have a similar mechanism of action, it is not the same. Namely, lactulose is metabolized by colonic bacteria, producing short-chain fatty acids and gases [20, 21]. Short-chain fatty acids are partially absorbed and have a laxative effect [20, 21]. Unlike lactulose, PEG is not metabolized or absorbed.

The mechanism of action of these osmotic laxatives causes differences in the therapeutic effect. Namely, with

the use of lactulose, the effect in addition to the dose depends on the metabolism of lactulose in the colon, as well as mucosal absorption, and the dose-response curve of lactulose is nonlinear [20, 21]. This means that increasing the dose of lactulose does not linearly follow the effect (stool weight and consistency) [20]. When using PEG, the dose-response curve is linear [20, 21]. Increasing the dose of PEG increases the effect [21]. Lactulose and PEG accelerate colonic transit [21].

Because lactulose metabolism produces gas in the colon, gas-related side effects (e.g., flatulence) are more common with its use [20]. The side effects of osmotic laxatives are dose-dependent, and the most common side effects are abdominal cramping and bloating [3]. Excessive use of osmotic laxatives can lead to electrolyte imbalance and volume overload, in patients with heart and renal failure [7, 17]. Osmotic laxatives may be used daily and long-term.

Stimulating Laxatives

Stimulating laxatives (bisacodyl, sodium picosulfate, sennoside, etc.) stimulate peristalsis and thus cause bowel emptying. Stimulating laxatives are used in patients who do not respond to bulk-forming and/or osmotic laxatives [17]. They are recommended as rescue therapy [17]. The most common side effects are abdominal pain, distension, diarrhea, nausea, and vomiting [2, 3, 17].

Secretory Laxatives

Secretory laxatives cause the secretion of chloride into the intestinal lumen. This group of drugs includes lubiprostone, linaclotide, and plecanatide.

Lubiprostone is a bicyclic fatty acid, which acts on chloride channels (type 2) localized on the apical membrane of intestinal cells [22]. By stimulating these channels, the secretion of chloride increases, and passively sodium and water, which leads to increased hydration of the stool and accelerated peristalsis (without acting on smooth muscles) [22]. Lubiprostone is administered in a dose of 8–24 µg, twice a day [22, 23]. Lubiprostone is an effective and safe drug. Its use reduces the severity of constipation, stool consistency, tension, bloating, and abdominal pain [24]. Side effects may include nausea, vomiting, and diarrhea [24].

Linaclotide is also a secretory laxative. According to its chemical composition, it is a peptide consisting of 14 amino acids [25]. It activates guanylate cyclase, which is located on the luminal membrane of intestinal cells, and stimulates the synthesis of cyclic guanosyl monophosphate, which stimulates the opening of chloride channels

[25]. Increased secretion of chloride passively leads to secretion of water and sodium, which leads to softening of the stool. Linaclotide is administered in a dose of 145 µg, once a day [23–26]. Linaclotide reduces the severity of constipation, stool consistency, and abdominal discomfort [27]. The main side effect of lubiprostone is diarrhea [27].

Plecanatide has a similar mechanism of action to linaclotide. It is a natural analog of uroguanylin, a peptide agonist of the guanylate cyclase-C receptor [28]. Its efficacy and safety profile are similar to those for linaclotide [28].

Prokinetics

Prucalopride is a 5-hydroxytryptamine 4 agonist, which acts on these receptors and causes accelerated peristalsis, and accelerates intestinal transit [3]. It belongs to the group of prokinetics. Due to its prokinetic effect, it is used for the treatment of primary and secondary constipation [29]. There is no arrhythmogenic potential. The dose is 2–4 mg, once a day [3, 29]. Increases the frequency of bowel emptying, reduces stool consistency, and strain [3]. Side effects include headache, nausea, and diarrhea [3].

Methylnaltrexone

Methylnaltrexone is a selective µ-opioid receptor antagonist. It acts on peripheral opioid receptors, while its passage through the blood-brain barrier is limited [30]. Thus, it antagonizes the peripheral effect of opioids (e.g., constipation), while it has no effect on the central, analgesic effect [31]. It is applied subcutaneously. The dose is 8–12 mg (or 0.15 mg/kg), on the second day or at 24 h [30]. It is effective in the treatment of constipation due to the use of opioids [31]. The most common side effects are abdominal pain and flatulence [31].

Surgical Treatment

Surgical treatment of constipation is reserved for cases of refractory constipation, with delayed intestinal transit, which cannot be adequately treated in any other way [17]. The 2 main treatment modalities are cecostomy and colectomy. Different techniques are used as follows: segmental colectomy with ileorectal, ileosigmoid or cecorectal anastomosis, proctocolectomy with ileoanal anastomosis, etc. Each patient requires an individual approach. It is necessary that surgical treatment is carried out in expert institutions. These procedures can also be performed laparoscopically.

Conclusion

A stepwise approach is recommended in the treatment of chronic constipation [32]. The diagnostic and therapeutic approach to patients with constipation begins with a detailed history and physical examination. These methods should exclude the presence of alarming symptoms and signs (blood in the stool, unexplained weight loss, inflammatory bowel disease, family history of colorectal cancer, the presence of other symptoms, and signs of organic diseases) [1, 33]. If an organic disease is suspected, it is necessary to perform appropriate diagnostic procedures (laboratory, colonoscopy, radiological methods, etc.) and in case of a positive finding, apply appropriate therapy [1, 33]. By selective application of specific diagnostic procedures (laboratory, imaging methods, etc.), it is necessary to exclude/confirm the presence of secondary causes of constipation and apply appropriate therapy. Be sure to take data on the use of drugs that can cause constipation and discontinue their use or reduce the dose [33].

After the basic diagnosis, it is necessary to apply general measures (improved rehydration, physical activity, and fiber intake) (Step I) [32]. If these measures have no effect, bulking agents are used (Step Ib) [1, 32, 33].

In case of failure, it is necessary to assess whether there are symptoms of evacuation disorders [32]. When constipation caused by pelvic floor dysfunction is suspected, appropriate diagnostic procedures are applied (colonoscopy, anal manometry, balloon expulsion test, defecography, colon transit study, etc.) [1, 32].

If there is no evacuation disorder, osmotic laxatives or stimulant laxatives are used first, alone or in combination with bulking agents (Step II) [32]. If these laxatives have no effect, prokinetics, secretagogues, or opioid antagonists are used (Step III) [1, 32]. Step III drugs are used only if Step II laxatives are ineffective, due to the higher cost of treatment and more side effects.

Step IV involves the use of a combination of laxatives from Step I–III, enemas, and lavage [32]. If all therapy is ineffective, sacral nerve stimulation and surgery are used (Step V) [32].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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