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Title Page

Chronic Idiopathic Constipation in Adults: Epidemiology, Pathophysiology, Diagnosis, and Clinical Management.

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Chronic idiopathic constipation (CIC) is one of the most common gastrointestinal disorders worldwide (1). CIC can be divided into three subtypes: dyssynergic defaecation (DD), which is a problem with rectal evacuation, slow-transit constipation, and normal-transit constipation, which is the most common subtype (2). This narrative review examines the epidemiology, pathophysiology, and clinical management of CIC in adults. It is based on a synthesis of relevant evidence from PubMed-listed articles until January 2018, including original research papers, consensus guidelines, and opinion papers.

Definition

Patients with CIC usually present with symptoms including hard or lumpy stools, reduced frequency of defaecation, a sensation of incomplete evacuation or blockage, straining at stool, and some may also report abdominal pain and bloating (3). Generally, symptoms are deemed to be chronic if they have been present for at least 3 months.

The Bristol stool form scale (BSFS) (Figure 1) is a validated tool, which describes the different consistencies of stool a patient may experience (4). Stool types 1 and 2 are indicative of hard stools, and types 6 and 7 loose or watery stools. This has been shown to correlate well with colonic transit time (5, 6), whereas the overall frequency of defaecation may not (6, 7), although the majority of patients presenting with CIC have normal colonic transit (8). This is also referred to as functional constipation, and is defined by the Rome IV diagnostic criteria as shown below (Table 1). In practice, these criteria can be difficult to apply and, because abdominal pain is so often reported in functional constipation, it can be difficult to distinguish functional constipation from irritable bowel syndrome with constipation (IBS-C) (9, 10).

Epidemiology

A previous meta-analysis demonstrated a pooled global prevalence of CIC across 45 population-based studies of 14%, with little variation by geographical region, although data from the Middle East, Central America, and Africa were scant (11). It has traditionally been held that the prevalence of CIC increases with age, with higher rates reported in the elderly (12), a trend which was confirmed, albeit modestly, by this meta-analysis (11). Regarding gender, most chronic gastrointestinal disorders, including IBS, are more common in women (13), and the same is true of CIC. The meta-analysis demonstrated that the prevalence of CIC among women was almost twice that in men (11). Finally, low socioeconomic status has been identified as a risk factor for CIC (14). There was a modest increase in the prevalence of CIC among patients of lower compared with higher socioeconomic status, but not when comparing medium with higher socioeconomic status (11).

Normal Colonic Physiology

To understand the investigation and treatment of CIC, it is helpful to briefly consider the normal physiological functioning of the colon.

Motility

Although peristalsis is observed in the colon, the main mechanism of propulsive motility is via mass movements, which occur a few times each day, ultimately leading to defaecation (15). They arise from the inhibition of distal haustral segments and contractions of the proximal bowel wall. The primary motor pattern associated with these mass movements is called a high-amplitude propagating contraction (HAPC) (16). HAPCs arise from the contraction of colonic smooth muscle, although the underlying neurophysiological mechanism remains incompletely understood.

Peristalsis, on the other hand, is predominantly mediated by serotonin, or 5-hydroxytryptamine (5-HT), which is synthesised and released by enterochromaffin cells (17). Serotonin activates receptors, which send signals via the myenteric nerve plexus, propagating a wave of intestinal smooth muscle contraction, and propelling luminal contents. The interstitial cells of Cajal act as a pacemaker, mediating between the signals of the enteric nervous system and intestinal smooth muscle (18).

Colonic contents can also move in a retrograde direction. This is more marked following a meal and potentially provides a "brake", in order to prevent rapid rectal filling (19). At the same time there is also a general post-prandial increase in colonic motor activity – the so-called gastro-colic reflex.

Fluid and Electrolytes

The colon has an important role in managing intestinal fluid and electrolyte content. This is not a major factor in the aetiology of chronic constipation, but it is relevant to pharmacological treatment. The colon reabsorbs approximately 1-2 litres of fluid per day (20). Prosecretory drugs can increase intestinal luminal fluid and electrolyte content sufficiently to saturate this process, thereby altering stool consistency, and reducing colonic transit time (21). Alternatively, osmotic laxatives increase luminal water content by creating an osmotic gradient across the intestinal epithelium, with similar effects (22).

Pathophysiology

Normal-transit (Functional) Constipation

Despite this being the most prevalent subgroup of CIC, the pathophysiology remains unclear (23). Changes in the colonic microbiota can increase bile acid metabolism (24), promote methane production (25), and affect epithelial function, all of which can alter colonic motility and fluid secretion, resulting in constipation (26). As with other functional

gastrointestinal disorders, there are also dietary, and other lifestyle, behavioural, and psychological factors that may be involved in the aetiology of symptoms (27-29).

Rectal Evacuation Disorders

These constitute the second most common cause of CIC. Emptying the rectum requires co-ordination of the rectal and abdominal wall muscles, the anal sphincters, and the pelvic floor muscles. DD, which is the most common disorder of rectal evacuation, arises when this co-ordination is impaired in some way, leading to paradoxical anal contraction, failure or impairment of anal relaxation, or inadequate rectal and abdominal propulsive force (30). Slower colonic transit is often present concurrently (31).

DD is an acquired and learned behavioural problem, often resulting from dysfunctional toilet habits. In one study, sexual abuse was reported in 22% of cases, and physical abuse in 32% (32), and there was a significant impact on health-related quality of life. Problems with rectal evacuation can co-exist with a structural cause, such as a rectocele, rectal prolapse, or rectal intussusception (33).

Slow-transit Constipation

Among patients with slow-transit constipation, which is the least prevalent subtype of CIC, there may be a limited, or absent, increase in post-prandial motor activity (34), and normal retrograde colonic propulsion may also be impaired (35). These patients may exhibit delayed emptying of the proximal colon (36, 37), and either a reduction or complete absence of HAPCs (35, 37, 38). Mediation of peristalsis via 5-HT can also be impaired (16). Moreover, individuals with severe slow-transit constipation can exhibit abnormal, or reduced numbers of, interstitial cells of Cajal (39, 40).

Clinical Assessment and Investigation

A thorough history is the most important element in the clinical assessment of the constipated patient. The physician must be vigilant for the presence of red flag symptoms, such as weight loss or rectal bleeding, which should prompt urgent investigation with colonoscopy or cross-sectional imaging as appropriate, primarily to exclude colorectal or other intra-abdominal malignancy (Figure 2). Otherwise, colonoscopy is not a useful investigation for constipation in general. Any association between chronic constipation and the development of colorectal cancer is controversial; a previous meta-analysis argues against such a link (41).

Enquiring about the patient's medical history is important. Constipation can arise secondary to neurological conditions, such as Parkinson's disease and multiple sclerosis, endocrine disorders, such as hypothyroidism and hypercalcaemia, and prescribed medications, such as opiates or tricyclic anti-depressants. Blood tests for thyroid function and calcium should be considered, as well as testing for coeliac disease. Coeliac disease, although more commonly associated with symptoms of diarrhoea, weight loss, and abdominal pain, was associated with constipation in 10% of patients in a large cohort study (42).

An obstetric and gynaecological history is also important when assessing symptoms of constipation in women (43). One study noted that the odds of obstructive defaecation increased two-fold in women who had undergone vaginal or laparoscopic hysterectomy (44), and vaginal delivery and higher parity have both been shown to increase the risk of defaecatory symptoms arising from pelvic floor dysfunction (45).

Digital rectal examination has been shown to be reliable for identifying DD in patients who have chronic constipation (46), with a sensitivity and specificity of 75% and 87% respectively (47). The presence of two of the following features is required: impaired

perianal descent, paradoxical anal contraction, or impaired push effort (48). If DD is suspected, based on digital rectal examination, physiological testing with high-resolution anorectal manometry may be useful to confirm the diagnosis.

High-resolution manometry enables measurement of both anal resting and squeeze pressures, and the rectal pressure during simulated defaecation, and can therefore help in identifying DD (49). However, many manometry patterns that were once considered abnormal have been observed in healthy asymptomatic individuals, which may limit utility (49). It is important to correlate the result with patient symptoms, and careful clinical judgement must be exercised. Defaecation proctography, traditionally using fluoroscopy, and more recently MRI, can elucidate obstructive causes of defaecation, such as rectal intussusception or rectocele (33).

The standard means of assessing colonic transit is the radio-opaque marker test (50), which is relatively simple, and widely available. A capsule containing 20 radio-opaque markers is swallowed by the patient, and a plain abdominal radiograph is taken 5 days later. Retention of five or more markers is indicative of slow transit, but care must be taken not to over-interpret the result, with a recent study showing that the number of retained markers does not correlate with symptom severity or quality of life in CIC (51).

Colonic transit can also be measured using other modalities. These include colonic scintigraphy (52), where patients are given a radio-isotope-labelled meal, and timed measurements of residual radioactivity are made to calculate transit, and wireless motility capsule (53), which utilises changes in pH along the gastrointestinal tract to determine transit time. In practice, these investigations are used in a limited number of specialist centres, and are not routine in investigating patients with constipation.

Management

Lifestyle

Modification of lifestyle factors, described below, is usually the first step in managing CIC (Figure 2).

Diet

Patients with CIC are often told to increase their dietary fibre intake, with guidelines suggesting 25g-30g of fibre per day. This should be introduced slowly, with gradual titration to avoid side effects. Insoluble fibres, such as wheat bran, may accelerate gastrointestinal transit, thereby increasing stool frequency (54). However, negative effects have been reported, particularly in patients with IBS-C in whom insoluble fibre may worsen symptoms including abdominal pain and bloating. Soluble fibre such as psyllium, derived from ground ispaghula husk, when ingested with water increases stool bulk and frequency (55). Sterculia may be an alternative in those who experience side effects with psyllium.

A systematic review by Suares and Ford, which included six randomised controlled trials (RCTs) of soluble and insoluble fibre, found evidence of limited benefit overall in CIC, but suggested that soluble fibre was more effective than placebo, and led to improvements in individual symptoms (56). A further systematic review with meta-analysis by Christodoulides *et al.* also suggested that soluble fibre was effective for treating CIC, but highlighted that it may also cause unwanted gastrointestinal side effects, such as increased flatulence (57). Overall, the quality of evidence was low, and the findings should be interpreted cautiously, due to a high risk of bias among all included studies. Both these systematic reviews identified a need for further large studies of fibre for the treatment of CIC.

Probiotics

Whether probiotics have a role in CIC is unclear. There is some suggestion they might improve gut transit time, stool frequency, and stool consistency (58). However, more rigorous RCTs are needed to overcome the potential biases that blight the currently available studies (59).

Hydration

There is no evidence that CIC can be successfully treated by increasing fluid intake, unless there is evidence of dehydration (60). In the only study to date of increased fluid intake alone, 117 adult patients, in whom constipation was defined as fewer than 3 bowel movements per week, were randomised to either unrestricted fluid intake, or 2L of mineral water daily, over a 2-month period (61). Stool frequency increased by 1.3 stools per week in the control group and 2.4 stools per week in the intervention group. However, the results are unreliable as baseline data were assessed by patient recall, and the mineral water contained magnesium, which could have exerted a laxative effect. Another study examined the effects of adding extra water to ingested wheat bran but found no beneficial effect on stool frequency or form (62).

Exercise

A study in patients with IBS found that increased physical activity improved gastrointestinal symptoms, and was also protective against a deterioration in symptoms (63), effects which might be mediated through positive effects on anti-inflammatory and anti-oxidant pathways, as well as immune function (64). In CIC specifically, although intervention programs to increase physical activity may be of some help in elderly patients (62), there is no evidence to suggest that increasing levels of physical activity in younger people is beneficial (23).

Pharmacological Treatments

Medications for treating constipation principally include osmotic or stimulant laxatives, prosecretory drugs, and 5-HT_4-receptor agonists.

Osmotic Laxatives

If patients fail to respond to lifestyle measures, osmotic laxatives such as polyethylene glycol and lactulose are the first-line drug treatment. A meta-analysis which included six RCTs comparing osmotic laxatives with placebo for treating CIC found that overall, osmotic laxatives were more effective, with a number needed to treat of 3 (65). In individual RCTs, polyethylene glycol appeared to be superior to both lactulose (66) and prucalopride, a 5-HT_4-receptor agonist, (67) when compared directly. Lactulose may also be poorly tolerated, as it frequently causes bloating.

Stimulant Laxatives

Stimulant laxatives may be used if there is no response to osmotic laxatives. Bisacodyl and sodium picosulfate are both well-tolerated, and improve bowel function, symptoms, and quality of life in RCTs (68, 69). Interestingly, a systematic review and network meta-analysis found bisacodyl to be superior, not only to sodium picosulfate, but also to prosecretory drugs and 5-HT_4-receptor agonists (70). Senna, an anthraquinone laxative, is frequently prescribed in CIC, but to date there are no placebo-controlled trials assessing its efficacy. Bisacodyl can also be given as an enema. Although other stimulants given per rectum, such as glycerol suppositories or phosphate or sodium citrate enemas, may provide individual patients with more predictability and control over their bowel habit, there are no RCTs to support their efficacy. (71) There is no evidence to suggest that patients become dependent on stimulant laxatives (72).

Prosecretory Agents

If a patient fails to respond to conventional laxatives, prosecretory drugs may be tried. Lubiprostone, linaclotide, and plecanatide all work by increasing fluid and electrolyte flux into the intestinal lumen, although at the time of writing none of these drugs are available in Australia. Lubiprostone achieves this by activating chloride-2 channels on the luminal epithelial cells, whereas linaclotide and plecanatide activate the CFTR chloride channel by increasing luminal cyclic-GMP. A meta-analysis by Li *et al.*, summarising data from nine RCTs of lubiprostone versus placebo in CIC and IBS-C, found significant improvements in severity of constipation, stool consistency, and degree of straining after 1 month, but there was no longer a significant difference between groups by 3 months (73). Side effects, particularly nausea, are commoner with lubiprostone (74).

Treatment of CIC with 12 weeks of linaclotide was found to significantly reduce bowel and abdominal symptoms when compared with placebo in two RCTs (75). Patients treated with linaclotide were also significantly more likely to reach the primary endpoint of three or more spontaneous bowel movements (SBMs) per week. Diarrhoea was the most frequent side-effect experienced by those taking linaclotide, resulting in discontinuation of the drug in 4% of patients.

In RCTs of plecanatide for treating CIC (76, 77), the drug improved constipation-related symptoms, when compared with placebo, over 12 weeks but diarrhoea was again the predominant side-effect. Patients on plecanatide had significantly more SBMs per week, as well as significant improvements in stool consistency.

5-HT_4-receptor Agonists

Prucalopride is a selective 5-HT_4-receptor agonist, which stimulates gastrointestinal and colonic motility. An integrated analysis of six phase III and IV RCTs showed that

significantly more patients with CIC achieved a mean of 3 or more SBMs per week with 12 weeks treatment with prucalopride 2mg once daily, compared with placebo (78). Overall, the drug was well tolerated; common side-effects included diarrhoea and headache. The dose should be reduced to 1mg once daily in the elderly, or those with renal or hepatic impairment.

Emerging Drug Treatments

Drug development continues with new treatments for CIC on the horizon. Like prucalopride, velusetrag and naronapride are both selective 5-HT_4-receptor agonists, with prokinetic effects (79, 80). These drugs have shown some promise in phase II clinical trials but are yet to be evaluated any further.

Elobixibat, which is currently being evaluated in two large phase III RCTs, is an inhibitor of the ileal bile acid transporter which effectively induces a state of bile acid malabsorption, resulting in increased colonic motility and fluid secretion (81). It may be a valuable new pharmacological therapy for CIC.

Other Treatments

Anorectal Biofeedback

Anorectal biofeedback, which is a behavioural training technique, can be used in the treatment of DD. It comprises measurement of anorectal physiology, with the abnormal responses shown to the patient in real-time, and targeted training to correct them, thus improving anorectal function. It employs a combination of techniques, which can include training to improve abdominal straining and push effort, training to relax the pelvic floor during defaecation, the simulation of defaecation by expulsion of a balloon from the rectum, and sensory retraining when rectal sensation is impaired (82). It has been demonstrated to be effective in RCTs, when compared with both standard treatment for CIC and sham therapies

(83). However, a Cochrane review reported the quality of evidence for use of biofeedback was poor overall, and recommended that larger RCTs were conducted (84).

Trans-anal Irrigation

Trans-anal irrigation is a commonly used treatment for disordered defaecation. In adults, this is predominantly in the context of neurogenic bowel, for which it is reimbursable in Australia, rather than CIC (85). It is a generally safe intervention, and can be considered for treating CIC in adults, when pharmacological treatments have proved to be ineffective, and particularly before irreversible surgical procedures are considered (86). However, a recent study revealed that although it can lead to significant improvements in bowel function and quality of life among patients with CIC at 12 months, more than one-third of patients discontinue it within the first year, largely due to an unsatisfactory effect (87).

Surgery

Surgical procedures include total colectomy with either ileo-rectal anastomosis or ileostomy formation. However, they are rarely indicated, and strict patient selection criteria are vital. Surgery is only suitable for patients with proven slow-transit, in whom other correctible causes of constipation have been excluded, and who have failed to respond to all available pharmacological treatments (23). This patient group may benefit from total colectomy with ileo-rectal anastomosis (88). Outcomes can be very good when strict selection criteria are applied, with high levels of patient satisfaction and improvements in quality of life reported (89). Surgery is not suitable for patients with IBS-C, nor for those with pure DD. When slow-transit and DD co-exist, DD should be corrected before surgery. If this is not achievable, then formation of an ileostomy is the only suitable surgical intervention (23).

Conclusion

CIC is a very common disorder. In the last 15 years, patients have benefitted from an expansion in treatment options, beyond simple dietary manipulation and the use of conventional laxatives. Further research in CIC should focus on understanding the neuropathophysiology responsible for normal-transit constipation, including additional exploration of the role of both the microbiome and probiotics in CIC. Larger RCTs investigating biofeedback for treating DD are needed, in conjunction with improving access to biofeedback for patients, as well as larger trials of dietary fibre. We need to better understand which investigations assess colonic physiology most accurately in clinical practice, how to make them more acceptable to patients, as well as more representative of real life e.g. assessing defaecatory function with the patient sitting instead of lying down, as is currently the case. Finally, head-to-head comparisons of the efficacy of existing pro-secretory drugs for treating CIC are required, and the results of further trials of drugs in development are also awaited.

Summary

- Chronic idiopathic constipation (CIC) is one of the most common gastrointestinal disorders, with a global prevalence of 14%. It is commoner in women, and its prevalence increases with age.
- There are 3 subtypes of CIC: dyssynergic defaecation, slow-transit constipation, and normal-transit constipation. Normal-transit constipation is the most common subtype.
- Clinical assessment of the constipated patient requires careful history-taking, in order to identify any red flag symptoms that would necessitate further investigation with colonoscopy to exclude colorectal malignancy.

- Screening for hypercalcaemia, hypothyroidism, and coeliac disease with appropriate blood tests should be considered.
- A digital rectal examination should be performed to assess for evidence of dyssynergic defaecation. If this is suspected, further investigation with high-resolution anorectal manometry should be undertaken.
- Anorectal biofeedback can be offered to patients with dyssynergic defaecation as a means of correcting the associated impairment of pelvic floor, abdominal wall, and rectal functioning.
- Lifestyle modifications, such as increasing dietary fibre, are the first step in managing other causes of CIC. If patients do not respond to these simple changes then treatment with osmotic and stimulant laxatives should be trialled.
- Patients not responding to traditional laxatives should be offered treatment with prosecretory agents such as lubiprostone, linaclotide, and plecanatide, or the 5-HT_4-receptor agonist prucalopride, where available.
- If there is no response to pharmacological treatment, surgical intervention can be considered, but it is only suitable for a carefully selected subset of patients with proven slow-transit constipation.

Abbreviations

CIC Chronic idiopathic constipation

DD Dyssynergic defaecation

IBS-C Irritable bowel syndrome with constipation

IBS Irritable bowel syndrome

HAPC High-amplitude propagating contraction

5-HT 5- hydroxytryptamine

RCT Randomised controlled trial

SBM Spontaneous bowel movement

Figures

Figure 1: The Bristol Stool Form Scale

Insert image and reference (awaiting source and copyright)

Figure 2: Recommended Management Algorithm for Patients with Chronic Idiopathic Constipation.

Tables

Table 1: The Rome IV diagnostic criteria for normal-transit (functional) constipation (Adapted from Mearin et al. (3))

Diagnosis of normal-transit constipation requires the presence of the following criteria for the past 3 months, with symptom onset more than 6 months prior to diagnosis:

1. Presence of 2 or more of the following criteria:
    - Straining during >25% of defecations
    - Bristol stool form types 1 and 2 for >25% of defecations
    - Sensation of incomplete evacuation for >25% of defecations
    - Sensation of anorectal obstruction or blockage for >25% of defecations
    - Manual manoeuvres to facilitate >25% of defecations (e.g. digital manipulation)
    - Less than 3 spontaneous bowel movements per week
2. Without the use of laxatives, loose stools are rarely present
3. Insufficient criteria for irritable bowel syndrome

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