Current management strategies and therapeutic targets in chronic constipation

Anton Emmanuel

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Abstract: Constipated patients who are refractory to simple lifestyle interventions will usually resort to laxatives, whether prescribed or over the counter. Clinical trial evidence is scarce for older medications such as laxatives, especially with a condition as chronic and subjective as constipation. Newer polyethylene glycol-based laxatives have been investigated under rigorous clinical trial settings, but comparisons between different laxatives are not available. Newer prokinetic agents, targeting peristalsis, intestinal secretion and the colonic flora, have been developed for laxative refractory constipation. This review focuses on the evidence for each of these agents, and the relative indications for each of them.

Keywords: evacuation difficulty, laxative, probiotic, prokinetic, serotonin, slow transit

Introduction

Chronic functional constipation is a chronic debilitating disorder associated in the more severely affected individuals by significant impairments in quality of life and social functioning [Belsey *et al.* 2010]. The aetiopathogenesis of chronic constipation is increasingly being accepted as related to either or both slow transit through the gut (primarily, but not exclusively, the colon) or rectal evacuatory dysfunction (which may be due to structural disorders or physiological in coordination) [Thoua and Emmanuel, 2006]. The latter conditions need identification through bimanual pelvic examination and occasionally evacuation proctography (barium or magnetic resonance imaging) in patients with suggestive symptoms. Subsequent management is either surgical or through biofeedback and pelvic floor retraining [Rao *et al.* 2010]. Whole gut or colonic transit can be measured by radio-opaque markers or scintigraphy: it helps to differentiate slow from normal transit. Anorectal manometry has been hypothesized to reflect pelvic floor incoordination (dyssynergia) [Rao, 2007], although this is controversial [Emmanuel and Kamm, 2001; van Ginkel *et al.* 2001].

Any current management strategies for chronic constipation must begin with cessation of any constipating medications, if possible. Thereafter, it is important to ensure that the

patient optimizes the opportunities for adequate defecation. This begins with ensuring that any spontaneous urge to defecate is not being ignored due to occupational or environmental stressors [Khaikin and Wexner, 2006]. Subsequently, advice about optimizing liquid intake and ensuring adequate, but not excessive, fibre intake [NICE, 2008] is important for both chronic constipation and patients with the irritable bowel syndrome (IBS). Adopting the correct toilet position with the knees slightly above the hips (a semi-squatting position) is appropriate if feasible for the patient [Sikirov, 2003].

For patients refractory to these lifestyle measures, for which it must be noted there is only a modest evidence base [Ramkumar and Rao, 2005], the next step is to proceed on to consideration of biofeedback or medical therapy.

Biofeedback

Once structural lesions of the anorectum (e.g. anal fissure, rectal prolapse, stool-trapping rectocele) have been excluded, first-line therapy is biofeedback, if the service is available. This statement is made based on the recent spate of randomized clinical trials comparing biofeedback with laxatives, assessing both long- and short-term outcomes [Rao *et al.* 2010, 2007; Chiarioni *et al.* 2005]. However, the treatment is not universally available and, for many patients, laxatives are used if lifestyle

Correspondence to:

Anton Emmanuel BSc,
MD, FRCP,

Senior Lecturer and
Consultant

Gastroenterologist, GI
Physiology Unit, University

College Hospital, 25

Grafton Way, London

WC1E 6DB, UK

a.emmanuel@ucl.ac.uk

modification has not improved symptoms (Figure 1). It has also become clear that the treatment is more effective in those with evacuatory dysfunction rather than slow transit [Rao *et al.* 2010; Chiarioni *et al.* 2005]. This is in contrast to earlier studies that suggested behavioural therapy, biofeedback, was equally effective in patients with slow and normal transit [Battaglia *et al.* 2004; Wang *et al.* 2003; Emmanuel and Kamm, 2001; Chiotakakou-Faliakou *et al.* 1998]. The content of biofeedback treatment remains variable between centres and seemingly, what is most important is the quality of interaction between patient and therapist [Heymen *et al.* 2003]. Importantly, biofeedback seems to have a long-term effect with no side effects for the majority of patients with chronic idiopathic constipation unresponsive to lifestyle intervention.

However, biofeedback is not available in all centres where patients with constipation are seen. With the variable description of biofeedback techniques between studies, compounded by the heterogeneous psychological factors between patients, it is clear that pharmacological therapies remain the most used modality of

treatment for patients with constipation. Of these pharmacological options, laxatives are the mainstay and the evidence supporting their use will be considered first.

Laxatives

Almost all people have taken some form of laxative by the time they consult about constipation [Schiller, 2001]. However, the majority of these subjects remain unsatisfied with the effect of these agents [Longstreth *et al.* 2006]. Despite their enormous use, there are relatively few well-conducted clinical trials of laxatives in the literature. The reasons for this dearth of research reflect the range of problems that are associated with undertaking studies in chronic constipation. Although attempts have been made to quantify and make objective the complaint, constipation is at root a symptom that is differently interpreted by different individuals (difficulty with defecation, stool frequency, urge frequency, stool consistency, abdominal bloating). This problem of subjectivity is compounded by recall bias (which can be countered to a degree by the use of prospective bowel diaries [Ashraf *et al.* 1996]). It is increasingly clear that stool frequency is not

Figure 1. Draft algorithm for initial management of chronic constipation.

as bothersome to patients as the need to strain and the passage of hard stools [Johanson and Kralstein, 2007]. In addition to these problems of symptom report, there are the complications that the symptom may result from both slow gut transit and evacuation difficulties. This means that targets that focus on one aspect may not help patients who have problems with the other. This can be countered by stratifying by transit in clinical trials, although this is difficult because of the overlap of symptoms between different pathophysiologicals [Bharucha and Fletcher, 2007]. The overlap with IBS represents a further challenge in trial interpretation. Finally, most trials do not extend beyond 12 weeks, which is inadequate for what is obviously a chronic condition.

Fibre laxatives

These agents are mostly indicated for patients with episodic constipation when stools are hard (i.e. lacking in water content). They are primarily organic polysaccharides that act by encouraging water retention in the stool. Some of the commonly used ones, such as methylcellulose and psyllium, also undergo bacterial fermentation, which may enhance this effect. However, this may be at the expense of the frequent side effect of bloating and flatulence. Much rarer side effects of bolus obstruction of the oesophagus or colon have been reported [Jones *et al.* 2002]. Reflecting the poverty of the literature and the modest effect of these agents, two systematic reviews have yielded conflicting conclusions [Jones *et al.* 2002; Tramonte *et al.* 1997]. The earlier review compared only bulking agents with placebo, showing an increase in stool frequency with the former. By contrast, the meta-analysis of Jones and colleagues compared stimulants, and osmotic and bulking agents, and showed no efficacy for the latter over placebo [Jones *et al.* 2002].

Psyllium is the husk of the seed of *Plantago ovata*. In two out of three placebo-controlled trials it improved stool frequency, consistency and ease of evacuation [Ashraf *et al.* 1996; Cheskin *et al.* 1995; Fenn *et al.* 1986]. In two other studies comparing psyllium with lactulose, the magnitude of effect in terms of fewer hard stools and greater stool frequency was similar with each agent [Dettmar and Sykes, 1998; Rouse *et al.* 1991]. However, these studies were of less than 4 weeks duration, a significant factor given that it is suggested that it takes 14 days for these drugs to exert an effect.

Bran failed to show a major improvement, in terms of stool frequency and moisture over placebo in three placebo-controlled studies [Badiali *et al.* 1995; Anderson and Whichelow, 1985; Graham *et al.* 1982].

Various doses of methylcellulose were compared with psyllium in one study, both agents exerting a modest and equal effect in terms of stool frequency and consistency. Tellingly, the effect of the drug was more marked in healthy controls than those with constipation [Hamilton *et al.* 1988].

Calcium polycarbophil was compared with psyllium in a nursing home-based crossover study, showing that whilst patients preferred the calcium salt, there was no effect on stool frequency or ease of defecation [Mamtani *et al.* 1989].

Stool softeners

These are indicated for occasional constipation and often as an adjuvant to a bulking or stimulant agent. They are anionic surfactants with an emulsifying and wetting action. Their effect depends on the strength of their action on the surface of the stool with a generally modest effect. Stool softeners are well tolerated.

Two placebo-controlled [Castle *et al.* 1991; Hyland and Foran, 1968], and one psyllium-controlled [McRorie *et al.* 1998] randomized studies have addressed the effect of docusate in chronic constipation. Significant improvements in stool frequency and overall subjective assessment were seen in the 1968 study, but not in the two more recent ones.

Stimulant laxatives

Despite being the most widely used agents (both over the counter and prescribed), there is a limited evidence base supporting the use of stimulant agents in chronic constipation. Pharmacologically, they are either naturally occurring agents (such as senna and cascara) or phenolphthalein analogues (such as bisacodyl). They are hydrolyzed in the gut (by either enterocyte enzymes or colonic flora) and act by stimulating peristalsis, sensory nerve endings (hence the frequent side effect of colic), and possibly interfering with electrolyte flux to inhibit water absorption. Stimulant agents are taken up by enterocytes and hence cause melanosis coli. Whilst classical thinking was that they caused a 'cathartic colon', there is no evidence that

currently available stimulants do this [Xing and Soffer, 2001]. There are no placebo-controlled studies of efficacy. Stimulants tend to be used for occasional constipation as a night-time dose prior to a morning bowel action, and have a particular (if unproven) place in neurogenic bowel dysfunction [Preziosi and Emmanuel, 2009].

There are two controlled studies of senna in the literature. The earlier one [MacLennan and Pooler, 1974] showed no difference in stool frequency between senna and sodium picosulphate, although the osmotic agent was more likely to cause loose stools. The later study compared senna liquid with bran and showed an equal effect of both in terms of stool frequency and consistency [McCallum *et al.* 1978].

A very old crossover trial of bisacodyl and bisoxatin (a stool softener) represents the only available randomized clinical trial of that widely used agent and it showed no difference between the agents [Rider, 1971].

Osmotic laxatives

This class of laxatives comprises both inorganic salts (magnesium compounds) and organic alcohols or sugars such as lactulose and polyethylene glycol (PEG). Their mode of action is by generating an osmotic gradient that encourages water retention in the lumen. Thus they have the potential to be dose titrated according to the stool output, and are usually used for both chronic and occasional constipation. The nature of their mechanism of action means that a number of electrolyte abnormalities may occur, but the commonest adverse effect is diarrhoea due to difficulty in titrating consistently the dose. Abdominal bloating, nausea and flatulence are common, but tolerable. These drugs are often used in slow transit and have a particular place in the megacolon [Szarka and Pemberton, 2006].

There are no placebo-controlled trials of magnesium salts in chronic constipation. However, there is strong evidence that magnesium sulphate (Epsom salts) has a potent laxative effect *in vitro* through the release of digestive hormones and neurotransmitters [Izzo *et al.* 1996].

Lactulose has been shown to be marginally better in improving stool frequency and consistency than placebo in two controlled trials [Sanders, 1978; Wesselius-De Casparis *et al.* 1968].

Having arrived on the market more recently, PEG-based laxatives have been subject to a larger number of clinical trials than other agents: there are five placebo-controlled studies [Cleveland *et al.* 2001; Corazziari *et al.* 2000, 1996; Di Palma *et al.* 2000; Andorsky and Gordner, 1990] and two lactulose-controlled ones [Attar *et al.* 1999; Freedman *et al.* 1997]. Stool frequency, and when assessed, stool consistency, was improved by PEG compared with placebo. In the lactulose-controlled studies, one showed improved stool frequency and ease of defecation with PEG over lactulose [Attar *et al.* 1999], whilst the other showed equal effect with both agents [Freedman *et al.* 1997]. Diarrhoea was the most common adverse effect, occurring in as many as 40% of subjects. Electrolyte abnormalities, again, may occur, especially in the elderly.

Suppositories and enemas

These are mainly used in patients where, despite having the urge to defecate, rectal evacuation is a problem. They are particularly indicated in patients who have a regular urge to defecate but who are then unable to defecate. Glycerine suppositories are first line, with bisacodyl suppositories or mini-enemas being used if glycerine does not fully relieve symptoms.

Novel targets

The limited evidence base for laxatives must be considered in relation to the widespread use of these agents. Plainly there is a high degree of clinical efficacy, which accounts for the annual £43 million prescribed laxative costs [Petticrew *et al.* 2001], which is not borne out by the trial evidence. These costs are an underestimate of true costs, in part due to the decade-old source of the data and the fact that many patients consume over-the-counter agents. Newer agents are subject to more rigorous burdens of evidence and cost-effectiveness. As such, any management algorithm reflects a tension between widely used (usually cheap) agents with a small database and novel (comparatively costly) agents with a much larger database. To help derive such decision-making strategies, it is important to appraise critically these newer agents.

Most of these recent higher quality studies of putative enterokinetics in chronic constipation have been placebo controlled, not laxative controlled. This 'low hurdle' to prove efficacy must be balanced against the fact that most have only

enrolled those subjects who have failed or were intolerant of laxative therapy. PEG could be used as an active comparator in constipation trials, as its efficacy in the short-term relief of constipation has been well documented [Cleveland *et al.* 2001; Corazziari *et al.* 2000, 1996; Di Palma *et al.* 2000; Andorsky and Gordner, 1990]. However, blinding is impossible when using PEG as a comparator since large volumes of fluid need to be consumed, and such ingestion would influence the pharmacokinetic and pharmacodynamic properties of any novel agent. Furthermore, the taste and appearance of PEG are too distinctive to allow production of a suitable placebo.

Serotonin agents

The serotonin-4 (5-HT₄) receptor plays a pivotal role in the regulation of gastrointestinal function [Beattie and Smith, 2008; Gershon, 2005]. 5-HT₄ agonism results in promotility and prosecretory effects in the small bowel and colon [Safsten *et al.* 2006], although the role of the 5-HT₄ receptor in visceral sensitivity remains unclear. The main drawback of these agents has been the close selectivity between agonism at the 5-HT₄ receptor and antagonism of the human cardiac potassium human *Ether-à-go-go* Related Gene (hERG) channel, resulting in a risk of cardiac arrhythmia side effects (as observed with tegaserod and cisapride).

Tegaserod. Tegaserod is a partial 5-HT₄ agonist that accelerates colonic transit in healthy volunteers and in patients with constipation-predominant IBS [Degen *et al.* 2001; Prather *et al.* 2000]. A Cochrane review of the large randomized, double-blind, placebo-controlled trials of oral tegaserod in patients with constipation-predominant IBS [Evans *et al.* 2007] has summarized the consistent result that tegaserod was superior to placebo in terms of subjective global assessment of relief and the secondary endpoints of pain, stool frequency and consistency. There are two large randomized placebo-controlled trials for chronic constipation that reported improved bowel frequency, but by less than 20% over placebo [Kamm *et al.* 2005; Johanson *et al.* 2004]. There are several other smaller studies showing similar or smaller magnitude of effect, but one in particular deserves mention. Di Palma and colleagues performed a randomized, open-labelled, parallel study comparing tegaserod and PEG laxative in chronic constipation [Di Palma *et al.* 2007]. PEG was superior to tegaserod in treating constipation over a 4-week period. However, the

drug has been withdrawn from the market due to concerns about cardiac and cerebrovascular events (which have a reported 0.01% incidence).

Prucalopride. Prucalopride is a highly selective, high-affinity 5-HT₄ receptor agonist with minimal activity on 5-HT₃ and hERG receptors. It accelerates transit and stool output in volunteers [Emmanuel *et al.* 1998] and patients [Emmanuel *et al.* 2002]. Three large regulatory studies have been performed, employing identical patient inclusion criteria, in the USA and Europe [Tack *et al.* 2009; Quigley *et al.* 2009; Camilleri *et al.* 2008]. In these mostly laxative-refractory patients (80% had less than one spontaneous complete bowel movement per week), there was a prucalopride-associated increase in bowel frequency to more than three per week in 24% of patients (compared with 11% with placebo). The side effects reported more frequently with prucalopride than placebo were headache, nausea and diarrhoea, which were mainly reported on the first day of treatment.

Other 5-HT₄ agonists. Renzapride is a mixed 5-HT₄ agonist and 5-HT₃ antagonist that accelerates gut transit and relieves symptoms of constipation in patients with constipation-predominant IBS [George *et al.* 2008]. However, the magnitude of effect is modest both for bowel frequency and abdominal pain symptoms [Scarpellini and Tack, 2008]. Other 5-HT₄ agonists, such as mosapride [Kim *et al.* 2008], are currently in development for chronic constipation.

Opioid antagonists

Antagonists at enteric μ -receptors, such as methylnaltrexone and alvimopan, are emerging agents for opiate-induced bowel dysfunction and for postsurgical ileus. These peripheral receptor antagonists do not cross the blood-brain barrier, and so do not antagonize the analgesic effect. In a randomized, double-blind, placebo-controlled study [Webster *et al.* 2008], alvimopan increased the mean spontaneous bowel movement frequency compared with placebo, and improved symptoms such as straining, incomplete evacuation, abdominal bloating and discomfort. In idiopathic chronic constipation alvimopan had minimal effects on colonic transit time and bowel frequency and did not benefit other bowel symptoms [Kelleher *et al.* 2006].

Methylnaltrexone has undergone phase III study in patients with opiate-induced constipation [Thomas *et al.* 2008]. Given as a subcutaneous injection, 52% of patients had a spontaneous (nonlaxative induced) bowel movement within 4 h after two or more of the first four doses compared with 8% in the placebo group. There are no studies that have tested the efficacy of methylnaltrexone in patients with idiopathic constipation.

Chloride channel activators

Lubiprostone, a derivative of prostaglandin E1, is a chloride channel activator, which stimulates intestinal fluid secretion. It acts on the enterocytes from the luminal side and is not systemically absorbed, accelerating colonic transit and softening stool consistency [Sweetser *et al.* 2009]. In the randomized controlled trials that saw the drug become the sole novel agent approved by the Food and Drug Administration for chronic constipation at this moment, lubiprostone was superior to placebo in improving the frequency of spontaneous bowel movements, stool consistency and straining. Diarrhoea and especially nausea were reported in up to 30% of patients [Johanson and Ueno, 2007].

Linaclotide is a 14-amino acid peptide that activates the luminal receptor guanylate cyclase C found on enterocytes. This stimulation results in increased chloride and bicarbonate secretion into the intestinal lumen. In chronic constipation, linaclotide has been shown to have a modest effect on frequency of bowel movement, stool consistency and need to strain [Johnston *et al.* 2009].

Neurotrophins

Neurotrophin 3 stimulates the development, growth and function of the nervous system and in a phase II randomized, double-blind, placebo-controlled trial, subcutaneous injection three times per week, significantly increased the frequency of nonlaxative-induced bowel opening [Parkman *et al.* 2003]. However, despite that initial promise there has been no further development of neurotrophins for the treatment of constipation.

Medical probiotics

For all the uncertainties of duration of treatment and potential adverse effects with many of the putative enterokinetics, one class of potential agents is extremely popular with patients,

namely the probiotics. Seen as 'natural' and 'restoring balance', the overlap between food probiotics and pharmabiotics is a source of confusion.

The gastrointestinal microflora is a complex ecosystem, a virtual organ, of approximately 300–500 bacterial species comprising nearly 2 million genes (the 'microbiome'). Intestinal peristalsis and gastric acid ensure that the stomach and proximal small intestine are relatively sterile. The colon, however, is rich in anaerobic and aerobic bacteria, which subserve a range of physiological functions relevant to colonic motility [O'Hara and Shanahan, 2007]. For instance, unabsorbed dietary sugars are converted by bacterial disaccharidases into short-chain fatty acids and used as an energy source by colonocytes. Secondly, colonic flora deconjugate primary bile acids, which in turn influences stool form and consistency. Finally, certain members of the commensal flora have a direct stimulatory effect on gut motility through stimulation of intestinal neuropeptides and gases [Ait-Belgnaoui *et al.* 2006].

It is not clear whether individuals with chronic constipation have altered flora compared with nonconstipated controls. A therapeutic bacterial effect could be achieved through either supplementation with commensal organisms (the probiotic approach), selectively stimulating the growth of certain commensals (the prebiotic approach), or by extracting components of commensal flora with biological activity.

Probiotics are defined as live organisms, which when ingested in adequate amounts, exert a health benefit to the host [Isolauri *et al.* 2004]. Most over-the-counter preparations fail to fulfil these criteria either because they have inadequate numbers of viable organisms, or they have no attestable health benefit. It remains to be proven whether individual bacterial strains, or cocktails of different species, are most therapeutically useful [Guarner and Malagelada, 2003]. Prebiotics are defined as nondigestible, but fermentable, foods that benefit the host by selectively stimulating the growth and activity of one or a limited number of colonic bacterial species [Roberfroid, 2007]. By definition, their relative efficacy will depend on the initial concentrations of the probiotic component of the flora and on colonic pH. The only prebiotics with an evidence base [Sabater-Molina *et al.* 2009], which is still

limited, are the fructo-oligosaccharides (which are present in wheat, onion, leeks, garlic and bananas) and, to a lesser extent, inulin. Synbiotics, which are a combination of a probiotic and prebiotic, aim to increase the survival and activity of proven probiotics and stimulate indigenous bifidobacteria and lactobacilli. Again, data for efficacy in human disease is scanty.

In contrast to the number studies in constipation-predominant IBS, probiotic research in chronic constipation is sparse. *Bifidobacterium lactis* DN-173010 is known to shorten colonic transit in healthy subjects [Meance *et al.* 2001]. Fibre supplementation and lactulose are thought to exert their laxative effect by promoting growth of several strains of bifidobacteria in human subjects [Bouhnik *et al.* 2004]. In adults with chronic constipation, increased stool frequency and

reduction in associated symptoms was demonstrated *versus* placebo for a probiotic beverage containing *Lactobacillus casei* Shirota [Koebnick *et al.* 2003] and *Bifidobacterium lactis* DN-173010 [Yang *et al.* 2008]; considerably more evidence is present in paediatric constipation [Chmielewska and Szajewska, 2010]. Importantly one of these paediatric trials compared *Lactobacillus* GG as an adjunct to lactulose [Banaszkiewicz and Szajewska, 2005] and found no additional benefit from the probiotic.

Alternative interventions

Given the prevalence of the symptom of constipation, amounting to almost 20% of the developed world population [Higgins and Johanson, 2004], there will be a large number of patients who do not respond to, are intolerant of, or simply cannot access the above interventions.

Figure 2. Draft algorithm for management of chronic intractable constipation.

Cheng and colleagues have recently reviewed the literature for traditional Chinese medicines in chronic constipation [Cheng *et al.* 2009]. The analysis of 35 generally low-quality studies supported Chinese herbal medicine and massage over laxatives and prokinetics. However, no specific herbal approach was better than any other.

At the other end of the spectrum of invasiveness is the operative intervention of sacral neuromodulation [Kamm *et al.* 2010]. A multi-centre European study reported that 63% of refractory patients reported increased bowel frequency, reduced straining and time spent toileting. Certainly there is little place for colonic resection for constipation, given the poor long-term outcome with this irreversible option [Kamm *et al.* 1988]. Poor outcome is almost the norm if there is any significant psychological comorbidity [Kamm *et al.* 1988]. The surgical management of pelvic floor evacuation disorders is beyond the scope of this review and has been recently reviewed [McCallum *et al.* 2009].

More recently, transanal irrigation using a single-use anal catheter and hand-pump system has emerged as a minimally invasive alternative for refractory constipation, which has a proven and central role in the management of neurogenic bowel dysfunction (such as the constipated subject with multiple sclerosis or spinal cord injury) [Emmanuel, 2010]. Its role in chronic functional constipation is beginning to emerge since it is a relatively straightforward and reversible intervention [Christensen and Krogh, 2010]. Antegrade irrigation through laparoscopically placed tubes or appendicostomies has also been used. Whilst undoubtedly an effective intervention in children, the long-term benefit in adults is less clear [Worsoe *et al.* 2008].

Management guidelines

Given the problems with the literature, as described in the earlier sections, it is perhaps unsurprising that there is no national or international consensus guideline for management of chronic constipation. Figures 1 and 2 are a personal assimilation of the data presented above as a putative algorithm to manage these patients. Figure 1 represents an approach to patients presenting initially with a history of chronic constipation; Figure 2 represents a putative algorithm for the minority of patients with laxative-refractory constipation. The challenge for the future is to deliver a better patient-centred evidence base

to inform consistently management of this troublesome and highly prevalent symptom. This should be based on pragmatic approaches as a start and the introduction of an escalating regime of interventions as required.

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Dr Emmanuel has provided scientific advice for Coloplast, GlaxoSmithKline, Medtronic, Movetis, Mundipharma, Pfizer and Takeda.

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