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Diagnosis and treatment of constipation: a clinical update based on the Rome IV criteria



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ABSTRACT

The aim of this study was to evaluate the published professional association guidelines regarding the current diagnosis and treatment of functional intestinal constipation in adults and to compare those guidelines with the authors' experience to standardize actions that aid clinical reasoning and decision-making for medical professionals. A literature search was conducted in the Medline/PubMed, Scielo, EMBASE and Cochrane online databases using the following terms: chronic constipation, diagnosis, management of chronic constipation, Roma IV and surgical treatment. Conclusively, chronic intestinal constipation is a common condition in adults and occurs most frequently in the elderly and in women. Establishing a precise diagnosis of the physiopathology of functional chronic constipation is complex and requires many functional tests in refractory cases. An understanding of intestinal motility and the defecatory process is critical for the appropriate management of chronic functional intestinal constipation, with surgery reserved for cases in which pharmacologic intervention has failed. The information contained in this review article is subject to the critical evaluation of the medical specialist responsible for determining the action plan to be followed within the context of the conditions and clinical status of each individual patient.

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Diagnóstico e tratamento da constipação crônica: atualização baseado nos critérios Roma IV

R E S U M O

Palavras-chave:

Constipação crônica
Disfunção do assoalho pélvico
Inércia cólica
Laxativos
Tratamento cirúrgico

O objetivo deste trabalho foi avaliar os consensos de sociedade de especialistas e *guidelines* publicados sobre o diagnóstico e tratamento da constipação intestinal crônica em adultos, e confrontar com a experiência dos autores, a fim de padronizar condutas que auxiliem o raciocínio e a tomada de conduta do médico. Foi realizada busca na literatura científica, mais precisamente nas bases de dados eletrônicos Medline/Pubmed, Scielo, EMBASE and Cochrane, tendo sido utilizado os seguintes descritores: *chronic constipation, diagnosis, management of chronic constipation, Roma IV and surgical treatment*. Pode-se concluir que constipação crônica é condição comum em adultos, ocorrendo com maior frequência em idosos e mulheres. Identificar com precisão a fisiopatologia presente na constipação crônica funcional é complexo, requerendo a realização de testes funcionais nos casos refratários. O entendimento da motilidade intestinal e do mecanismo defecatório é importante para o manejo da constipação intestinal crônica funcional, sendo o tratamento cirúrgico indicado para casos selecionados, onde a abordagem medicamentosa não surtiu efeito. As informações contidas neste artigo de revisão devem ser submetidas à avaliação e à crítica do médico especialista responsável pela conduta a ser tomada, frente à sua realidade e ao estado clínico de cada paciente.

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Introduction

Chronic Intestinal Constipation (CIC) is a highly prevalent ailment in Western society, afflicting from 15% to 20% of adults, of whom 33% are over the age of 60 years, with a notably female predominance.¹⁻⁵ Although the syndrome is characterized by intestinal symptoms that require a high level of medical attention, in most cases, it is not life threatening or debilitating for the patient; however, it has a significant effect on quality of life, particularly in chronic cases.^{1,6,7}

The diagnosis of intestinal constipation requires a careful analysis of the clinical history and physical examination, including proctological assessments and further diagnostic investigation in cases with persistent symptoms and refractoriness to initial treatment (diet, lifestyle changes and fiber-based medications). Other anatomical disorders that may alter intestinal transit should be excluded, mainly in cases of recent-onset or unexplained constipation, constipation with anal bleeding and/or unexplained weight loss, and altered intestinal habits in the elderly population.^{2,8-10}

Recommendations for the management of constipation are based on the GRADE system, which divides them in strong (1) and weak (2), with high (A), moderate (B) or low (C) quality of evidence.

Classification

Intestinal constipation may be classified as primary or secondary.^{1,6,11}

Primary or functional

An entity in which the cause of constipation cannot be identified from the clinical history and physical examination.¹² Following functional tests, primary constipation may be further classified as: Normal transit constipation (NTC); Slow transit constipation (STC), colonic inertia; outlet obstruction or pelvic floor dysfunction; and combined causes (slow transit constipation and pelvic floor dysfunction).

Nullens et al. evaluated 1411 patients with chronic constipation at a medical center and found that 68% had constipation with normal transit, 27.6% with outlet obstruction and 4.3% with slow transit or colonic inertia.¹³ Similar findings were reported by Nyam et al. in a study of more than 1000 patients with chronic constipation. Their study reported 59% with normal intestinal transit, 25% with outlet obstruction, 13% with slow transit and 3% with a combination of slow transit and outlet obstruction.¹⁴

Secondary or organic

Constipation for which the clinical assessment and workup identifies intestinal or extra-intestinal abnormalities, metabolic or hormonal factors and medications as responsible for the defecatory disturbances.¹⁵

- Intestinal: Tumors, diverticulitis, inflammatory strictures, ischemia, volvulus, endometriosis, postoperative strictures, anal fissure, thrombosed hemorrhoids, mucosal prolapse, ulcerative proctitis.

Table 1 – Historical evolution of the Rome consensuses and their diagnostic criteria.

Symptoms and diagnosis	Rome I	Rome II	Rome III	Rome IV
Straining to evacuate	>25% of defecations	>25% of defecations	>25% of defecations	>25% of defecations
Lumpy or hard stools	>25% of defecations	>25% of defecations	>25% of defecations	>25% of defecations
Sensation of incomplete evacuation	>25% of defecations	>25% of defecations	>25% of defecations	>25% of defecations
Sensation of anorectal obstruction/blockage	–	>25% of defecations	>25% of defecations	>25% of defecations
Manual maneuvers to facilitate defecations	–	>25% of defecations	>25% of defecations	>25% of defecations
Less than three evacuations per week	Yes	Yes	Yes	Yes
Number of criteria for diagnosis	≥2	≥2	≥2	≥2
Chronological factor	3 months	12 weeks/12 months	3–6 months ^a	3–6 months ^a

^a Criteria fulfilled over the previous 3 months with symptom onset at least 6 months prior to diagnosis.

- Medication-induced: Antidepressants, antiepileptics, anti-histamines, antispasmodics, anticholinergics, calcium channel blockers, calcium and iron supplements, and non-hormonal anti-inflammatories.
- Metabolic diseases: Hypothyroidism, hypoparathyroidism, hypercalcemia, hypokalemia, hypomagnesemia, diabetes mellitus, uremia, and heavy metal poisoning.
- Neuropathies: Medullar lesions or neoplasia, cerebrovascular disease, multiple sclerosis, autonomic neuropathy, and Parkinson's disease.
- Myopathies: Amyloidosis and scleroderma.
- Other conditions: Chagas disease, cognitive impairment, immobility.

Clinical diagnosis

Frequently, patients and perhaps medical professionals less experienced in disturbances of the pelvic floor define constipation only in terms of evacuatory frequency and the consistency of the feces.⁵ However, a cross-sectional study by Collete et al.^{16,17} found low concordance ($\kappa = 0.59$) between self-reported constipation and constipation confirmed by certain consensus criteria, for example, Rome I,¹⁸ II,¹⁹ III²⁰ and IV (Table 1).²¹

Therefore, with the intention of standardizing the diagnosis and management of intestinal constipation, researchers initially described the criteria of Rome I,¹⁸ which included four symptoms that should be present over the previous 3 months: less than three evacuations per week, straining to evacuate, the presence of hardened feces and a sense of incomplete evacuations. Subsequently, the Rome II criteria¹⁹ encompassed the four aforementioned symptoms and two additional symptoms: a sensation of obstruction or interruption of evacuation and manual maneuvers to facilitate evacuations.

Finally, the Rome III²⁰ and Rome IV²¹ criteria chiefly modified the chronological factor, that is, the symptoms should have originated 6 months before the diagnosis and have been present during the previous three months.

The medical history of patients with constipation should be analyzed along with fecal consistency (Fig. 1), defecatory frequency, straining when defecating, digital maneuvers, sensation of incomplete evacuations, pain and abdominal discomfort, laxative use, surgical history, comorbidities, lifestyle, diet and occupation.¹⁵ Warranting crucial emphasis is the



Fig. 1 – Bristol scale of fecal consistency.

considerable overlap of symptoms between the functional intestinal disturbances described in Rome IV – Irritable Bowel Syndrome (IBS), functional constipation, functional diarrhea, functional distention/swelling of the abdomen, non-specific functional disturbances and Opiate-Induced Constipation (OIC), which may vary over the ongoing follow up of the patient.²¹ The presence of pain is predominant in patients with IBS, in contrast to functional intestinal constipation, in which the painful sensation is of low intensity and is also not the predominant symptom. In the Rome IV consensus, a new syndrome denominated opiate-induced constipation was added, which is associated with the chronic use of these medications.^{21,22}

The Bristol stool form scale may be useful for patients to assess and describe aspects of their feces, facilitating the recognition of the constipation severity.²³ Rome IV suggests the use of the Bristol scale and bowel diaries, which are good predictors of colonic transit time and efficient methods to characterize bowel habits and facilitate the diagnosis.²⁴

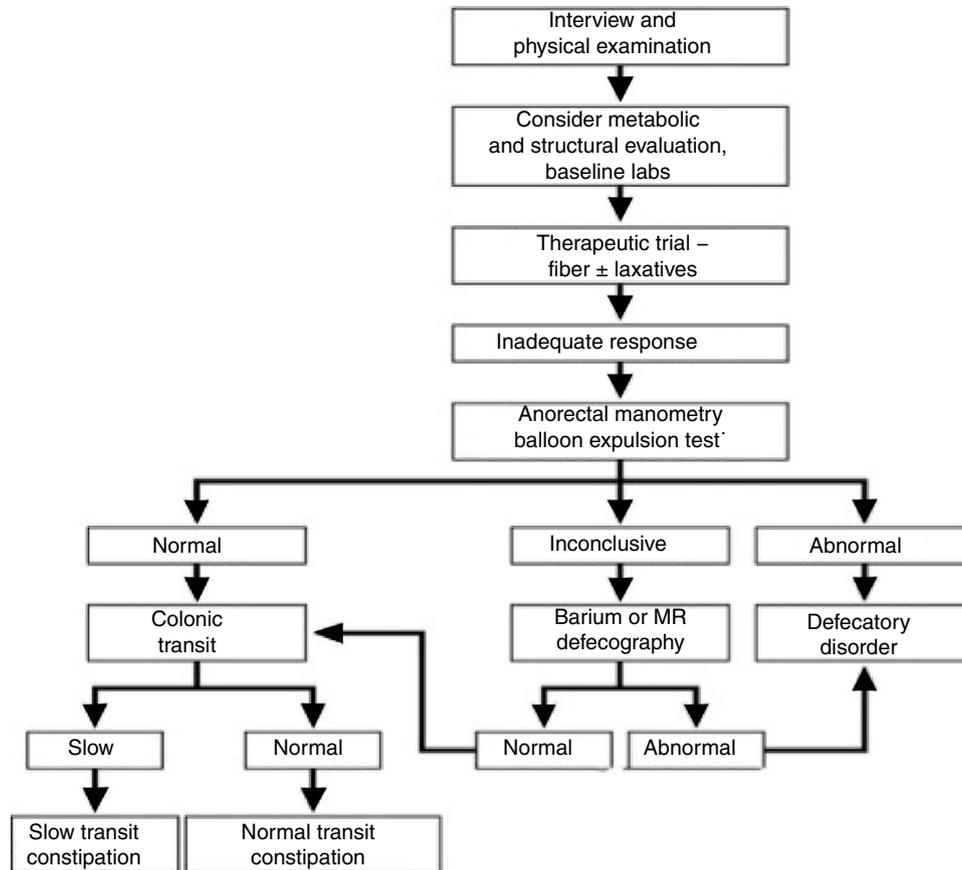


Fig. 2 – Diagnostic algorithms for chronic constipation. MR, magnetic resonance. Adapted of Bharucha et al.¹ *Because anorectal manometry, rectal balloon expulsion test may not be available in all practice settings, it is acceptable, in such circumstances, to proceed to assessing colonic transit with the understanding that delayed colonic transit does not exclude a defecatory disorder.

Evaluation of constipation (Fig. 2)

- (a) The clinical history obtained and physical examination conducted in patients with intestinal constipation should seek to identify its beginning, the presence of a causal factor and alarming features.

A detailed analysis of the clinical history enables the assessment of whether the patient does indeed fulfill the objective clinical criteria for intestinal constipation, such as the aforementioned Rome IV criteria. Such analysis confirms the presence of risk factors for constipation such as an inadequate diet, low fluid intake, a sedentary lifestyle, psychiatric disease, medication use, comorbidities, prior surgery and symptoms of irritable bowel syndrome.^{19,21,23} Moreover, it allows the identification of alarming features such as hematochezia, significant weight loss, a family history of cancer, anemia, anal bleeding and alterations in intestinal behavior that indicate the need for colonoscopy and/or radiological examination to rule out secondary causes of constipation.

The medical history and proctological examination may suggest the cause of intestinal constipation. In the case of

obstructed defecation, the history verifies the presence of excessive and prolonged evacuatory efforts, low feces volume, the sensation of incomplete evacuation and the need for digital maneuvers of the perineum, anus or vagina, along with a sensation of vaginal bulging. An examination of the perineal region and anus with a digital rectal and vaginal examination may identify sphincter hypertonia, the presence of a rectocele or enterocele, fecal impaction, and secondary causes of constipation (anorectal neoplasia, rectal prolapse, anal fissure, stenosis and extrinsic compression).^{24,25}

- (b) Fecal, radiological or endoscopic examinations in constipation without alarming features is not routinely indicated.
- (c) Blood tests: Tests include a complete blood count, serological test for Chagas disease (for patients in endemic areas), serum calcium, thyroid, parathyroid and renal function tests, fasting blood glucose levels, and potassium and magnesium levels. These examinations should be ordered mainly in clinically suspicious cases and not as routine investigations.
- (d) Barium enema: This examination may be recommended to identify colorectal diseases (diverticular disease, neoplasia

and megacolon) although currently, the test is less frequently used.

A complementary workup to investigate constipation should be conducted 12 weeks after clinical treatment, in persistent cases or following a lack of success with dietary measures and functional readjustment.¹

- (e) Anorectal manometry: This test should be performed in cases of chronic constipation refractory to medical treatment, with the aim of identifying or excluding aganglionosis (chagasic megacolon or Hirschsprung's disease) and psychogenic megacolon. The manometry provides important information about the rectoanal inhibitory reflex, the musculature tone of the internal and external sphincter, and the rectal sensitivity, capacity and compliance.
- (f) Videodefecography, magnetic resonance defecography or echodefecography: These examinations should be performed to study pelvic floor disturbances, preferably conducted together with anorectal manometry in patients with signs suggesting Obstructed Defecation (OD) or obstructed exit by history and physical examination. Videodefecography is the radiological study of evacuatory dynamics and is useful to investigate anatomical abnormalities responsible for obstructed exit such as rectocele, intussusception, enterocele, sigmoidocele, anismus and paradoxical contraction of the puborectalis muscle.^{26,27} In addition to structural abnormalities, VDG may be used to assess pelvic floor mobility, diagnose perineal descent syndrome and evaluate the degree of rectal emptying. Recently, because of its high radiation exposure to young and elderly patients, some authors have performed videodefecography using only video recording, without radiography, whereas others have chosen magnetic resonance defecography or echodefecography, which are well correlated with the results obtained by VDG, without the use of ionizing radiation.^{28,29}
- (g) Colonic Transit Time (CTT): The CTT examination is conducted to assess the time required for elimination of the feces and may be performed with the use of radiopaque markers or by the scintigraphy method.²⁵ A capsule containing 24 radiopaque markers is swallowed and an abdominal radiography is taken 5 days later. Normally, less than 5 markers should be seen in the colon.³⁰ It is a simple and useful test because it allows the identification of three basic patients: those with normal transit time (who eliminate 80% of the markers by the fifth day), those with slow transit (who retain more than 20% of the marker by the fifth day, distributed throughout the colon), and those with outlet obstruction (who retain more than 20% of the markers on the fifth day, accumulated in the rectosigmoid region). CTT has the advantages of being a low-cost and relatively non-invasive test; its disadvantage is exposure to radiation, albeit in low doses. It should be the first test performed when the clinical and proctologic examination does not indicate outlet obstruction. CTT may be recommended to assess the response to the clinical or surgical treatment of chronic constipation.
- (h) Balloon expulsion test: This is a simple and useful method, primarily indicated as a screening test for symptoms of outlet obstruction (pelvic floor dyssynergia). A balloon

filled with water (50–60 mL) is positioned in the rectal ampulla and the patient is asked to make an evacuatory effort to expel it. When expulsion is achieved, pelvic floor dysfunction may be excluded. This test has been recommended by most constipation evaluation guidelines.³¹

- (i) Electromyography of the anal sphincter (EMG): This method is recommended to diagnose paradoxical contraction of the puborectalis muscle. The test measures the electrical activity of the striated component of the anorectal sphincter during voluntary contraction, at rest, and with coughing and evacuatory effort. Its major disadvantage is patient pain due to the needle insertion in the external anal sphincter to obtain the response.
- (j) Hydrogen breath test: Recommended to assess the oro-cecal transit time, this test is a valuable aid to differentiate dysmotility of the gastrointestinal tract (superior and inferior) from isolated colonic inertia. It is recommended for serious and refractory cases of colonic inertia, prior to the indication of a colectomy.

Clinical treatment

The initial management of patients with symptomatic constipation typically includes lifestyle modification, a fiber-rich diet and increased fluid intake. Although the efficacy of this approach cannot be estimated reliably because the quality of the evidence is very low (1C).

Empirical treatment of constipation comprising an increase in dietary fiber content to approximately 25–30 g per day and increased hydration (2–2.5 L per day) is an inexpensive and effective method to increase evacuatory frequency and reduce laxative use.^{22,32}

Thus, the combined beneficial therapeutic effect, low cost, safety and other general health benefits of these methods justify their use as the first step in the treatment of constipation, notably in primary healthcare.²

Laxatives

When the aforementioned lifestyle and dietary measures fail, the second step in the management of intestinal constipation involves the use of osmotic laxatives, such as polyethylene glycol (PEG) (1A) and lactulose (1C) and laxatives associated with the formation of fecal matter (psyllium, methylcellulose and polycarbophil)^{32–35} (1C). Osmotic laxatives create an intra-luminal osmotic gradient that increases electrolyte secretion, resulting in reduced fecal viscosity and increased fecal biomass, with beneficial effects on peristalsis.

A review of randomized studies that compared polyethylene glycol with lactulose found PEG superior, with better results regarding the frequency and consistency of the feces and fewer abdominal pain symptoms.³⁴

Stimulating laxatives (senna, cascara buckthorn, bisacodyl, sodium picosulfate and anthraquinone derivatives) may be used for cases in which fiber and osmotic laxatives have not been successful (1B). In addition to reducing the absorption of water and stimulating intestinal motility, they also increase prostaglandin release. Their main advantage is the rapid mechanism of action, with evacuation occurring on

average within 6–12 h. Because of their collateral effects (electrolyte disturbances, hypokalemia and abdominal colic), they should not be used for prolonged periods.

Prokinetic pharmaceuticals such as Tegaserod (a 5-HT₄ agonist) and Prucalopride (a highly selective 5-HT₄ receptor agonist) act to increase peristalsis, thereby accelerating gastrointestinal transit (1B). They are recommended for cases unresponsive to laxatives. Prucalopride may be used at a dose of 2–4 mg per day and has been considered a good option for the treatment of chronic constipation in women who do not respond to fiber and laxatives. In a comparative study with placebo, Prucalopride showed clear superiority and the ability to produce three intestinal movements per week compared to placebo.³⁶

Probiotics have been recommended with the aims of restoring the intestinal microbiota, increasing evacuatory frequency, improving fecal consistency and diminishing flatulence (2C). The most studied bacteria are *Bifidobacterium lactis* DN 173 010, *Lactobacillus casei* Shirota, VSL#3 (a mixture of 8 different strains) and *E. coli* Nissle 1917. Currently however, scientific evidence confirming their benefit in the treatment of CIC is lacking.^{37,38}

Enemas or suppositories may be used in select cases of chronically constipated patients (e.g., those with psychogenic megacolon) or fecal impaction, in which the initial measures (fiber, fluids and laxatives) were ineffective. Transanal irrigation stimulates the rectum and hydrates the feces, allowing intestinal discharge. The use of these methods should be limited to brief periods, and the agents may be composed of sodium phosphate or vegetable oils.

Other drugs stimulate the secretion of fluids by the intestine (Lubiprostone and Linaclotide), thereby increasing the fecal water content. Currently in use in various European countries and the USA, such agents have shown promising results (1A).^{1,4} Lubiprostone stimulates the intestinal secretion of fluids via chlorine channels and has been prescribed for adults with chronic constipation. The modulation of biliary acids at the intestinal level has also been employed for the treatment of chronic intestinal constipation. Elobixibat (A3309) is a non-absorbable molecule that alters the absorption of bile at the terminal ileus, which increases the supply of biliary acids in the proximal colon, with a consequent increase in secretion and colic motility.

Treatment of pelvic floor dysfunction (biofeedback)

Biofeedback has been used to train the musculature of the pelvic floor through specific exercises, which, in cases of pelvic dysfunction (synonyms: anismus, paradoxical contraction of the puborectalis muscle or spastic pelvic floor syndrome), aids the relaxation of this musculature during evacuatory efforts (2C). This approach is recommended for children over 6 years of age and adults. Biofeedback therapy with the aim of training patients to relax the pelvic floor during defecation is appropriately recommended for the treatment of patients with symptoms of pelvic dysfunction.

The success rate of biofeedback therapy for pelvic floor dysfunction varies widely between 40% and 90%.³⁴ In a randomized trial, Chiaroni et al.³⁹ demonstrated clinical improvement of intestinal constipation after 6 weeks of

treatment in 80% of the group treated with biofeedback versus 22% of patients using laxatives alone.

Surgical treatment

A detailed and diligent evaluation of the patient is required prior to any invasive treatment for intestinal constipation.⁴⁰ Furthermore, the causes of obstruction should be treated prior to the use of surgical procedures to alter colonic transit. For the treatment of rectal disorders associated with slow transit, a thorough investigation is imperative to treatment success.⁴¹

Slow transit constipation

Patients with STC refractory to conservative treatment and without outlet obstruction may benefit from subtotal colectomy with ileorectal anastomosis. The presence of dysmotility of the superior gastrointestinal tract (gastroparesis and intestinal pseudo-obstruction), severe psychiatric disorders, and systemic neurological disorders such as diabetes mellitus and multiple sclerosis should be excluded before surgical treatment is indicated.

The success rate of full colectomy with ileorectal anastomosis varies between 72.5% and 100%, whereas segmental colectomy may be associated with high failure rates.^{42,43} However, the constipation recurrence rates after total colectomy range between 8% and 33%; additionally, postoperative complications such as diarrhea and fecal incontinence may occur, which generally improve after one year of follow up.⁴⁴

Some studies report that the most common postoperative complication of total colectomy with ileorectal anastomosis is intestinal obstruction by adhesions, which occurs in between 7% and 50%.⁴⁵ Picarsky et al. reported an incidence of this complication of 10% after 27 months of follow up.⁴³

Pelvic floor dysfunction (outlet obstruction)

The principal indications for the surgical treatment of constipation by obstructed defecation syndrome are rectocele, enterocele, sigmoidocele and prolapse with the appropriate surgical option assessed for each case individually.

Although sacral neuromodulation to control slow transit constipation and outlet obstruction appears effective, the results are highly variable depending on the study. The United States Food and Drug Administration (FDA) have not licensed its use for constipation to date. After definitive implantation, most studies have demonstrated symptomatic improvement in less than 50% of patients after follow up.^{46–50}

Conclusion

In chronic constipation cases, alarming features should first be excluded and a family history of cancer probed. The clinical history and physical examination, specifically with functional sphincter examination through digital rectal examination should be the first step of the clinical evaluation.

The first line of medical treatment is the use of a fiber-rich diet, increased fluid intake, physical exercise and attempts

to recognize and follow evacuatory desire most of the time. Notably, a diary of evacuatory frequency and fecal consistency and form (Bristol scale) should be kept during clinical treatment.

Additional investigative tests may be employed in refractory cases. In suspected cases of pelvic floor dysfunction (outlet obstruction), anorectal manometry, videodefecography or magnetic resonance defecography should be used. For outlet obstruction, specific treatment should be instituted, for example, biofeedback for paradoxical contraction of the puborectalis muscle or surgical treatment for rectocele, enterocele, prolapse or rectoanal intussusception.

However, in cases of suspected colonic inertia, a detailed study of the colorectal function should be conducted with a colonic transit time study with radiopaque markers and defecography to rule out the presence of associated pelvic floor dysfunction.

Notably, because more than 50% of individuals with pelvic defecatory disturbances have slow intestinal transit times, correlation between the functional tests and the clinical data is crucial.

An indication for colectomy to treat slow transit constipation is exceptional and is only recommended for selected cases, only after conservative measures have failed. The treatment of choice is subtotal colectomy with ileorectal anastomosis, which should be performed at specialized tertiary centers.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

- Bharucha AE, Dorn SD, Lembo A, Pressman A. American gastroenterological association medical position statement on constipation. *Gastroenterology*. 2013;144:211-7.
- Bharucha AE, Pemberton JH, Locke GR III. American gastroenterological association technical review on constipation. *Gastroenterology*. 2013;144:218-38.
- Chang FY, Chen PH, Wu TC, Pan WH, Chang HY, Wu SJ, et al. Prevalence of functional gastrointestinal disorders in Taiwan: questionnaire-based survey for adults based on the Rome III criteria. *Asia Pac J Clin Nutr*. 2012;21:594-600.
- Jiang C, Xu Q, Wen X, Sun H. Current developments in pharmacological therapeutics for chronic constipation. *Acta Pharm Sin B*. 2015;5:300-9.
- Santos Junior JCM. Constipação intestinal. *Rev Bras Coloproct*. 2005;25:79-93.
- Tack J, Muller-Lissner S, Stanghellini V, Boeckxstaens G, Kamm MA, Simren M, et al. Diagnosis and treatment of chronic constipation: a European perspective. *Neurogastroenterol Motil*. 2011;2:697-710.
- Neri L, Basilisco G, Corazziari E, Stanghellini V, Bassotti G, Bellini M, et al. Constipation severity is associated with productivity losses and healthcare utilization in patients with chronic constipation. *United Eur Gastroenterol J*. 2014;2:138-47.
- Acosta A, Camilleri M. Elobixibat and its potential role in chronic idiopathic constipation. *Ther Adv Gastroenterol*. 2014;7:167-75.
- Oliveira JC, Albuquerque FRPC, Lins IB. Projeção da população do Brasil por sexo e idade para o período de 1980-2050 – Revisão 2004. Rio de Janeiro: IBGE; 2004.
- Campion EW. The oldest old. *N Engl J Med*. 1994;330:1819-20.
- Camilleri M. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med*. 2012;367:1626-35.
- Mertz H, Naliboff B, Mayer E. Physiology of refractory chronic constipation. *Am J Gastroenterol*. 1999;94:609-15.
- Nullens S, Nelsen T, Camilleri M, Burton D, Eckert D, Iturrino J, et al. Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut*. 2012;61:1132-9.
- Nyam DC, Pemberton JH, Ilstrup DM, Rath DM. Long-term results of surgery for chronic constipation. *Dis Colon Rectum*. 1997;40:529-30.
- Lindberg G, Hamid S, Malfertheiner P, Thomsen O, Fernandez LB, Garisch J, et al. World Gastroenterology Organization global guideline: constipation—a global perspective. *J Clin Gastroenterol*. 2011;45:483-7.
- Collete VL, Araújo CL, Madruga SW. Prevalência e fatores associados à constipação intestinal: um estudo de base populacional em Pelotas, Rio Grande do Sul Brasil. 2007. *Cad Saude Publica*. 2010;26:1391-402.
- Collete VL. Tese de Mestrado Prevalência e fatores associados à constipação intestinal: um estudo de base populacional. Universidade Federal de Pelotas; 2008.
- Thompson WG, Drossman DG, Heaton DA, Kruis KWW. Irritable bowel syndrome: guidelines for the diagnosis. *Gastroent Int*. 1989;2:92-5.
- Drossman DA. The functional gastrointestinal disorders and the Rome II process. *Gut*. 1999;45 Suppl 2:II1-5.
- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130:1480-91.
- Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology*. 2016, <http://dx.doi.org/10.1053/j.gastro.2016.02.032> [Epub ahead of print].
- Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. *Gastroenterology*. 2016;150:407-1393.
- Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920-4.
- Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Roma IV. *Gastroenterology*. 2016;150:1262-79.
- Ternent CA, Bastawrous AL, Morin NA, Ellis CN, Hyman NH, Buie WD. Practice parameters for the evaluation and management of constipation. *Dis Colon Rectum*. 2007;50:22-013.
- Sobrado CW, Pires CEF, Amaro E, Cerri GG, Habr-Gama A, Kiss DR. Videodefecografia. Aspectos técnicos atuais. *Radiol Bras*. 2004;37:283-5.
- Sobrado CW. Contribuição da videodefecografia dinâmica computadorizada no estudo de doentes submetidos a graciloplastia. São Paulo: Tese (Doutorado) – Faculdade de Medicina da Universidade de São Paulo; 1999.
- Sobrado CW, Pires CEF, Araujo SEA, Amaro E, Habr-Gama A, Kiss DR. Computerized videodefecography vs. defecography: do we need radiographs? *São Paulo Med J*. 2005;123:105-7.
- Sobrado CW, Pires CEF, Araujo SEA, Lopes RMG, Habr-Gama A, Kiss DR. Dose de radiação na defecografia e na videodefecografia computadorizada. *Rev Bras Coloproctol*. 2003;23:20-4.
- Sobrado CW, Pires CEF, Habr-Gama A, Kiss DR. Avaliação do tempo de transito colônico com marcadores radiopacos: estudo com voluntários assintomáticos. *Rev Col Bras Cir*. 2005;32:111-4.

31. Rao SSC, Rattanakovit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. *Nat Rev Gastroenterol Hepatol*. 2016;13:295-305.
32. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60:209-18.
33. Anti M, Pignataro G, Armuzzi A, Valenti A, Iascione E, Marmo R, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. *Hepatogastroenterology*. 1998;45:727-32.
34. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database Syst Rev*. 2010;7:CD007570.
35. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. *Aliment Pharmacol Ther*. 2011;33:895-901.
36. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Murad MH. Systematic review with meta-analysis: highly selective 5-HT₄ agonists (prucalopride, velusetrag or naronapride) in chronic constipation. *Aliment Pharmacol Ther*. 2014;39:239-53.
37. Chmielewska A, Szajewska H. Systematic review of randomized controlled trials: probiotics for functional constipation. *World J Gastroenterol*. 2010;16:69-75.
38. Ojetti V, Ianiro G, Tortora A, D'Angelo G, Di Rienzo TA, Bibbò S, et al. The effect of *Lactobacillus reuteri* supplementation in adults with chronic functional constipation: a randomized, double-blind, placebo-controlled trial. *J Gastrointest Liver Dis*. 2014;23:387-91.
39. Chiaroni G, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. *Gastroenterology*. 2006;130:657-64.
40. Pinto RA, Sands DR. Surgery and sacral nerve stimulation for constipation and fecal incontinence. *Gastrointest Endosc Clin N Am*. 2009;19:83-116.
41. Sbahi H, Cash BD. Chronic Constipation: a review of current literature. *Curr Gastroenterol Rep*. 2015;17:47.
42. Nylund G, Oresland T, Fasth S, Nordgren S. Long-term outcome after colectomy in severe idiopathic constipation. *Colorectal Dis*. 2001;3:253-8.
43. Pikarsky AJ, Singh JJ, Weiss EG, Noguera JJ, Wexner SD. Long-term follow-up of patients undergoing colectomy for colonic inertia. *Dis Colon Rectum*. 2001;44:1898-9.
44. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med*. 2003;349:1360-8.
45. Piccirillo MF, Reissman P, Wexner SD. Colectomy as treatment for constipation in selected patients. *Br J Surg*. 1995;82:898-901.
46. Thomas GP, Dudding TC, Rahbour G, Nicholls RJ, Vaizey CJ. Sacral nerve stimulation for constipation. *Br J Surg*. 2013;100:174-81.
47. Ratto C, Ganio E, Naldini G, GINS. Long-term results following sacral nerve stimulation for chronic constipation. *Colorectal Dis*. 2015;17:320-8.
48. Maeda Y, O'Connell PR, Lehur PA, Matzel KE, Laurberg S, European SNS Bowel Study Group. Sacral nerve stimulation for faecal incontinence and constipation: a European consensus statement. *Colorectal Dis*. 2015;17:74-87.
49. Kamm MA, Dudding TC, Melenhorst J, Jarrett M, Wang Z, Buntzen S, et al. Sacral nerve stimulation for intractable constipation. *Gut*. 2010;59:333-40.
50. Ortiz H, de Miguel M, Rinaldi M, Oteiza F, Altomare DF. Functional outcome of sacral nerve stimulation in patients with severe constipation. *Dis Colon Rectum*. 2012;55:876-80.