

## REVIEW

# Recent Advances in Colonic Preparation for an Accurate Colonoscopy - How to Improve Our Practice to Meet the Quality Criteria

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## Abstract

Colorectal cancer (CRC) remains a major problem of global health. Screening colonoscopy is the gold standard in detection of CRC. A quality colonoscopy needs good indication, adequate bowel preparation, adequate examination time (30 to 45 minutes), a minimum 6 minutes time for mucosal examination during colonoscopy descent, a good centre adenoma detection rate. In 28-33% of the colonoscopies, the bowel preparation is unsatisfactory which leads to several hidden costs including the rise of preventable and treatable death rate regarding colorectal carcinoma. The ESGE (European Society of Gastrointestinal Endoscopy) recommends a maximum of 10% poor preparations, threshold that is difficult to reach in many centres. Newer low-volume laxative regimens for bowel cleansing are better in the fields of compliance and tolerability than the classic 4L PEG with 2L PEG-CS (Clensia®) being one of the new promising low-volume formulas. The low fibre diet is now preferred due to better compliance and tolerability.

**Conclusions:** One of the easiest ways to improve colonoscopy quality is through improved compliance. Two of the most effective measures are using newer laxative bowel cleansing formulas (like 2L PEG-CS) and a low-fibre diet.

**Keywords:** bowel preparation, 2L PEG-CS, low-volume laxatives, simethicone, low fibre diet.

## Rezumat

Cancerul colorectal (CCR) rămâne o problemă majoră de sănătate publică. Calitatea colonoscoپیilor trebuie să fie îmbunătățită pentru a preveni CCR și pentru aceasta ESGE recomandă o pregătire intestinală adecvată, timpul dedicat colonoscoپیei să fie între 30-45 de minute, timpul minim de observare a mucoasei la coborâre de minimum 6 minute, o rată satisfăcătoare de detecție a adenoamelor sau a polipilor la nivelul centrului, necesitatea intubației cecale, necesitatea indicației, etc. În circa 28-33% dintre colonoscopii, pregătirea intestinală este nesatisfăcătoare, aceasta ducând la costuri ascunse precum rata de decese prevenibile sau tratabile a cancerului colo-rectal. ESGE recomandă un maximum de 10% pregătiri neadecvate, limită ce este dificil de atins. Noi formule laxative de volum mic pentru curățarea intestinului sunt mai bune în ceea ce privește complianța și tolerabilitatea în comparație cu regimul clasic 4L PEG. 2L PEG-CS (Clensia®) este formula cu datele cele mai promițătoare, dintre cele de volum mic. Dieta săracă în fibre a ajuns să fie și ea preferată din motive similare. **Concluzii:** Cea mai facilă cale de a îmbunătăți calitatea colonoscoپیilor este creșterea complianței. Două metode ușoare de a realiza aceasta sunt folosirea noilor formule laxative pentru curățarea intestinului (precum 2L PEG-CS) și dieta săracă în fibre.

**Cuvinte cheie:** pregătire intestinală, 2L PEG-CS, laxative de volum mic, simeticonă, dietă.

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## INTRODUCTION

Large bowel preparation is a highly important step in the process of a successful colonoscopy. Nowadays, ESGE (European Society of Gastrointestinal Endoscopy, Germany, EU) and UEG (United European Gastroenterology, Austria, EU) are recommending a rate of adequate bowel preparation of at least 90% calculated on a daily basis for the entire endoscopy centre and also for every practitioner in part<sup>1</sup>.

Due to the poor tolerability, acceptability and compliance of the standard 4L PEG regimens<sup>2</sup>, newer low volume PEGs were formulated and brought to the market with solid evidence in terms of efficacy and also of tolerability. Recently a formulation of 2L PEG + citrate and simethicone (PEG-CS) became commercially available (Clensia<sup>®</sup>, Alfasigma SpA, Italy, EU). Its main advantage is that it adds to the regular low volume regime 2L PEG and citrate, the de-foaming agent simethicone that is effective in cleaning the bubbles formed on the bowel mucosa which can hinder the detection of small lesions<sup>3,4</sup>. Simethicone, as an anti-foaming agent, was employed for decades but after concerns regarding the biofilm that simethicone makes when flushed through endoscopic channels and which might raise the potential of an infection risk, this practice was no longer recommended<sup>5</sup>. The main benefit of PEG-CS is that simethicone is administered per os with the low volume preparation itself.

The low fibre diet is also gaining momentum versus the classical clear liquid diet. This is so because it had been observed in several meta-analyses that the same efficacy can be gained but with better tolerability and compliance than the standard clear liquid diet<sup>2</sup>.

### Quality colonoscopy-role of a good preparation

In order to perform an adequate colonoscopy, ESGE and UEG, had published a number of quality criteria 1: clear indication for the examination, adequate bowel preparation, sufficient time recommended to perform the exam (30 to 45 minutes, at least 6-10 minutes for withdrawal time), good adenoma detection rate (ADR) or polyp detection rate (PDR) for the centre and each practitioner, adequate control of cecal intubation rates, appropriate technique of polypectomy etc.

There are a lot of scales that were put in place to standardize the quality of colonic preparation, the most important ones being the Boston Bowel Preparation Scale (BBPS), Ottawa Scale and Aronchick Scale<sup>6</sup>. A

new scale that assesses the bubbles that are forming on the bowel mucosa surface and how they can impair detection of lesions, named Colon Endoscopic Bubble Scale (CEBuS), is now under validation with promising results<sup>3</sup>.

Several studies<sup>7,8</sup>, have shown that the missed lesions at preceding colonoscopies, were most of the times a result of low-quality examinations. The missed lesions are developing mostly in right colon but also in the rectum, regions hard to carefully examine without a good cleanliness of the mucosa. In the near future, we should expect that the AI software will improve detection of lesions, coming handy for most of the colonoscopists but with the same condition of an adequate preparation.

The poor tolerance at the administration of oral bowel cleansing laxatives can create a low compliance leading to poor colonic cleaning and consequently a risk for lower ADR and interval cancer hence a necessity to repeat the examination in the following three months. In order to avoid patient discomfort and excess costs and risks, a lot of importance was given to patient education regarding the need of a good preparation (smart phone apps, instruction forms with photos, surveillance of certain at-risk patients by a dedicated nurse etc) but also for developing lower volume preparations that will increase acceptance and compliance.

The two main classes of bowel cleansing osmotic laxatives are the ones based on polyethylene-glycol (PEG) and the ones based on sodium phosphate. More than half of the patients can have side effects, most frequently nausea, bloating and abdominal pain, all of which associated with dehydration and electrolyte loss. Several cases of acute renal injury were published with the sodium phosphate regimens use, which lead to formal avoidance of these preparations nowadays<sup>6</sup>.

The patient should be also aware of the importance of the oral hydric input, because this can prevent most of the unwanted effects and it would improve the adequate colonic preparation and the quality of the colonoscopy<sup>9</sup>.

Once the *American Cancer Society* (Georgia, USA) proposed the modification of the threshold age for colorectal cancer screening start from 50 to 45<sup>10</sup>, a significant number of patients being diagnosed with early stage CRC or even high-risk precancerous lesions at an earlier age. Most of those are small lesions, flat lesions difficult to spot even by an experimented endoscopist, if the preparation is not optimal<sup>11</sup>.

## Colonic preparation regimens

A retrospective study on 133 patients, showed a miss rate of almost 50% for the detection of adenomas or high-risk dysplasia, in patients with an inadequate initial bowel preparation<sup>12</sup>. The latest recommendation on behalf of the expert's panel of ESGE<sup>2</sup> suggest a minimum 90% rate of adequate bowel preparation for every centre and endoscopist as a quality criterion.

In a 2012 prospective study of 2811 patients, 33% had an inadequate level of bowel preparation<sup>13</sup>, associated with cirrhosis, Parkinson disease, diabetes mellitus and previous colorectal surgery.

A recent retrospective study of inflammatory bowel disease (IBD) patients which due to their pathology and due to the necessity to undergo many colonoscopies for CCR surveillance already have a poor adherence to their screening regimen, concurred that 28% of the colonoscopies are also poorly prepared (BBPS <6)<sup>14</sup>. Hence, indication of preparation regimen should be personalized and extensive explanations about the importance of a clean mucosa should be given for each patient.

In Romania the annual rate of preventable or treatable deaths associated with CRC (ICD: C18-C21) was estimated in 2017 at 20.4/100000 inhabitants<sup>15</sup>, so we find mandatory to improve patients' access to screening and also to increase adherence and compliance by using the right colonic preparation regimens.

Today, the main guidelines<sup>2,16</sup> are accepting lower volume laxative regimens. We recognise that as long as the cleansing is similar, the smaller the volume, the greater is the tolerability and acceptance of the patient. However, in regard with the very-low volume regimes (<1L), there are still conflicting studies as recently as 2020<sup>17,18</sup>. None of the studies detected any significant improvement in bowel cleansing, the main improvement being a better tolerability in one of the studies.

There are several meta-analyses published on the topic low volumes of 2L PEG-based regimens, we will concentrate only on the most recently published ones.

Spadaccini et al.<sup>19</sup> analysed 17 RCTs, comprising 7528 patients that were administered low-volume split-dose regimens and found no difference in the efficacy, stating they managed to see an improvement in tolerability and compliance compared with the regular 4L PEG regimens. A Chinese meta-analysis<sup>20</sup> showed similar results as Spadaccini et al., only to add that low volume regimens are enjoying also a higher acceptability and a lower nausea in non-selected population.

Several RCT's published recently are analysing efficacy, safety and tolerability of 2L PEG-based bowel cleansing laxatives. A French randomized multi-centric, prospective study<sup>21</sup>, that enrolled 278 patients, has managed to conclude that low volume 2L PEG and Pico based regimens were more efficient, better tolerated and equally safe as the 4L PEG-based regimens. Even if the aforementioned study is focusing only on IBD patients, other randomized prospective studies, with a larger focus group had managed to achieve similar outcomes. A 2019 Chilean study<sup>22</sup> that standardised bowel cleansing with BBPS found in the 2L PEG group a 5% improvement of the colonic cleansing, although it was not statistical relevant, and no differences in regard with the safety and tolerability of newer regimens.

In choosing the best type of low-volume bowel preparation we should be also aware of the pre-endoscopic factors that could impair quality of preparation. Brown liquid rectal effluent, cirrhosis, low 3-days diet compliance and more than 2 hours between last defecation and colonoscopy are independent predictors for poor colonic preparation in the moment of the examination as shown by a 2019 Korean prospective study<sup>23</sup> using 2L PEG-ASC formula.

The 2L PEG-CS (polyethylene-glycol + citrate and simethicone) is a relatively new but promising bowel cleansing laxative formula. This formula represents an improvement of the regular 2L PEG-C with the addition of simethicone, an anti-foaming agent that is capable of reducing the bubble formation on the colonic mucosa<sup>3</sup>. Even if simethicone was used through endoscopic channels for intra-procedural bubble cleansing, it frequently developed a biofilm that was difficult to remove.

The fact that simethicone is now added to the laxative regimen represents nothing a breakthrough. The PEG-CS regimen has been the subject of a lot of validation studies with at least similar efficacy in terms of bowel cleansing as 4L regimens or PEG ASC. Spada et al.<sup>24</sup> proved via an observer-blind RCT on 422 patients that compared it with the 4L PEG regimen, that 2L PEG-CS had an improvement of 1.3% in bowel cleansing with no side effects observed. Gastrointestinal tolerability, acceptability on behalf of patients and willingness-to-repeat were far greater with the new formula.

In 2018, a group of European experts, compared in a multicentre observer-blind RCT<sup>25</sup> the 2L PEG-CS formula this time with another low-volume regimen,

namely the 2L PEG-ASC. They concluded that there are no differences in terms of bowel cleansing, safety and acceptance between the two formulas.

Some trials are preferring to see if combining the 2L PEG-CS regimen with administration of bisacodyl within several days before the colonoscopy will improve the preparation. Bisacodyl is an orally available laxative, indicated in constipation, that works by irritating the smooth muscle of the bowel that in turn will increase peristalsis and also increases intestinal fluid accumulation<sup>26</sup>. There is an RCT<sup>27</sup> that demonstrated the superiority in efficacy of PEG-CS with bisacodyl versus PEG-ASC, and another one<sup>28</sup> that showed similar efficacy with 4L PEG, but with better tolerability and acceptance.

The ESGE guideline<sup>2</sup> presents the main options in the field of low volume laxative bowel cleansing regimens (Table 1). Even if newer formulas as 2L PEG-CS (Clensia®) are not part of the latest recommendation, they are similar with 2L PEG + citrate and the guideline states very clearly that any clinically validated routine bowel preparation should be administered if the practitioner finds it effective. Also, there is a formal recommendation for adding oral simethicone to bowel preparation, a low fibre diet on the day preceding the exam, the use of enhanced instructions, splitting of the dose of bowel cleansing laxative, starting the last dose within 5 hours before examination and completing it at least 2 hours before colonoscopy and same-day preparation for afternoon colonoscopies.

### Low-fibre diet

Despite the classical dogma accepted until very recently that the day preceding colonoscopy, the patient should have a clear liquids diet, there are more and more evidences that there is no difference in efficacy between clear liquid diet and low-residue diet.

Table 1. Low volume PEG based bowel cleansing laxative formulas given as example by ESGE 2

Type of low volume regimen	Not recommended in:
2L PEG + citrate	Severe renal insufficiency, congestive heart failure, unstable angina or acute myocardial infarction
2L PEG + ascorbate	Severe renal insufficiency, congestive heart failure, phenylketonuria, G-6-PD deficiency
2L PEG + bisacodyl	Congestive cardiac failure. Occasional reports of ischemic colitis.
1L PEG + ascorbate	Severe renal insufficiency, congestive heart failure, phenylketonuria, G-6-PD deficiency

The latest ESGE guideline<sup>2</sup> is recommending a low fibre diet in the day before the colonoscopy. A low fibre diet is made up by aliments like cheese, meat, fish, white bread, some fresh peeled and pitted fruits or cooked vegetables (like apples or carrots). Even if there is no difference in efficacy, the compliance and tolerability was far better than in those with clear liquid diet.

We identified two RCT<sup>29,30</sup> that concluded the low fibre diet is superior in terms of tolerability in regard with the clear diet protocol. While Alvarez-Gonzalez et al. found a better efficacy in 1-day normocaloric low-fibre diet, Thukral et al. found none, but emphasizes that the low-fibre diet should be recommended in regards with better satisfaction scores.

In regard with the necessary time for the special diet, two RCT<sup>31,32</sup> found no improvement in the 3-day diet versus 1-day diet, both with the low-fibre regime. Taveira et al. also found statistically significant difficulties for the patients in performing the diet for 3 straight days.

We should acknowledge the existence and acceptance by the ESGE of a pre-packaged low-residue diet. In a 2019, an endoscopist-blinded RCT<sup>33</sup> that included 173 patients showed a statistically significant improvement in bowel preparation, as measured with BBPS of 5,7% in the group that used pre-packaged low-residue diet. Also, a significant satisfaction and willingness to repeat the procedure was obtained in this group.

## CONCLUSION

In order to improve colonoscopy quality and reach the 90% adequate bowel preparation milestone imposed by current recommendations a lot of measures should be taken. Patient education, low volume preparations including the new 2L polyethylene-glycol citrate simethicone (PEG-CS) and a low residue diet in the day preceding the examination seem to be effective and easy to employ measures that will increase the quality of colonoscopy for the benefit of our patients.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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