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Slow Down to Speed Up Quality: Longer Withdrawal Time of 9 Versus 6 Minutes Increases Adenoma Detection Rate

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Guest Contributor

This article reviews Zhao S, Yang X, Wang S, et al. Impact of 9-Minute Withdrawal Time on the Adenoma Detection Rate: A Multicenter Randomized Controlled Trial. Clin Gastroenterol Hepatol 2020 2020 Nov 19:S1542-3565(20)31553-6. https://pubmed.ncbi.nlm.nih.gov/33220526/

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STRUCTURED ABSTRACT

Question: Is adenoma detection rate higher with a minimum withdrawal time of 9-minutes versus 6-minutes?

Design: Multicenter, unblinded, randomized controlled trial stratified by endoscopists.

Setting: Twelve endoscopy centers in China.

Patients: Included 1,027 outpatients (52.3% men, mean age 56.5 – 56.8) presenting for diagnostic (67.3%), screening (18.8%) or surveillance colonoscopy (14.0%) between January 2018 to July 2019. Patients with inadequate bowel preparation or failed cecal intubation were excluded.

Interventions/Exposure: Outpatients were randomized to get a minimum withdrawal time (WT) of 6 or 9 minute after cecal intubation. Using a timer, minimal WT was 2 or 3 minutes per segment (right, transverse, and left colon). Time used for biopsy or polypectomy was excluded from WT. A timer went off at pre-specified reminder intervals 1 minute before each assumed endpoint, but the endoscopist could extend WT if desired.

Outcome: Adenoma detection rate (ADR) overall and classified by anatomic location, polyp size, morphology, histology, as well as polyp detection rate, number of adenomas per colonoscopy, and adverse events.

Data Analysis: Intention-to-treat analysis and per protocol for all outcomes. Outpatients with an extended WT due to difficult exam or long colon were included in the ITT analysis but excluded from the per-protocol analysis. Comparison of means and percentages by student t and χ^2 Fisher exact test respectively, Mantel-Haenzel test to examine differences in subgroups, and multivariate regression to evaluate risk factors for ADR.

Funding: Grant support from National Key R&D Program of China, National Natural Science Foundation of China Shu Guang project of Shanghai Municipal Education Commission and Shanghai Education Development Foundation, Three Engineering Trainings Funds in Shenzhan.

Results: In the ITT analysis, mean WT was 6 min 15 sec $\pm$ 40 sec and 8 min 53 sec $\pm$ 51 sec in 6 and 9 minute WT groups, respectively **(Table 1)**. Minimum 9-minute WT was superior to minimum 6-minute WT for ADR overall (36.6% vs 27.1%, *P*=0.001), proximal colon ADR (21.4% vs 11.9%, *P*<0.001) and ADR among less experienced (1,000-3,000 colonoscopies performed) endoscopists (36.8% vs 23.5%, *P*=0.001). On multivariate logistic regression, 9-minute WT was an independent predictor of increased ADR (*P*=0.005). Advanced adenoma detection rate and sessile serrated lesion detection rate were numerically higher in the 9-minute WT group but did not achieve statistical significance.

COMMENTARY

Why Is This Important?

Professional society guidelines recommend a mean colonoscopy WT of $\geq$6 minutes for average-risk CRC screening colonoscopies without polypectomy or biopsy to ensure adequate time for thorough inspection and detection of precancerous polyps.[1] This recommendation is primarily supported by a seminal retrospective database study of colonoscopies performed in 2003-04, which found that endoscopists with WT >6 minutes had higher ADR compared to endoscopists with WT <6 minutes (28.3% vs 11.8%, P<0.001). This well-established quality metric is critical to ensure the effectiveness of colonoscopy because it is a surrogate of time spent inspecting and ensures adequate time to identify adenomas. A longer WT seems to provide additional opportunity for

Outcome (%)	6-minute WT (n=513)	9-minute WT (n=514)	*P* value
Adenoma detection rate (ADR)	27.1	36.6	0.001
ADR proximal colon	11.9	21.4	<0.001
ADR diminutive ≤5mm polyps	13.8	18.7	0.04
ADR small 6-9mm polyps	11.5	17.3	0.008
Polyp detection rate	47.8	58.0	0.001
Polyps per colonoscopy	0.9 ± 1.2	1.1 ± 1.3	0.002
Adenomas per colonoscopy	0.4 ± 07	0.5 ± 0.7	0.008
Advanced adenoma detection rate	5.8	7.6	0.27
Sessile serrated lesion detection rate	2.2	4.2	0.15

Table 1. Summary of findings

finding polyps and indeed studies have indicated higher ADR with longer WT up to 11 minutes.[2,3] However, the data is mixed, and other studies show no incremental benefit or a ceiling effect. A recent systematic review and meta-analysis of 9 studies (2 RCTs, 2 cancer registries, 3 retrospective studies) including 69,551 patients showed higher odds of adenoma detection with a ≥9 min versus 6-9 minute WT (OR 1.54, 95%CI 1.30-1.82).[4] Additionally, sessile serrated lesion detection rate was also higher with ≥9 minute versus 6-9 minute WT. This is particularly important since sessile serrated lesions in the right-side of the colon are flat, easy to miss, and are a common precursor lesion for interval CRC. Zhao et al. present the first large multicenter prospective RCT to address this question of optimal WT.

This interaction between WT and ADR is crucial since we know that higher ADRs are associated with lower rates of interval CRC.[5] Also, the performance target is ADR ≥ 25%, so an ADR of 25% should be considered a minimum acceptable ADR. Endoscopists should aspire to higher ADRs since every 1% increase in ADR has been associated with an additional 3% reduction in risk of interval CRC. Thus, if your ADR is 25-30%, then it's probably worthwhile to consider interventions to increase your ADR, including longer WT. In a large community-based study with approximately 77,000 screening colonoscopies, withdrawal time of >6 minutes was shown to be independently associated with a reduced risk of post colonoscopy colorectal cancer (despite an adequate ADR).[6]

Key Study Findings
Colonoscopy with longer minimum WT of 9 versus 6 minutes significantly improved the ADR and adenomas per colonoscopy, especially in the proximal colon and among less experienced colonoscopists. Sessile serrated lesion

detection rate and advanced adenoma detection rate were numerically higher in the 9-minute WT group, but these differences were not statistically significant. Notably, when a 6-minute WT was used, endoscopists achieved an acceptable ADR (27.1%), but ADR surpassed 35% when a 9-minute WT was enforced.

Caution

The study population was heterogenous with mostly diagnostic exams and only 17-%20% were screening exams, which is the typical population for calculating ADR. Although recent studies suggest that ADR can be interpreted in a mixed group, the impact of WT on true screening did not quite achieve statistical significance (30.5% vs 42.9%, *P*=0.08), which reflects that the study was underpowered for this group. The study was unblinded and the authors were aware of the study hypothesis which may play a role in careful inspection.

My Practice

Results of this study indicate that the benefit of a longer withdrawal time is particularly advantageous for less experienced colonoscopists but may be less impactful for an individual who has been practicing for many years and already has a high ADR. These findings resonate with us. Using an audible timer, or the timer on the monitor in the procedure room is a good exercise to get in the habit of spending at least 6-8 minutes during withdrawal, and at least 2 minutes per segment.

It is important to remember that the time spent on withdrawal is meant to be used for careful segmental inspection. In my practice, I (JK) prioritize techniques for a high-quality exam such as thorough washing to remove mucus especially in the right colon where serrated lesions hide, a second look in the right colon, detailed inspection behind folds, and possible use of a distal attachment device. My WT is routinely longer than 9 minutes since I'm very thorough when scoping and I often scope with GI fellows.

In my practice (AS), we generate quarterly report cards for each endoscopist, and data for the whole group is aggregated. We strive for an ADR of >35%, but more important is to identify anyone below 25% and provide them tools to improve. There are many interventions that improve

ADR, ranging from technique, technology and educational interventions. Improving withdrawal time and technique leads to improvement in ADR, but may have benefit in reducing post colonoscopy colorectal cancer even when the ADR is adequate. Ensuring adequate preparation, using water exchange, and changing the patient position during the exam are additional low cost but effective interventions to consider. If further improvement is desired, I would recommend trying a distal attachment device, which helps expose more mucosa and identify polyps. It is important to be receiving regular feedback, such as report cards during these phases and being patient but persistent!

For Future Research

There is minimal research about interventions to help endoscopists with ADR < 25%. Simply prolonging WT won't be helpful if withdrawal technique is poor, so studies assessing impact of longer WT in those poor performing endoscopists would be helpful. Since we have multiple tools and interventions to improve ADR, studies are needed to understand the role of combining these interventions with withdrawal time and technique to understand improvement in ADR, such as distal attachment device plus enhanced withdrawal, or artificial intelligence plus a distal attachment device compared to withdrawal time alone.

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Drainage for Infected Pancreatic Necrosis – Earlier Is Not Better

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STRUCTURED ABSTRACT

Question: Is early catheter drainage of infected pancreatic necrosis superior to delayed drainage (after necrosis is walled-off)?

Design: Patients with infected pancreatic necrosis were randomized to immediate (within 24 hours of diagnosis) percutaneous or endoscopic drainage versus postponed drainage (after necrosis is encapsulated or walled-off).

Setting: Twenty-two centers in the Netherlands, in collaboration with the Dutch Pancreatitis Study Group.

Patients: Hospitalized acute pancreatitis patients with infected necrosis diagnosed within 35 days of onset of acute pancreatitis. Infected necrosis confirmed by gram stain/culture from fine needle aspirate or gas collections on imaging in first 14 days of hospitalization. On hospitalization days 15-35, clinical signs of infection, persistent organ failure or persistent elevation of 2 inflammatory variables (temperature, C-reactive protein, leukocyte count) for 3 consecutive days were also diagnostic of infected necrosis. Key exclusion criteria included previous intervention for necrotizing pancreatitis, inability to undergo percutaneous or endoscopic drainage, or acute pancreatitis symptoms for more than 35 days.

Interventions: Patients were assigned to immediate (within 24 hours) drainage by percutaneous or endoscopic modality versus supportive care with drainage postponed until after the development of walled off pancreatic necrosis. Patients in the postponed group could undergo drainage earlier if clinical decompensation occurred. If catheter drainage was unsuccessful, necrosectomy was performed (either endoscopic transluminal necrosectomy or videoscopic-assisted retroperitoneal debridement). All study patients received antibiotics immediately after diagnosis of infected necrosis.

Outcomes: The Comprehensive Complication Index, which is a validated tool that incorporates all complications over the course of 6 months of follow-up and is weighted based on severity of complication, was the primary outcome. It was originally developed to assess postoperative complications, but is used in non-surgical interventional fields as well.[1] Secondary endpoints included death, organ failure, and health care utilization, such as number of procedures, length of stay, and cost.

Data Analysis: Intention to treat analysis with reported relative risks and mean differences.

Results: Of 932 patients assessed for eligibility, 104 underwent randomization: 55 to the immediate drainage group, 49 to postponed drainage. The mean time after pancreatitis to the first intervention was 24 days in the immediate drainage group, and 34 days in the postponed group. In the intention to treat analysis, there was no significant difference between the groups when evaluating the Comprehensive Complication Index, mortality, or organ failure (**Table 1**). Secondary endpoints evaluating health care utilization found that more persons in the immediate drainage group underwent necrosectomy at a future date, 51% vs 22% (relative risk [RR] 2.27; 95% confidence interval [CI] 1.27–4.06). Those in the immediate drainage group underwent numerically higher mean surgical, endoscopic, and radiologic interventions vs the postponed-drainage group (4.4 vs 2.6; mean difference, 1.8; 95% CI, 0.6 to 3.0), and numerically more total catheter drainages (3.1 vs 1.9; mean difference 1.2; 95% CI 0.3 to 2.2). There was no difference in cost or length of stay between the groups. Importantly, in the postponed group, 39% (19/49) improved with antibiotics alone and no drainage or necrosectomy was indicated.

Funding: None.

Endpoint	Immediate Catheter Drainage (N=55)	Postponed Catheter Drainage (N=49)	Mean Difference (MD) or Relative Risk (RR) (95% CI)
Comprehensive Complication Index score	57 (50 to 65)	58 (50 to 67)	MD: −1 (−12 to 10)
Death within 6 months	7 (13)	5 (10)	RR: 1.25 (0.42-3.68)
New-onset organ failure	4 (7)	8 (16)	RR: 0.45 (0.14-1.39)
Necrosectomy	28 (51)	11 (22)	RR: 2.27 (1.27–4.06)
Mean total surgical, endoscopic, and radiologic interventions for infected necrosis	4.4 (3.6 to 5.3)	2.6 (1.8 to 3.6)	MD: 1.8 (0.6 to 3.0)

Table 1. Summary of findings

COMMENTARY

Why Is This Important?

Necrotizing pancreatitis can develop in up to 30% of acute pancreatitis cases, and subsequent infection frequently requires procedural intervention.[2,3] Infection can be hard to differentiate from the pancreatitis itself, due to the systemic inflammatory response syndrome, but the distinction becomes apparent 2 to 4 weeks after the onset of disease, when the incidence of infected necrosis peaks. Signs of infection include clinical instability, gas bubbles within the pancreatic fluid collection, or a positive gram stain or culture from a fluid collection.

Currently, the recommended approach to infected necrotizing pancreas is a step-up algorithm, with institution of antibiotics that penetrate pancreatic tissue: carbapenems, quinolones, and metronidazole.[4] This is frequently followed by either percutaneous or endoscopic catheter drainage and/or debridement if symptoms such as abdominal pain, nausea, and vomiting persist, or if there are complications, such as gastric outlet obstruction, biliary obstruction, or ongoing clinical symptoms.[5] If minimally invasive retroperitoneal necrosectomy failed, open necrosectomy was performed.[4] It is important to note that this approach is based on the era when open surgical necrosectomy, which has a high morality, was performed.[6]

However, the timing of catheter drainage for infected pancreatic necrosis is unclear. Prior research from the surgical management era indicated that open

surgical necrosectomy/drainage of infected necrosis should be delayed until clearly demarcated walled-off pancreatic necrosis developed, which usually occurred after 4 weeks of developing pancreatitis. Since we can now use a minimally invasive approach to drain infected necrosis (via endoscopy or percutaneous approach), it is unknown if we should initiate this drainage as soon as infection is identified or if patients have better clinical outcomes if drainage is delayed until the collection is walled-off.

Key Study Findings

This is a well-designed randomized control trial to evaluate the hypothesis that earlier catheter drainage of infected pancreatic necrosis leads to better outcomes than postponed drainage (i.e., after walled-off pancreatic necrosis developed). The trial shows no difference in the primary outcome, the Comprehensive Complication Index. There was also no difference between groups regarding mortality or organ failure, and no difference in outcomes including length of stay or hospital costs. In fact, those in the postponed drainage group underwent fewer interventions, and almost 40% of those in the postponed drainage group were able to be treated with antibiotics alone (**Figure 1**).

Caution

Prior to randomization, 37 patients died, underlining the potential for rapid deterioration and high mortality associated with infected necrotizing pancreatitis. Thus, postponed drainage may not be suitable for all patients.

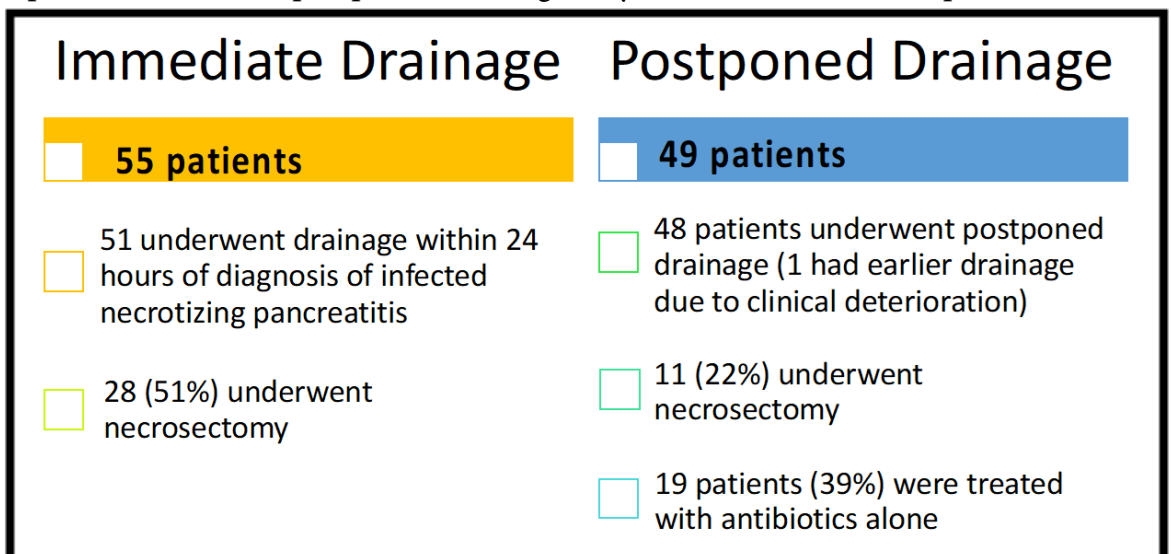| Immediate Drainage	Postponed Drainage
55 patients	**49 patients**
51 underwent drainage within 24 hours of diagnosis of infected necrotizing pancreatitis	48 patients underwent postponed drainage (1 had earlier drainage due to clinical deterioration)
28 (51%) underwent necrosectomy	11 (22%) underwent necrosectomy
	19 patients (39%) were treated with antibiotics alone

Figure 1. Outcomes in the immediate vs postponed drainage groups

There was cross-over of 1 patient from the postponed drainage group, also highlighting the need for close attention to clinical status. Additionally, the trial was unable to include those persons in whom catheter drainage was not feasible, and excluded those with previous drainage.

This underscores that management of pancreatitis is a nuanced issue, and depending on clinical status, accessibility of infected collections, and specialist availability, the approach may still need to be tailored to each patient. This study primarily evaluated timing of intervention, not method of intervention. There are marked differences between percutaneous, endoscopic, and surgical techniques, including efficacy and risk. The timing difference should also be highlighted: immediate catheter drainage occurred at 24 days after symptom onset, while postponed drainage occurred 34 days after symptoms.

My Practice
This study supports our own practice patterns, where we attempt to delay drainage until the collection has walled off. At the time of suspicion of infected necrotizing pancreatitis, we initiate antibiotics, preferring those that can penetrate pancreatic necrosis: carbapenems, quinolones, and metronidazole.[4] We attempt to delay drainage for 4 weeks, then proceed with an endoscopic transluminal approach to facilitate drainage and, if necessary, debridement. For infected necrosis that is not amenable to endoscopic drainage (either in location or if <4 weeks from pancreatitis onset), we proceed with percutaneous catheter drainage. Additionally, if a patient has clinical deterioration and the collection is not yet mature enough for endoscopic drainage, we proceed with percutaneous catheter drainage, which is supported by the results of this trial.

For Future Research
The benefit of early endoscopic drainage in collections that are <4 weeks old should be assessed in comparison to percutaneous drainage, as this could be a practice changing paradigm. Additionally, in this study, there was no difference in healthcare utilization, but in a different setting, and perhaps in the US itself, there may be differences in the cost-effectiveness of immediate vs postponed drainage.

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EVIDENCE-BASED GI
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Hereditary Syndrome Risk Assessment in all Colorectal Cancer Patients: Keep it Simple!

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This article reviews Pearlman R, Frankel WL, Swanson BJ, et al. Prospective Statewide Study of Universal Screening for Hereditary Colorectal Cancer: The Ohio Colorectal Cancer Prevention Initiative. JCO Precision Oncology 2021; 5:779-91. doi.org/10.1200/PO.20.00525

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STRUCTURED ABSTRACT

Question: How effective is universal mismatch repair deficiency (dMMR) testing of Colorectal Cancers (CRCs) in diagnosing patients with hereditary cancer syndromes?

Design: Prospective multi-center cohort.

Setting: Patients were recruited from 51 Ohio hospitals in the Ohio Colorectal Cancer Prevention Initiative from January 2013 to December 2016.

Patients: Adults undergoing resection for primary colorectal adenocarcinoma were included. Those with insufficient tissue, non-adenocarcinoma histology, or a diagnosis made outside of the study period or outside of Ohio were excluded. Of the 3,310 participants included in the study, 52.4% were male, 89.3% were non-Hispanic white, 78.3% were diagnosed after age 50 and 38.5% had right-colon tumors.

Intervention: All patients underwent tumor-based screening for dMMR with microsatellite instability (MSI) or immunohistochemistry (IHC) for mismatch repair proteins at a centralized laboratory. Those with abnormal

tumor screening and those who met clinical criteria underwent multi-gene panel germline genetic testing with a minimum 25-gene panel. Clinical criteria included CRC diagnosed under age 50 years, a personal history of synchronous or metachronous CRC and/or endometrial cancer (EC), or a family history of a first-degree relative with CRC or EC.

Results: Of the 3,310 patients with colorectal adenocarcinoma, 525 (15.9%) had dMMR by either MSI or IHC testing. Of the entire cohort, 1,498 met criteria for germline genetic testing based on tumor screening or clinical criteria. Germline testing was completed in 1,462 patients. Of all patients tested, 248 pathogenic or likely pathogenic variants were found in 234 patients (7.1% of the entire cohort, 16.0% of those tested). The majority of variants (69.2%) were found in genes associated with a high risk of colorectal cancer, such as Lynch Syndrome or polyposis. 6.8% of variants were found in genes associated with a high risk for non-colorectal cancers, such as *BRCA1* and *BRCA2* (**Figure**). Only 145 of 234 patients with a hereditary cancer syndrome had abnormal tumor-based screening. There were 9 patients diagnosed with Lynch Syndrome who had normal tumor-based screening.

COMMENTARY
Why Is This Important?

Hereditary cancer syndromes, caused by a pathogenic variant in a cancer predisposition gene, significantly increase risk of multi-organ cancers. Diagnosis of these patients is of utmost importance because it can change cancer treatment (such as extended colectomy or immunotherapy for Lynch Syndrome patients) and provide the opportunity for future multi-organ cancer prevention in patients and their family members.[1]

The current standard of care is to perform tumor-based screening for mismatch repair deficiency (dMMR) in all CRC patients to determine which patients should get germline testing.[2] This requires an organized multi-disciplinary program wherein all CRC tumor samples undergo MSI or IHC testing and requires an infrastructure to interpret results and ensure patients
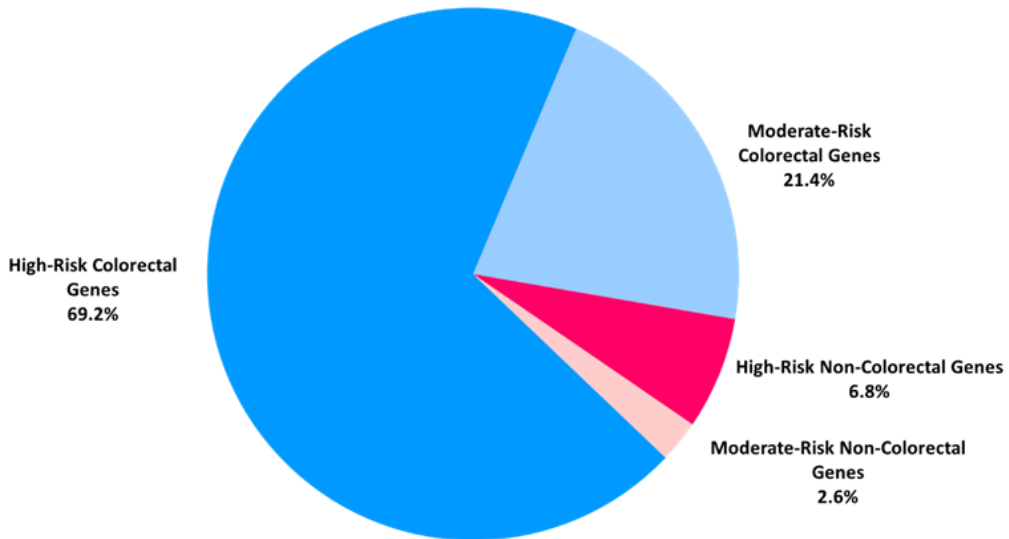
Figure 1. Spectrum of Pathogenic Variants found in Patients with CRC
High-Risk Colorectal genes included Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Familial
Adenomatous Polyposis (*APC*), *MUTYH* Associated Polyposis (biallelic *MUTYH*) and Juvenile Polyposis
Syndrome (*BMPR1A*, *SMAD4*).
Moderate-Risk Colorectal genes included monoallelic *MUTYH, APC I1307K, CHEK2, ATM*.
High-Risk non-colorectal genes included *BRCA1*, *BRCA2*, *PALB2*, *CDKN2A*, *NTHL1*, *POT1*
Moderate-Risk non-colorectal genes included *BRIP1, NBN, GALNT12, RPS20*
For patients who had more than one pathogenic variant, the variant with higher risk and/or colorectal risk was
counted.

are appropriately referred for germline testing. Even when implemented
perfectly, this approach only screens for the most common hereditary CRC
syndrome, Lynch Syndrome. There is minimal population-based data on the
effectiveness of tumor-based screening for diagnosing hereditary cancer
syndromes.

With the emergence of accessible and affordable multi-gene panel testing,
where patients can get direct germline testing for all hereditary cancer
syndromes, it is unclear if tumor-based screening should remain our standard
of care or whether we should consider offering all CRC patients direct multi-
gene panel germline testing.

Key Study Finding
This is the largest, and closest to population-based, cohort of CRC patients to
undergo tumor-based screening. This study found that 7.1% of 3,310
unselected CRC patients have a hereditary cancer syndrome. 76% of
syndromes are associated with a significantly increased risk of CRC (69%) or
non-colorectal   cancers   (7%),   where   there   are   guideline-based

recommendations for more intensive screening, chemoprevention and even prophylactic risk-reduction surgeries. Identification of these syndromes would substantially change clinical management of patients and family members and has the potential to decrease cancer-related burden.

Unfortunately, the current standard of care of tumor-based screening for mismatch repair deficiency missed 38.6% of patients with a hereditary cancer syndrome, including 9 patients with Lynch Syndrome.

Caution
Because widespread multi-gene panel testing emerged in the midst of this study period and the extent of genes included on panels continually changes, genetic testing panels in this study included 25-66 cancer genes. Thus, the testing performed was not uniform.

My Practice
This study shows that even when tumor-based screening is perfectly implemented in a study setting, this approach misses almost 40% of patients with hereditary cancer syndromes. Based on this data, I recommend all CRC patients undergo hereditary risk assessment with 3 simple steps: (1) We should be thinking about a possible hereditary syndrome in all patients we diagnose with CRC, regardless of age at diagnosis, family history or tumor characteristics. (2) I recommend ensuring that our pathology colleagues are performing tumor-based screening for dMMR on our CRC biopsy specimens instead of waiting until resection, since surgical management can change based on presence of a hereditary syndrome. (3) Finally, I recommend all patients with CRC be referred to a genetic counselor who can interpret tumor-based testing, collect multi-generation cancer family history and review the indications, benefits and expected yield of multi-gene panel testing for all CRC patients.

For Future Research
If a universal germline testing strategy is ultimately supported based on studies like this, more research will need to be done to determine exactly which genes should be included on a panel and how best to ensure equitable access to genetic testing and appropriate follow up care for newly diagnosed patients and their family members.
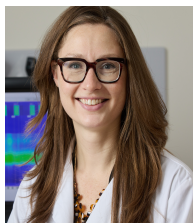
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Treating All the Symptoms of IBS-C: Linaclotide Significantly Decreases Abdominal Pain, Bloating, and Discomfort

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Guest Contributor

STRUCTURED ABSTRACT

Question: Is linaclotide superior to placebo in irritable bowel syndrome with constipation (IBS-C) patients for reducing abdominal symptoms (bloating, discomfort, and pain) using a new patient-reported outcome tool: Diary for IBS Symptoms-Constipation (DIBSS-C)?

Design: Multicenter, double-blind, placebo-controlled randomized controlled trial (RCT).

Setting: Seventy-eight United States centers.

Patients: Included 614 outpatients meeting Rome III IBS-C criteria, with the following criteria in the 2 weeks prior to randomization: average daily abdominal pain ≥ 3 on 11-point numerical rating scale with 0= none and 10= worst possible; <10 spontaneous bowel movements (SBMs); and <6 complete spontaneous bowel movements (CSBM) with sense of complete evacuation.

Interventions/Exposure: Regimen of 290ucg linaclotide daily vs identical placebo for 12 weeks followed by 4-week randomized withdrawal period. All placebo-treated patients switched to linaclotide during withdrawal period and linaclotide-treated patients were re-randomized to linaclotide or placebo for duration of withdrawal period.

Outcome: The primary endpoint was change from baseline in weekly abdominal score (AS) derived from DIBSS-C questionnaire throughout the 12-week treatment period. Weekly AS was calculated by averaging daily AS in a given week. Daily AS was calculated by averaging daily assessment of bloating, abdominal discomfort, and abdominal pain, which were each rated on a 0-10 scale on a daily basis. Two secondary endpoints included the change from baseline based on the average of daily AS from the 12-week period assessed with a cumulative distribution function and proportion of $\geq$6/12 week responders, defined as individuals who had 2-point reduction from baseline in weekly AS for >6 of 12 week study period. Change from baseline for each abdominal score symptom (bloating, abdominal discomfort, and abdominal pain) was also reported individually.

Data Analysis: For the primary efficacy endpoint, a mixed model with repeated measures (MMRM) framework was used to account for multiple variables. For $\geq$6/12 week responders, linaclotide-treated patients were compared to placebo-treated patients using a Cochran-Mantel-Haenszel test controlling for geographic region.

Funding: Ironwood Pharmaceuticals and AbbVie Pharmaceuticals.

Results: 614 IBS-C patients were randomized and received at least 1 dose of medication (mean age: 46 years old; 81% female; 63% White; Baseline Symptoms: Abdominal Score = 6.4 on 0-10 scale; 0.26 CSBMs/week; 1.6-1.7 SBMs/week). Approximately, 92% of patients completed entire 12-weeks of treatment. Overall AS reduction was greater with linaclotide vs placebo (-1.9 vs -1.2, $p < 0.0001$) as well as for reduction in individual symptoms of bloating, abdominal discomfort, and abdominal pain (**Table 1, Figure 1**). Linaclotide-treated patients were more likely to be $\geq$ 6/12 week responders compared to placebo-treated patients: 40.5%vs 23.4% (OR = 2.2, 95% CI: 1.55-3.12, *P*< 0.0001). In the randomized withdrawal period, patients who switched from linaclotide to placebo had a diminished treatment response without suffering from rebound worsening of symptoms. Discontinuation of study medication due to diarrhea occurred in 1.6% of lincaclotide-treated IBS-C patients vs none in the placebo group.

Outcome (%)	Linaclotide (n=306)	Placebo (n= 308)	*P*-value
Abdominal Score (AS) Reduction	- 1.9	- 1.2	< 0.0001
Bloating	- 1.9	- 1.1	< 0.0001
Abdominal Discomfort	- 1.9	- 1.2	< 0.0001
Abdominal Pain	- 1.9	- 1.2	< 0.0001

Table 1. Change from Baseline in Abdominal Score Symptoms Based on 11-point Likert Scale with 0 = None and 10= Worst Possible

COMMENTARY

Why Is This Important?
Optimal treatment of IBS-C requires improvement in abdominal discomfort symptoms as well as improvement in constipation symptoms. The recent American College of Gastroenterology (ACG) Guideline on Management of IBS[1] suggests *against* using polyethylene-glycol products (e.g., MiraLax®) to relieve global IBS symptoms in IBS-C since RCTs report no significant
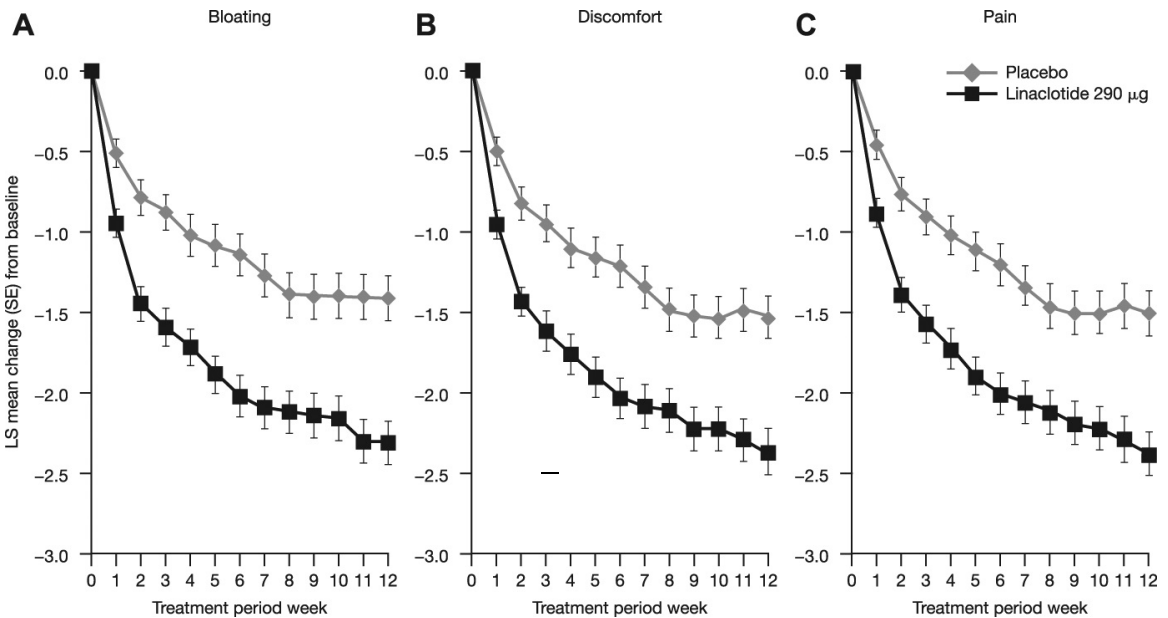

Figure 1. Reduction in Bloating, Abdominal Discomfort, and Abdominal Pain during 12-week treatment period.

differences versus placebo for improvement in abdominal discomfort symptoms. Having said that, many practitioners may still prefer to start IBS-C treatment with an osmotic laxative. We typically inquire about over-the-counter medication use carefully with these patients as the majority have already tried these and failed to get adequate relief, which drives them to seek out medical care.[2]

In the ACG Guideline, guanylate cyclase-C agonists, which include linaclotide (Linzess®) and plecanatide (Trulance®), are the only IBS-C treatments that are strongly recommended based on high quality evidence from RCTs. In those RCTs, a combined responder endpoint of CSBM increase and 30% decrease in abdominal discomfort from baseline for $\geq$ 6/12 weeks defined a responder. Nevertheless, there is limited data using patient-reported outcomes that quantifies decreases in separate abdominal symptom domains, such as bloating and abdominal pain. This focus is important since abdominal symptoms often drive IBS severity and healthcare utilization.

Key Study Findings
Linaclotide is clearly superior to placebo for improvement in abdominal discomfort, and this holds for bloating as well as abdominal pain. Linaclotide-treated patients were more likely to be $\geq$ 6/12 week responders compared to placebo-treated patient (40.5% vs 23.4%; OR 2.2, 95% CI: 1.55-3.12, *P* <0.0001). This is substantial improvement vs placebo, but it's also a reminder that many IBS-C patients may not improve with prescription strength medications alone. For those patients, complementary and alternative approaches such as peppermint oil, neuromodulators, low FODMAP diets, and other similar therapies may be helpful.

Caution
The patient-reported outcomes (PROs) currently favored by the FDA are quite complicated to define, so it's difficult to properly educate patients about how much improvement in abdominal discomfort is likely. Both linaclotide and plecanatide are guanylate cyclase-c agonists. Plecanatide may produce similar improvement in abdominal symptoms, but plecanatide RCTs assessing this are still needed. Although diarrhea is the most commonly reported side effect with

linaclotide, only 4.6% of linaclotide-treated patients reported diarrhea and only 1.6% discontinued linaclotide-treated patients discontinued treatment due to diarrhea, which is lower numerically than in previously reported RCTs.

My practice

Both authors have very similar practices. Guanylate cyclase-C agonists are the cornerstone of our treatment for IBS-C. Consistent with the study findings, we emphasize to patients that it may take 8-12 weeks to achieve optimal decrease in abdominal discomfort symptoms, and we encourage our patients to continue treatment even if there is only mild improvement in the first 1-2 weeks. Furthermore, we try to set appropriate expectations: success means decrease in frequency of abdominal discomfort and decrease in severity of symptoms when they do occur. Near-total resolution of symptoms is not the expected goal, although it does happen for some patients. We proactively educate our patients that loose stools may occur in the first week of treatment.

Since we both treat more severe IBS-C patients, we frequently combine therapies. This includes using peppermint oil capsules as an on-demand or daily anti-spasmodic treatment. We avoid using anticholinergic agents, like dicyclomine (Bentyl®), which could worsen constipation and has not demonstrated significant reductions in abdominal pain vs placebo. These practices are also consistent with the ACG Guideline recommendations. If bloating is a predominant symptom, we advise low FODMAP diets, but try to do this in coordination with a dietitian. We frequently use neuromodulators as additional treatment for abdominal discomfort and to manage brain-gut dysfunction as a cause of IBS symptoms. Our preferred agent is duloxetine (Cymbalta®), which is FDA-approved for neuropathic pain, but it's important to note that there are no well-designed, large RCTs of duloxetine in IBS-C patients. Many patients benefit from complementary therapies, including referral for cognitive behavioral therapy with a specialized psychologist, yoga, relaxation techniques and guided breathing exercises; these are frequently offered at academic medical centers that have multi-disciplinary teams.

For Future Research

There is no RCT data about the efficacy of combination therapy (e.g., linaclotide plus neuromodulator) and there is minimal research comparing

guanylate cyclase-c agonists versus an active comparator, such as psyllium. From a practical perspective, it would be helpful to understand the impact of different doses of linaclotide on abdominal discomfort since we frequently decrease the dose of linaclotide if a patient complains of diarrhea.

Conflicts of Interest

P. Schoenfeld reports serving on advisory boards, consultant and speakers bureau for Ironwood Pharmaceuticals, AbbVie Pharmaceuticals, and Salix Pharmaceuticals, and serving as an advisory board member for Takeda Pharmaceuticals, Ardelyx Pharmaceuticals, and Phathom Pharmaceuticals. J. Deutsch has no reported disclosures.

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