

Novel frontiers of agents for bowel cleansing for colonoscopy

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Abstract

The incidence of colorectal cancer (CRC) is characterized by rapid declines in the wake of widespread screening. Colonoscopy is the gold standard for CRC screening, but its accuracy is related to high quality of bowel preparation (BP). In this review, we aimed to summarize the current strategy to increase bowel cleansing before colonoscopy. Newly bowel cleansing agents were developed with the same efficacy of previous agent but requiring less amount of liquid to improve patients' acceptability. The role of the diet before colonoscopy was also changed, as well the contribution of educational intervention and the use of adjunctive drugs to improve patients' tolerance and/or quality of BP. The review also described BP in special situations, as lower gastrointestinal bleeding, elderly people, patients with chronic kidney disease, patients with inflammatory bowel disease, patients with congestive heart failure, inpatient, patient with previous bowel resection, pregnant/lactating patients. The review underlined the quality of BP should be described using a validate scale in colonoscopy report and it explored the available scales. Finally, the review explored the possible contribution of bowel cleansing in post-colonoscopy syndrome that can be related by a transient alteration of gut microbiota. Moreover, the study underlined several points needed to further investigations.

Key Words: Colonoscopy; Bowel preparation; Cleansing agents; Polyethylene glycol; Adequate cleansing; Constipation

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Core Tip: Colonoscopy is the best modality for colorectal cancer (CRC) screening, preventing death from CRC through removal of adenomatous polyps and early detection of CRC. The accuracy of colonoscopy is related to quality of bowel preparation (BP). International guidelines underlined the methods to improve BP. In this review, we aimed to summarize the current strategy to increase bowel cleansing before colonoscopy.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in both genders[1] with an incidence characterized by rapid declines in the wake of widespread screening. Colonoscopy is considered the gold standard for CRC screening. Colonoscopy with removal of adenomatous polyps prevents death from CRC[2].

To perform screening colonoscopy, the high quality of endoscopic procedure is mandatory. An adequate bowel preparation (BP) is one of the most important factors, ensuring a high accuracy of procedure, thought an optimal visualization of colonic mucosa increasing adenoma detection rate (ADR)[3-5]. ADR is defined as the percentage of screening colonoscopies in which one or more conventional adenomas are detected[6]. ADR is inversely associated with the risks of interval and lower long-term CRC incidence and mortality[7,8].

Moreover, an inadequate BP is associate to prolonged procedures, higher cost leaded to repeat colonoscopy (longer hospital stay and no cost/efficacy of screening program), lower cecal intubation rates, higher risk of electrocautery and unsatisfactory patient experience with an increased likelihood of repeat procedure.

Despite European Society of Gastrointestinal Endoscopy (ESGE) Guidelines recommended a minimum of 90% procedure with adequate BP, with a target of > 95% [9], suboptimal BP is still encountered in clinical practice[10].

Other review papers regarding bowel cleansing were published[11,12]. However, new evidences change same feature of bowel cleansing process.

The aim of the present review is to describe the current literature regarding BP options, in order to explore factors that can be improved.

BP QUALITY SCALE

ESGE guidelines recommend recording the BP quality using a validated scale[9]. Validity refers to how well the scale measures what it is aimed to assess. For BP, validity could be assessed by comparison of different scales or with another parameter of colonoscopy quality. Another essential attribute of a scale is the reliability that indicates the reproducibility of the results in the same operator (intrarater reliability) or between different endoscopist (interrater reliability).

Several scales were proposed in the last decades to describe the quality of BP of colonoscopy.

The first one was the Aronchick Scale[13] and it is still one of the most commonly used validated BP quality scales in clinical trials and clinical practice.

The quality of the preparation is described as the percentage of entire colonic mucosa covered by stool, before washing or suctioning, ranging from 1 (excellent) to 5 (inadequate). No study has evaluated a threshold to define adequate the BP described by Aronchick Scale.

Validity was not evaluated in clinical studies, while inter-observer reliability was assessed in one study (coefficient was 0.77 in the total colon)[14].

The second developed scale was the Ottawa Bowel Preparation Quality Scale (OBPQS)[14]. This scale is composed by two separate scores. One score is assigned

according to global fluid quantity in the entire colon, from 0 (small amount of fluid) to 2 (large amount of fluid). The second score quantifies the visibility of three separate colon segments (right colon, mid colon and rectosigmoid colon) and also the amount of washing or suctioning required achieving optimal visualization and it ranges from 0 to 4. The total score is obtained by adding the score of each segment and total colon fluid score, ranging from 0 (excellent) to 14 (poor), before washing or suctioning. In one study, the value of at least 8 was proven to be an optimal cut-off value to define inadequate BP because of the inability to detect a 5 mm polyp[15].

The validity was also demonstrated in two study comparing OBPQS with visual analogue scale[16] and with Boston Bowel Preparation Scale (BBPS)[17].

The study of Martinato *et al*[16] detected also a good agreement between nurses and physicians, [$r = 0.6010$ (95%CI for r 0.4877 to 0.6944)]. One prospective study demonstrated the high interobserver agreement and reliability of OBPQS compared to Aronchick Scale[14] with no statistically significant differences between segment evaluations. Intra-observer reliability and clinical relevance were not evaluated.

BBPS described the colonic mucosa that can be evaluated. The advantages of this scale are multiple. First of all, it is a numeric score ranging from 0 (unprepared colon mucosa) to 9 (entire mucosa well seen) for the entire colon, avoiding the use of qualitative and subjective terms. Second vantage is that a score is assigned for each colonic segment (right colon, transverse, left colon-each one from 0 to 3), allowing a detailed description of BP. Third, the score is assigned after washing and suctioning as recommended by United States Multi-Society Task Force on Colorectal Cancer[18]. Finally, the validity and the reliability of this score has been evaluated in several studies.

The validity of the score was proven in several studies, demonstrating the association with polyp detection rate, insertion and withdrawn times, needed to repeat colonoscopy for inadequate BP. Lai *et al*[19], including 633 screening colonoscopies (22 clinicians), found an association with BBPS ≥ 5 , higher polyp-detection rate, an inversely correlation with BBPS and insertion and withdrawal times, and an inverse relation between BBPS and the need to repeat colonoscopy for an inadequate preparation. The latest inverse correlation was confirmed in the study of Calderwood *et al*[20] and in the study of Kim *et al*[21] that also confirmed a correlation with polyp detection rate (PDR). Calderwood conducted a second study with a very large sample size (74 endoscopists performed 2516 colonoscopies) finding that a total score of ≥ 6 and score of ≥ 2 for each segment is the definition of adequate BP[22]. The best cut-off of 2 in each segment as definition of adequate BP is proven also by Clark *et al*[23].

The reliability was determinate in different studies demonstrating a good interobserver agreement, quantified as intraclass correlation coefficient or weighted kappa (ranging between 0.67-0.93)[19-21,24,25]. Indeed, a good intraobserver agreement were found in three different studies (weighted kappa = 0.77; 95%CI: 0.66-0.87[19]; weighted kappa = 0.78; 95%CI: 0.73-0.84)[20] and weighted kappa = 0.67; 95%CI: 0.51-0.84)[24].

The results of these large and very well conducted studies corroborating the validity and the reliability of BBPS, allowed to suggest the routine use of BBPS in the clinical practice as proposed by Parmar *et al*[26].

Promising data come from artificial intelligence, as recently described by Zhou *et al* [27]. They developed a deep convolution neural network called ENDOANGEL to assign BBPS, with a 91.9% of accuracy. In the unique study on this topic, so further data are needed to support the routinely use of this system.

Bubbles scale

None of the previous scales provided an adequate evaluation of presence of bubbles that can impact on mucosa evaluation. This inadequacy affects also the strength of the conclusions of two recent meta-analyses reporting a benefit of added oral simethicone to increase BP[28,29].

The amount of foam/bubble interfering with colonic visualization was also measured in different studies regarding BP[30-42].

Parente *et al*[30] evaluated the presence of bubble in terms of the overall impact on mucosal visualization, as excellent (clear imaging, no or minimal amount of bubbles or foam that can be easily removed), fair (modest amount of bubbles and foam that can be cleared, with some waste of time) and insufficient (a large amount of foam and bubbles that reduces significantly the clear visualization of the mucosa) in each bowel segment.

A Bowel Bubble Scale, a four-point scoring system (0, no bubbles; 1, minimal or occasional bubbles; 2, moderate or obviously present; and 3, severe or many bubbles that vision is obscured) was developed by McNally *et al*[32] and used by Guo *et al*[31] and Yuanchao *et al*[33].

Another intraluminal Bubbles Scale was used in studies performed by Matro *et al* [34] graded 4 segments of the colon (cecum, right colon and hepatic flexure, transverse colon and splenic flexure, and colon distal to the splenic flexure) and each colon segment was graded using a 3-point scale (A = no/minimal bubbles, B = moderate bubbles/interfere with detecting a 5 mm polyp, and C = severe bubbles/interfere with detecting a 10 mm polyp).

Repici *et al*[35] measured the bubble score according the overall mucosal visibility using a 3-grading scale from grade 0 (optimal) to grade 2 (insufficient), the same scale was used by Spada *et al*[38] to asses mucosal visibility.

Yoo *et al*[36,37] used a scale assigned the bubble score in accordance with the degree of obscuration by bubbles, bile, or debris from 0 (severe obscuration) to 3 (no obscuration), applied also by Zhang *et al*[40].

A revised version of this scale was adopted by Rishi *et al*[39], who assigned the score (from 1 to 4) according the percent circumference of colonic mucosa clear of all bubbles/foam, not divided between segments of the colon.

Movareji *et al*[41] used a bubble scale used adapted from the one previously described by Sudduth *et al*[42], evaluating the entire colon by adding each individual segment score (from 0, no or minimal bubbles, to 3, bubbles filling the entire lumen).

In the two latest studies, the authors failed to validate and establish the reliability of the colon bubble scales. In particular, the interobserver agreement for bubble scale score was moderate ($\kappa = 0.537$ [41], $\kappa = 0.4024$ [39]).

Recently a new scale, named Colon Endoscopic Bubble Scale (CEBuS) was developed and its reliability was determined in a multicentre prospective observational study[43]. The scale CEBuS ranged from 0 (no or minimal bubbles, covering < 5% of the surface) to 2 (bubbles covering > 50%). A high intraobserver reliability [$\kappa = 0.82$ (95% CI: 0.75-0.88) *vs* 0.86 (95% CI: 0.85-0.88)] and high interobserver agreement [ICC 0.83 (0.73-0.89) *vs* 0.90 (0.86-0.94)] were reported in both experts group and mix expert/non-expert group. These encouraging preliminary results needed to be confirmed with a larger study.

CLEANSING AGENTS FOR BP

Four-liter high-volume polyethylene glycol (PEG)-based preparations were the first formulations introduced for bowel cleansing prior to colonoscopy. These isosmotic solutions provide rates of adequate BP > 90% [44-47], without producing relevant fluid shifts or electrolyte imbalances[11]. Despite high efficacy and safety, the large volume of liquids and poor solution taste may decrease patients' compliance to the assumption of these preparations[12].

PEG-based and non-PEG-based low-volume solutions have been developed in order to reduce the total volume of preparation and improve patients' acceptability. The hyperosmotic 2 L PEG-based agents (containing PEG plus ascorbate, citrate, or bisacodyl) showed similar efficacy in bowel cleansing with higher patients' tolerability and willingness to repeat the preparation compared to high-volume PEG-based solutions in meta-analyses[44,45] and randomized trials[38,48-51]. Additionally, comparable adenoma detection rates were found between 2 L PEG plus ascorbate and 4 L PEG solutions[49,50]. A recently developed low-volume solution of 1 L PEG plus ascorbate had similar quality of BP, adenoma detection rate, and safety profile compared to 2 L PEG plus ascorbate in a randomized trial[52]. This preparation showed higher rate of adequate colon cleansing compared to 4 L high-volume PEG (84.3% *vs* 77.4%, $P = 0.039$) in hospitalized patients, with no differences in electrolyte imbalances, creatinine and haematocrit[53]. However, these results are based on a post-hoc analysis of an observational study. The non-PEG-based hyperosmotic low-volume preparations include magnesium citrate with sodium picosulfate, oral sulfate solution (*i.e.* trisulfate), and oral sodium phosphate. As the PEG-based low-volume solutions, these formulations showed non-inferiority in terms of efficacy and better safety profile as well as patients' tolerability compared to 4 LPEG[54-58].

On these bases, current ESGE guidelines recommend low-volume PEG-based and non-PEG-based solutions as alternatives of equal efficacy to high-volume PEG-based formulation for routine BP, with the exception of oral sodium phosphate for the relevant risk of kidney injury[59]. However, safety concerns have been raised on hyperosmotic low-volume agents in patients at risk for hydroelectrolyte imbalances, such as those suffering from severe renal insufficiency or congestive heart failure. Moreover, ascorbate-containing solutions are contraindicated in people with phenylketonuria or glucose-6-phosphate dehydrogenase deficiency[60]. Thus, the

choice of the adequate preparation for bowel cleansing prior to colonoscopy should be individualized, especially in specific categories of patients at high risk of adverse events.

TIMING OF BP

Timing of consuming BP is highly important. The last dose of BP should be started in the 5 h before colonoscopy and ended 2 h before the scheduled time of the procedure [59]. This recommendation is translated in clinical practice in two different timings for colonoscopy of the morning and colonoscopy of the afternoon.

For morning colonoscopy, both American and European Guidelines strongly recommend split-dose regimens [59,61,62].

Split-dose regimen is defined as assuming half of the BP the day before the colonoscopy and half on the day of the colonoscopy. Several evidences provided the superiority of split dose regimens over a day-before preparation to achieve a better colon cleaning, regardless the cleansing agent [48,63-69]. Moreover, the split-dose preparation showed better patient tolerability and higher proportion of patients willing to repeat the regimen [47,70].

Effectiveness of colonoscopy is highly dependent on the quality of BP. Different observational studies and also a recent meta-analysis found that split dose preparations increase adenoma detection rate [69,71-75]. The meta-analysis demonstrated also an increase rate of advanced adenomas and sessile serrated polyps in split-dose regimen, including seven trials comparing split-dose *vs* day-before BP regimens. No differences in the same variables were found comparing split-dose and same-day BPs [75]. Another meta-analysis did not confirm the increase of ADR with split dose regimen, but it included only 4 randomized controlled trials (RCTs) [70] with moderate overall quality of evidence.

For afternoon colonoscopy, the same-day BP is recommended [59].

Considering studies including higher number of colonoscopies scheduled in the afternoon, same-day BP showed similar rate of adequate bowel cleaning, with no difference in tolerability and patient willingness to repeat it, comparing to split-dose regimens. The ADR was similar for the two regimens as showed by two different meta-analysis [75,76]. Moreover, patients in same-day regimens reported better sleep quality (OR 0.44, 95% CI: 0.24-0.82) [77].

Instead, the same-day regimen showed a significantly lower quality of BP considering studies including only morning colonoscopies [78], or lower patient tolerability and compliance [79,80], with lower willingness to repeat the same preparation in the future [79].

DIET BEFORE COLONOSCOPY

Diet restriction has traditionally been recommended before colonoscopy because it can reduce the amount of stools in the intestines, but adherence is low. The European and American Societies of Gastrointestinal Endoscopy actually recommended the use of a low residue diet (LRD) for colonoscopy defined as a diet with a total fiber intake inferior of 10 g/day [59,81].

Two meta-analysis [82,83] including studies comparing LRD with clear liquid diet (CLD) on the day before colonoscopy examination, found a significantly higher odds of tolerability and willingness to repeat preparation with no differences in adequate BPs or adverse effects.

In the last year two new meta-analysis comparing LRD *vs* CLD for BP before colonoscopy were published [84,85].

Zhang *et al* [84] performed a systematic literature search until September 2019 and they included twenty RCTs. Adequacy of bowel cleansing and polyps detection rate were similar in both groups ($P = 0.79$ and $P = 0.68$ respectively). There were significantly fewer adverse events in individuals in LRD group: nausea ($P = 0.02$) vomiting ($P = 0.04$), hunger ($P < 0.001$), and headache ($P = 0.02$). In addition, significantly more individuals in the LRD group found it easy to complete the diet ($P = 0.01$) and showed willingness to repeat it ($P = 0.005$).

Chen *et al* [85] included 16 studies and found a significantly better tolerability and willingness to repeat intestinal preparation in patients with LRD compared with CLD (both $P < 0.05$), but no differences with adequate intestinal preparations, detected polyp or overall adverse reactions.

These latest evidences showed that LRD is a promising approach for BP before colonoscopy with comparable adequacy of BP with that of CLD.

A recent study of Gimeno-Garcia *et al*[86] aimed to assess if a 3 d LRD is better regarding bowel cleansing than a single day LRD regimen, concluded that there is not a concrete advantage.

Recently, Avalos *et al*[87] performed a meta-analysis of randomized trials comparing BP outcomes between a LRD or regular diet (RD) compared with a CLD. Twelve RCTs, grouped patients taking a LRD (8 RCTs) or a RD (4 RCTs) and compared them to patients taking a CLD. In the 7 high-quality studies included, they no found differences in BP quality among the LRD/RD and CLD groups (RR 0.98; 95%CI: 0.93-1.04). Tolerability and willingness to repeat were better in the liberalized diet arm. There was no significant difference in the adenoma detection rate, whereas hunger was more common in the CLD group (RR 1.93, 95%CI: 1.13-3.3)[87]. Further studies are needed to confirm other findings, [Table 1](#).

ADJUNCTIVE DRUGS

Various adjuvant drugs have been added to standard BP regimens to increase quality of BP by direct action (as simethicone) or by the improving of patient experience.

Simethicone

Simethicone is an antifoaming agent using to reduce excessive gas, abdominal discomfort, and bubble formation in the gastrointestinal tract.

Several RCTs have investigated the effect of oral simethicone on bowel cleansing.

Since 2011, four meta-analyses were conducted. The first one[88] included 7 RCTs (714 patients) comparing purgative plus Simethicone with purgative alone for colonoscopy. The air bubbles were significantly decreased, while no difference in adequate colon preparation was found.

The role of added oral simethicone on ADR was investigated in meta-analysis of Pan *et al*[89]. Such meta-analysis included 6 RCTs (1855 patients) and found an increase of ADR in simethicone group. Different result was found by another meta-analysis[28], including 12 randomized controlled studies (6003 participants) that found no difference in ADR between the groups with or without simethicone.

The last meta-analysis by Moolla *et al*[29] aimed to determine the effect that simethicone has on bowel cleanliness, ADR and tolerability, and included 16 RCTs (5630 patients) using PEG for bowel agent cleaning. Authors found an increase rate of adequate BP in PEG cohort with simethicone compared with PEG alone (OR 1.48), considering all 16 RCTs.

This finding was confirmed in three subgroup analysis: (1) Excluding RCT with bisacodyl or with different volume preparation; (2) Including only preparation with PEG 2 L; and (3) PEG single dosing the day before. On the other hand, considering patients with split dose regimen, no difference was found in adequate bowel colonoscopy rate between PEG group and PEG + simethicone group.

Regarding ADR, no difference was found considering all studies evaluating ADR (7 studies). However, ADR was significantly higher increase in simethicone group and in the subgroup analysis considering single-dosing preparations (3 RCTs). Moreover, the authors found an increase of bloating in PEG alone group, while no differences were found in the incidence of nausea, vomiting and abdominal pain.

Currently, ESGE guidelines suggest the use of oral simethicone for BP[59].

Instead, the routine use of simethicone through the working channel is advised against by ESGE guidelines[90], due to evidence that simethicone may contribute to biofilm formation in the endoscope working channel, reducing reprocessing effectiveness[91].

Recently, multi-society guideline[92] underlined factors associated to simethicone persistence in the endoscope channel. The first is the concentration, the second is the modality of delivering. So, when simethicone is needed, the guideline suggested the use of lowest concentration (less the 5%) and the smallest volume needed avoiding the simethicone delivering *via* water bottle/irrigation jet channel.

Similar recommendations were reported by Gastroenterological Society of Australia [93], despite allowing the administration of simethicone the endoscope irrigation channel.

Both guidelines recommended a strict adherence to manufactures' instruction for each passage of simethicone use (way for simethicone administration, cleaning and disinfection of the scope).

Table 1 Low fiber diet on the day preceding colonoscopy

Type of food	Allow	Avoid
Milk and milk products	Skim or low-fat milk; Buttermilk; Low-fat cheeses; Low-fat ice cream; Sherbet; Yogurt without seeds, berries, rinds or nuts	Yogurt with seeds, berries, rinds or nuts
Vegetables	Any well-cooked vegetables without seeds (<i>e.g.</i> , carrots, pumpkin); Lettuce; Potatoes without skin; Strained vegetable juice	All raw vegetables, except lettuce; Broccoli; Brussels sprouts; Cabbage and sauerkraut; Cauliflower; Corn; Fried vegetables; Greens (mustard, turnip, collards); Mushrooms; Okra; Onions; Peppers; Potato skins
Meats and other protein foods	Eggs; Smooth nut butters; Tofu; Tender, well-cooked meat, poultry and fish	Chunky nut butters; Legumes; Nuts or seeds; Tough or chewy cuts of meat
Grains	Bread, bagels, rolls, crackers, pasta and cereals made from white or refined flour (<i>e.g.</i> , crispy rice cereal and cornflakes); Cooked cereals (farina and creamy rice); White rice	Brown rice and wild rice; Cereals made from whole grains; Grain products made with seeds or nuts; Whole-wheat or whole-grain breads, rolls, crackers or pasta
Fruits	Fruit juice without pulp (except prune juice); Most canned, soft and pureed fruit without skin (except pineapple); Peeled apple; Ripe banana or melons	All raw fruits except peeled apple, ripe bananas and melon; Canned berries, canned cherries; Dried fruits, including raisins; Prunes and prune juice
Beverages	Coffee, tea, chamomile; Sports drinks; Water	
Condiments	Ketchup and mustard; Margarine, butter, oils, mayonnaise, sour cream and salad dressing; Plain gravies; Spices, cooked herbs, bouillon, broth, and soups made with allowed vegetables; Sugar, clear jelly, honey and syrup	

Agents improving patient experience

To increase the quality of BPs, several adjuncts were evaluated. All of them act through the increasing of tolerability and palatability of bowel cleaning agents.

Four studies evaluated the role of drinks different from water. One study evaluated the BP, the palatability and the adverse effects of Coca-Cola (Coke) Zero as solvent for PEG comparing with water. The authors found a better quality of BP and palatability in Coke group, with no difference in rate of adverse events neither in PDR[94]. The palatability is also increased with orange juice intake before drinking 2 L of PEG plus ascorbic acid[95], while no differences were found in quality of BP. Also, pineapple juice was tested to increase palatability of BP. In one single randomized study[96], patients were assigned to one of the following regimens: 4 L PEG or 2 L PEG or 2 L PEG plus 1 L of pineapple juice. The third group had better quality of bowel cleansing in the right side and in transverse colon, but no difference in tolerability.

A prospective, randomized controlled recent study of Hao *et al*[97] aimed to evaluate the effectiveness and safety of concomitant use of green tea (GT) with 2 L PEG in BP for colonoscopy. Adding GT increased the compliance, reduced adverse events with comparable bowel cleanliness in BP.

Five studies evaluated the role of tablets and gum chewing in the BP. The study of Lan *et al*[98] compared two groups of patients received 2 L PEG alone or plus citrus reticulata peel in form of "buccal tablet" eaten between drinks. The second group had higher acceptable taste, lower rate of swallowing difficulty and adverse events with no differences in quality of colonic cleansing. Three randomized studies evaluation the contribution of gum chewing[99-101] and in all of them, patients' tolerability was better in gum chewing group than the other group. In one study[99], better quality was reached in gum chewing group, no difference was found in the other two studies.

The menthol candy drops[102] were used in one randomized study demonstrating the better grade preparation in candy drops-added group, with no difference in side effects.

A recent systematic review and meta-analysis was performed including 6 single-blind RCTs (1187 patients)[103]. The included adjuncts were citrus reticulata peel, orange juice, menthol candy drops, simethicone, Coke Zero and sugar-free chewing gum. The study concluded that the adjunct improved palatability and willingness to repeat BP, with fewer side effects as bloating, vomiting, but no difference in nausea or abdominal pain. Moreover, the rate of adequate BP was higher in the adjunct group.

EDUCATIONAL INTERVENTION

In the effort to improve BP, several methods emphasizing the importance of BP quality and the instructions for BP were evaluated. Different methods were tested, including

pictures, cartoon visual aids, booklets, video, instructions by the nurse, short message service, smartphone applications were evaluated separately with conflicting results.

Seven meta-analyses[104-110] were conducted to compare the adequacy of BP in patients who received enhanced instructions and patients who received standard ones. All of them demonstrated that enhanced instructions are useful to improve the quality of BP, and in the same time to increased ADR.

So, both European and United States guidelines suggested the enhanced instruction before colonoscopy[18,59].

SPECIFIC CATEGORIES OF PATIENTS

Lower gastrointestinal bleeding

Colonoscopy has an important role for optimal management of acute lower gastrointestinal bleeding (LGIB), with diagnostic and therapeutic potential[111].

Colonoscopy should be performed after hemodynamic stabilization. Moreover, adequate colon cleansing is crucial to achieve before performing colonoscopy for LGIB, because of the increasing risk of perforation, and major risk of missed bleeding mucosal lesions in poorly prepped colon and properly evaluation of the entire mucosa [112].

However, cleansing the colon from stool, clots and blood is difficult to accomplish [111].

According to the latest European guidelines, preparation for colonoscopy should include 4-6 L of a polyethylene glycol solution or the equivalent, administered over 3-4 h until the rectal effluent is clear. A nasogastric tube can be placed to facilitate colon preparation in intolerant to oral intake patients. Prokinetic/anti-emetic agent immediately prior to initiating the colon preparation may reduce nausea and facilitate gastric emptying[59].

Although colonoscopy has several advantages in the management of LGIB (identification of bleeding sources, multiple therapeutic options, definitive diagnosis, reduction of hospital length of stay and safety), it also has several disadvantages (need for colon preparation and sedation, experienced staff and endoscopy facilities, low prevalence of stigmata of hemorrhage, invasive nature, and rare but serious complications)[111].

A higher risk of urgent colonoscopy adverse events may occur in elderly patients with comorbidities or on antithrombotic therapy[113,114]. BP may increase the risk of vomiting, aspiration pneumonia a volume overload[111].

Niikura *et al*[115] in a retrospective review investigated adverse events and hemodynamic instability during BP and colonoscopy in hospitalized patients with acute LGIB. They showed that during BP, the 9% of LGIB patients experienced an adverse event. None of them experienced volume overload, aspiration pneumonia or loss of consciousness; however, 7% had hypotension and 2% vomited. There were no significant differences in the five BP-related adverse events between LGIB and non-GIB patients.

The use of lower volume or alternative colon preparation solutions in LGIB patients is not well defined, only preliminary data are available and seems encouraging[116].

The American College of Gastroenterology, ESGE and British Society of Gastroenterology recommends against un-prepped colonoscopy in the setting of acute LGIB[59, 117,118].

A prospective pilot study of Repaka *et al*[119] in severe LGIB subjects reported the feasibility and safety of unprepared hydroflush colonoscopy that combined three 1-L tap water enemas, a water-jet pump irrigation system, and a mechanical suction device to cleanse the colon. Cecal intubation was performed in 69.2% of patients and definitive bleeding sources of 38.5% of patients were detected. However, localization of diverticular bleeding, can be difficult in the setting of residual blood and stool and poor visualization may also increase the risk of perforation.

A recent single-center study performed on elderly patients with severe LGIB investigated the efficacy, safety and outcomes of unprepared polyethylene glycol-flush retrograde colon cleansing colonoscopy[120]. In this study cecal intubation was 100%, the rate of definitive bleeding sources was 90.9%. They concluded that this approach was safe, effective and reduced the time of hospital stay, therefore further data are necessary.

Although, the international guidelines recommend BP of this cohort of patients, the best modality to achieve the cleaning of the colon is still an open problem.

Chronic kidney disease and hemodialysis

The assessment of renal function is a key point in the choice of the most adequate and safe bowel cleansing agent prior to colonoscopy, since the assumption of hyperosmotic solutions may lead to dehydration and electrolyte imbalances in people with pre-existing chronic renal disease[59]. Although the relevance of the issue, high quality evidence on different preparations for this high-risk population is lacking, with available data deriving from observational studies. Lee *et al*[121] found no difference in electrolytes or estimated glomerular filtration rate (eGFR) between 4 L PEG and 2 L PEG plus ascorbate in patients with an eGFR < 60 mL/min before colonoscopy. A transient > 30% rise in creatinine levels was recorded in 7.5% and 11.5% of high-volume and low-volume group, respectively ($P > 0.05$). In a similar population, Russman *et al*[122] showed that oral sodium phosphate was associated with a 12.6 (95% CI: 1.5-106.5) times increased risk of renal function worsening compared to 4 L PEG. Frazzoni *et al*[53] compared 1 L PEG plus ascorbate with 4 L PEG, including 52 patients with chronic kidney disease, showing no different shift in serum electrolytes levels and creatinine. Considering these results, PEG-based preparations may be a safe choice in people with pre-existing mild to moderate chronic kidney disease (eGFR ranging from 89 to 30 mL/min), whereas current international guidelines do not recommend hyperosmotic low-volume PEG-based agents in people with severe renal insufficiency (eGFR < 30 mL/min) for the high risk of electrolyte imbalances. However, high quality randomized trials are needed to better clarify the safety profile of PEG-based solutions in the setting of chronic kidney disease. On opposite, the use of non-PEG-based low volume preparations should be avoided in this population due to possible magnesium toxicity or acute phosphate nephropathy[53,123].

Some warnings have been raised on the safety of bowel cleansing agent administration in people on haemodialysis[124]. Indeed, potential intravascular depletion following bowel cleansing agent intake may lead to hypotension and thrombosis of the arteriovenous fistula. Moreover, the association of BP assumption and hemodialysis treatment may cause severe hypovolaemia. Additionally, high-volume PEG-based solutions may produce fluid overload in these anuric patients. Despite these relevant concerns, there is currently no high quality evidence on the safety of the different formulations of bowel cleansing agents in this population, which has been systematically excluded from randomized trials. Only two studies explored the efficacy and safety of PEG-based preparations prior to colonoscopy in patients with pre-existing chronic kidney disease, including a cohort of people receiving hemodialysis[121,125]. The authors found no significant variation in serum electrolyte levels after the assumption of PEG-based formulations. However, these studies have a retrospective observational design and enrolled a total of 37 patients on hemodialysis. On these bases, specific recommendations on the use of bowel cleansing agents in this at-risk population are not provided. The first randomized trial comparing the efficacy and safety of 4 L PEG *vs* 2 L PEG plus citrate prior to colonoscopy in people receiving hemodialysis is currently ongoing (NCT04709770).

Inflammatory bowel disease

Adequate BP is crucial to assess disease activity in patients with inflammatory bowel disease (IBD). Moreover, the widespread promotion of dye-based and virtual chromoendoscopy as appropriate diagnostic techniques for neoplasia surveillance in this population at high risk of CRC further emphasizes the relevance of achieving high quality BP[126-128].

Evidence from randomized trials showed comparable efficacy between high-volume and low-volume PEG-based solutions in people with IBD. Manes *et al*[129] found no significant difference in adequate bowel cleansing between 4 L PEG and 2 L PEG plus bisacodyl in 216 patients with ulcerative colitis (75.0% *vs* 81.5%, respectively). Kim *et al* [130] demonstrated comparable rates of satisfactory BP between 4-liter PEG and 2-liter PEG plus ascorbate (96.2% *vs* 92.9%; $P = 0.68$) in a cohort of 109 participants with ulcerative colitis. Similarly, Kato *et al*[131] showed the non-inferiority of 2 L PEG plus ascorbate in terms of bowel cleansing compared to 4 L PEG in 70 patients with ulcerative colitis or Crohn's disease. In these trials low-volume formulations had higher patients' tolerability and willingness to repeat the preparation than 4 L PEG. Based on these results, both high-volume and low-volume PEG-based BPs are recommended in patients with IBD before colonoscopy[59], although low-volume agents may be a more advisable choice in people undergoing a considerable number of colonoscopies during their lifetime[132]. Conversely, low-volume non-PEG-based preparations should be avoided in this population, since they may cause mucosal alterations mimicking IBD[18,59]. Lawrance *et al*[133] showed a 10-fold higher rate of

preparation-induced mucosal inflammation with magnesium citrate plus sodium picosulfate and sodium phosphate compared to 4 L PEG in a randomized trial enrolling 634 participants without pre-existing or suspected IBD. Sodium phosphate-related inflammatory abnormalities were detected in 3.3% of patients in a prospective observational study including 730 participants without previous diagnosis of IBD and not using non-steroidal anti-inflammatory drugs[134].

Inpatient

Previous evidence underlined that inpatient status is one of the associated factors with inadequate BP[135-138]. In this cohort of patients, the percentage of colonoscopy with adequate preparation is between 50% and 75%[135,139,140], thus increasing the hospital length and costs[138].

It is crucial to identify predictive factors associated with inadequate BP in this cohort of patients, and in the same time, to found the best bowel cleansing agent.

The explanation could be the worse American Society of Anesthesiologists status in inpatient setting[141] prolonged immobility and the use of concomitant drugs that can impair bowel motility[142], as opiate drug[139].

The multicenter observational study of Fuccio *et al*[143] identified the factors associated with a more proper colon cleansing (physicians' meetings to optimize BP, written and oral instructions to patients, admission to gastroenterology unit, split-dose regimens, a 1 L polyethylene glycol-based bowel purge, and 75% or more intake of BP). The authors, also, found factors associated to an increased risk of inadequate colon cleansing (bedridden status, constipation, diabetes mellitus, use of anti-psychotic drugs, and 7 or more days of hospitalization).

Considering the modifiable factors, Gkolfakis *et al*[140] evaluated the role of education interventions to increase adequate BP in a recent meta-analysis. In the six included studies, the adequacy was achieved in 77% (62%-91%) of patients with education interventions *vs* 50% (32%-68%) of patients with no intervention. However, this strategy is not enough to reach to 90% of adequate colonoscopy as required by ESGE guidelines.

Regarding the choice of BP, only one study was aimed to assess the role of low volume PEG solution in inpatient cohort. In a retrospective post-hoc propensity matching score analysis of a previously prospective observational study, Frazzoni *et al* [53] found a higher rate of adequate bowel cleansing in group prepared with 1 L-PEG plus ascorbate hyperosmolar preparation than patients with the 4 L-PEG preparation. A specifically designed study is needed to better investigate the efficacy and the safety of low volume bowel agent in this setting of patients.

Elderly people

Patients with more than 65 years require special attention during the BP before colonoscopy, due to fragile equilibrium and/or increase incidence of concomitant diseases. Large volume of BP has a better risk profile, causing less electrolyte abnormalities and low risk of dehydration, but requires a high patient's compliance. Low volume cleaning agents with magnesium citrate or bisacodyl or sodium phosphate should be avoided in this fragile category of patients, due to an increased risk of electrolyte unbalance, ischemic colitis and renal function impairment, respectively [144-146].

Only two RCTs were specifically designed to evaluate BP in elderly people. Jung *et al*[48] enrolled 230 patients aged > 65 years with normal renal function and electrolytes, randomly assigned to one of 3 arms (single-dose 4 L-PEG on the day before colonoscopy; split-dose 4 L-PEG; or split-dose 2 L-PEGA). The rate of adverse events did not differ among the 3 groups, however, patients in 2 L-PEGA group had higher willingness to repeat the same preparation than other groups. The second study[57] evaluated the efficacy safety and efficacy, safety, and acceptability of the oral sulfate solution (OSS) preparation, comparing to 4 L-PEG, in elderly patients. This RCT, enrolling 193 patients, concluded that OSS with a split-dose regimen has greater acceptability and comparable efficacy in bowel cleansing compared to 4 L PEG.

So, despite low evidence, ESGE guidelines[59] suggested the use of PEG solution in elderly patients, and ASGE guidelines[147] recommended to avoid sodium phosphate preparations in these patients.

Congestive heart failure

People with congestive heart failure are at high risk of electrolyte imbalances following the intake of BPs. Indeed, this clinical condition is associated with a decrease in renal blood flow and eGFR. This may lead to acute phosphate nephropathy, due to the reduction in phosphate excretion, or hyponatraemia, linked to hypovolaemia and

high-volume water assumption[124]. Despite the substantial lack of evidence on the efficacy and safety of BPs in this population, high-volume isotonic PEG-based solutions may represent the most adequate option for their reduced risk of causing electrolyte imbalances and fluid shifts[59,124]. Low-volume PEG-based solutions may be an alternative approach due to the reduction in the total volume of liquid intake, although they are currently not recommended in patients with significant congestive cardiac failure (New York Heart Association class III or IV) for the potential harms linked to the osmotically active components included in the formulations[59]. Regardless of the preparation used, strict monitoring is advocated when PEG-based bowel cleansing agents are administered in people with congestive heart failure. On the other hand, low-volume non-PEG based solutions should be avoided in patients with congestive cardiac failure, especially oral sodium phosphate for the risk of causing acute phosphate nephropathy[59,124].

Randomized trials comparing high-volume *vs* low-volume PEG-based preparations in people with congestive heart failure are needed to assess the efficacy and safety of these agents and inform clinical decisions.

Patients with constipation

Constipation is a common gastrointestinal disorder in the community with a global prevalence of 12%–17%[148]. It has been found that constipation exists in 11.9%–17.5% of patients undergoing colonoscopy[137,149] and it is considered one of the risk factors for inadequate BP[137,149–151].

Chen *et al*[152] investigated the efficacy, tolerance, and safety of oral sodium phosphate compared with PEG in patients with chronic constipation and demonstrated that oral sodium phosphate provides better quality BP, despite a smaller amount of intestinal air bubbles than standard 4-L PEG.

Another study of Pereyra *et al*[153] compared the efficacy of different doses of sodium phosphate (NaP) and PEG alone or with bisacodyl for colonic cleansing in constipated and non-constipated patients. In constipated patients the combination of NaP plus bisacodyl presented higher rates of satisfactory colonic cleansing than PEG (95% *vs* 66%; $P = 0.03$).

Although NaP has been shown to be effective in BP of patients with constipation, its use may be causally related to serious organ toxicity (*i.e.* renal damage and permanent renal failure). Therefore, its routine use is not recommended[59].

Despite the low quality of the evidence, additional bowel purgatives are often considered in patients with chronic constipation[59].

An Italian RCT[30] compared bowel cleansing efficacy, tolerability and acceptability of 2 L polyethylene-glycolcitrate-simethicone (PEG-CS) plus 2 d bisacodyl (reinforced regimen) *vs* 4 L PEG in patients with chronic constipation undergoing colonoscopy. There was no statistically significant difference in bowel-cleansing efficacy between the enhanced regimen 2 L PEG-CS plus 2-d bisacodyl and split-dose 4 L PEG in patients with chronic constipation. However, the low-volume PEG preparation containing simethicone showed greater patient acceptability and compliance and was associated with a reduced amount of foam and bubbles over the colonic mucosa.

In a study of Lu *et al*[154] 90 patients with constipation were enrolled and randomly divided into study group (lactulose oral solution and polyethylene glycol electrolyte powder), and control group (polyethylene glycol electrolyte powder only) with 45 patients in each group. Cleansing was significantly better in the study group than in the control group ($P < 0.05$).

One nonrandomized study of Kunz *et al*[155], including 372 patients, compared the effectiveness of high-volume (4 L) PEG solution with low-volume (2 L) PEG solution with ascorbate in constipated and non-constipated adults: no statistically significant difference between the two group was found.

A prospective, randomized, investigator-blinded trial[156] randomized 227 patients with constipation into three groups; enema before purgative use, enema after purgative use, and no enema. The authors found a statistically significant better colon cleansing in the female patients in the enema before purgative group and they concluded that use of enemas before purgatives in patients with constipation significantly improves adequacy of right colon cleansing.

In a multicenter, retrospective cohort study of Yoshida *et al*[157], the efficacy of short duration of polyethylene glycol plus electrolytes (PEG + E Movicol) in improving BP with highly concentrated PEG for colonoscopy in patients with chronic constipation was analyzed. Two or four sachets of PEG + E were prescribed for 1 wk before colonoscopy. They found an improvement rate of BP of 72.6%, regardless of gender, age, and underlying diseases. Also, insertion time and pain score were improved.

Recently, Dang *et al*[158] performed a systematic review of the literature aimed to determine the ideal BP regimen for patients with chronic constipation. Patients receiving NaP had a higher chance of a successful BP than patients receiving PEG ($P = 0.003$). So, they concluded that, in chronically constipated patients undergoing colonoscopy, the use of NaP may result in superior colonic cleanliness when compared to PEG, however quality of evidence was low. In summary, evidence that would allow recommendation of a special regimen or supplemental treatment for BP in patients with chronic constipation is still lacking. Further studies are needed to establish patient-specific colonoscopy preparation protocols, indeed ESGE does not suggest any specific BP in patients with constipation[59].

Patient with previous bowel resection

Patients with previous bowel resection for neoplasia need to undergo a strictly follow up with colonoscopy to detect anastomotic recurrence and prevent metachronous lesion[159]. A good BP is extremely important in these cohorts of patients. Unfortunately, the history of colorectal surgery is a risk factor for inadequate colon preparation. In fact, the study performed by Lim *et al*[160] is the first one demonstrating that the percentage of inadequate BP is higher in the resection group (gastric or colonic resection) than in the control group. This data was confirmed by Pontone *et al*[161] using the same cleaning agent (4 L PEG).

However, other evidence did not support this data. Indeed, In Yoo *et al*[162] did not found a statistically significant difference in adequate cleansing between patients with colonic resection and control group. So, if the patients with colonic resection are a category of patients “hard to prepare” is still debated.

Moreover, the right bowel cleaning agent is still an open problem for this cohort. In a study by Yoo *et al*[162], the BP was performed using two types of agents (2 L and 4 L). In the resection group, the univariate analysis showed a better bowel cleansing in patients who received 2 L of PEG-Asc (1 L at 8:00 PM the day before the colonoscopy, the second 1 L 5 h before the procedure).

A specifically designed study to assess the better cleaning agent in this cohort of patients was performed by Mussetto *et al*[163]. The authors did not find any difference in adequate BP between patients with prior colorectal resection using low volume *vs* high volume preparation; however, the first preparation was better tolerated. The authors demonstrated as well a greater efficacy of low volume preparation in the right colon. However, this finding needs to be taken with caution because the study was not adequately sized and powered to specifically assess this issue. So, a larger study is needed to investigate the better cleaning agent for these patients.

Recently, a prospective, single-center, randomized controlled, endoscopist-blinded study was performed aiming to compare morning-only 2 L PEG group or a split-dose 4 L PEG in patients with previous colorectal surgery for CRC[164]. Adequate BP rate and patients’ satisfaction were higher in the 4 L PEG group than in the other one.

No significant differences were found in PDR, ADR, patient compliance, tolerance, willingness to repeat the preparation or difficulty of the BP process.

Pregnant/lactating patients

Colonoscopy should be performed only if is strongly indicated in pregnant/breast-feeding women. According to ESGE guidelines there are insufficient evidence to determine for or against the use of specific regimens. PEG regimens may be preferred and tap water enemas may be considered for sigmoidoscopy[59].

Limited information is available about the safety of bowel cleansing agents during pregnancy. The systemic absorption of PEG is minimal and abdominal bloating and gas symptoms are infrequent. However, polyethylene glycol solutions have not been studied during pregnancy. Sodium phosphate solutions should be avoided during pregnancy because of it may cause fluid and electrolyte disturbance and may be associated with the risk of phosphate nephropathy. In addition, newborns may have bone demineralization and bone growth failure because of maternal phosphate overload. BP with phosphate enemas before flexible sigmoidoscopy may be safe, but has not been studied in pregnancy; instead, sigmoidoscopy with tap water enemas may be sufficient.

Therefore, flexible sigmoidoscopy with tap water enemas is preferred instead of colonoscopy[165,166]. To our knowledge, no study in the publicly available literature has yet reported the safety profiles of the various BP agents/regimens in lactating women. Interrupting breastfeeding during and after BP with cathartic agents or application of a tap water enema for sigmoidoscopy it would seem the more careful choice[167].

BP AND POST-COLONOSCOPY SYNDROME

Post-colonoscopy syndrome is a condition characterized by persistent abdominal pain, discomfort and bloating after the procedure. In more than 30% of patients, the symptoms affected the normal activity and became persistent for at least 48 h after the procedure[168].

It is more common in females and when the procedural time is long, and may be predicted by conscious sedation and irritable bowel syndrome diagnosis[169].

In this regard, it has been speculated that a transient alteration of gut microbiota, induced by bowel cleansing, could partially concur to its pathogenesis.

It is easily hypothesizable that a profound cleansing induced by ingestion of a purgative solution rich in minerals and PEG may induce a change in microbiota composition. Several studies have tried to address this issue.

In a study on ten adult patients receiving a 4 L-PEG solution, after one month a reduction in *Firmicutes* and an increase in *Proteobacteria* was observed; in particular gamma-proteobacteria were 2.5 times more abundant. At family level, an increase of *Enterobacteriaceae* and a suppression of *Lactobacillaceae* was recorded; overall, authors concluded that this profile change was hallmarked by a reduction of beneficial species [170]. In another study conducted on a pediatric population of 31 children receiving sodium picosulphate, magnesium citrate and senna, a lower diversity in microbial communities was observed after preparation, with increased *Faecalibacterium* and decreased *Ruminococcus*, *Escherichia*, *Pseudobutyrvibrio* and *Subdoligranum*[171]. Chen *et al*[172] enrolled twenty male overweight adults undergoing bowel cleansing with water and sodium phosphate and checked microbiota composition 28 d after the procedure. They identified two different microbiota phenotypes at baseline: *Bacteroides*-dominant and *Prevotella*-dominant. In the first group, preparation induced *Bulleida* appearance, while in the second one an increase in *Akkermansia* was noted. Interestingly, authors underlined that both *Bulleida* and *Akkermansia* are associated with type 2 diabetes and obesity.

It is a debated topic whether the change in microbiota composition is transient. Mai *et al*[173] have demonstrated that these alterations may persist for several weeks.

On the other hand, a study[174] conducted on 23 healthy adults receiving 2 L-PEG and ascorbate showed a 31-fold reduction of microbiota load. However, within 14 d, normalization of such imbalance was observed. Interestingly, a single dose (instead of split preparation) implied more profound changes with increase of *Proteobacteria* and *Fusobacteria*. Additionally, it was demonstrated that the preparation increased pH, thus lowering species producing short chain fatty acids and reducing mucous layer. Someone has speculated that in this study the reversion to microbiota normality could have been justified by the fact that only young patients have been enrolled, thus prompting the need of studies on a more variegated population[175].

However, some studies did not find radical difference in taxonomic abundance after BP[176]. For example, in a Japanese study[177] on eight young adults receiving sodium picosulphate and sennosides, it was observed only a transient modification with increase of *Streptococcus* that reverted after 14 d. However, in this study, a more evident change in microbiota-derived metabolites was found, with increase in alanine, carnitine, choline and others. Similarly, O'Brien *et al*[178] recruited 15 adults who were given 2 L-PEG plus bisacodyl, and, after 3 mo, only four patients did not return to pre-colonoscopy microbiota state.

Only one study was specifically aimed to evaluate the microbiota composition in post-colonoscopy syndrome. In a South Korean study[179], 24 patients underwent colonoscopy after 2 L-PEG plus ascorbate bowel cleansing with evaluation of microbiota composition. Five out of 24 experienced abdominal pain, discomfort, distension, constipation or diarrhea after the endoscopy. It was found that these patients had a high ratio *Firmicutes/Bacteroidetes* compared to those without post-colonoscopy syndrome. Moreover, they exhibited a higher alpha diversity, which progressively improved after the colonoscopy, paralleling the regression of symptoms.

Two RCT studies evaluated the role of probiotic administration after colonoscopy in the resolution of bloating, abdominal pain and altered bowel function post colonoscopy. In the first one probiotic group had a lower number of pain day after colonoscopy performed with air insufflation[180]. The same group did not found significant difference in post-procedural discomfort, bloating nor time to return of normal bowel function between probiotic and placebo groups, after colonoscopies performed with CO₂ insufflation[181].

Therefore, despite the evidences are scarce and worth of investigation in the future, these researches could represent a hint about the involvement of microbiota, BP and insufflation in pathogenesis of minor complications after colonoscopy.

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