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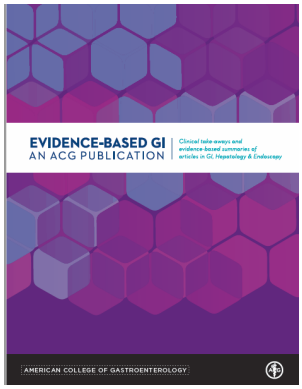

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Cooking Up Something New With a One-Food Elimination Diet: A Simpler Approach to Dietary Therapy for Eosinophilic Esophagitis

Jennifer M. Kolb
Associate Editor

Devin B. Patel
Guest Contributor

Jennifer M. Kolb MD, MS[1] and Devin B. Patel, MD[2]

[1]Assistant Professor of Medicine

[2]Gastroenterology Fellow

Division of Gastroenterology, Hepatology, and Parenteral Nutrition, VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, Los Angeles, CA.

This summary reviews Kliewer K, Gonsalves N, Dellon E, et al. One-food versus six-food elimination diet therapy for the treatment of eosinophilic esophagitis: a multicentre, randomized, open-label trial. Lancet Gastro Hepatol 2023; 8: 408-21

Correspondence to Jennifer M. Kolb, MD, MS. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: In adults with active, symptomatic eosinophilic esophagitis (EoE), is a 1-food elimination diet (1FED) of animal milk similar to a 6-food elimination diet (6FED) of animal milk, egg, wheat, soy, nuts, and seafood, for histological remission and clinical symptoms?

Design: Multicenter, open-label, randomized controlled trial (RCT).

Settings: Ten tertiary care sites of the Consortium of Eosinophilic Gastrointestinal Disease Researchers in the United States.

Patients: Adult patients aged 18-60 years with diagnosis of EoE who were non-responders to a trial of proton pump inhibitors (PPI) were screened. Patients with active EoE symptoms and histologically active disease (defined as >15 eosinophils per high-power field (eos/hpf) in at least 1 segment among the distal, mid, and proximal regions of esophagus) during the 12-week screening period were randomized. Medications, including PPIs, were required to be maintained at same dose.

Exclusion criteria included: 1) use of topical swallowed corticosteroids within 2 months of enrollment or systemic corticosteroids within 3 months; 2) eosinophilic gastrointestinal disease beyond the esophagus; 3) gastrointestinal malabsorption disorders; 3) mild avoidance due to allergy; 4) already on dietary therapy; and, 5) previous non-response to topical corticosteroids.

Interventions/Exposure: Patients were randomly assigned in a 1:1 ratio to either 1FED or 6FED. Randomization was stratified into blocks of 4 by age (≤30 years or >30), sex, and study site. This study followed an open-label design where site investigators, staff, and participants were aware of treatment allocation, however, pathologists who were assessing biopsies were blinded.

Phase 1: Participants followed the 1FED (animal milk elimination) or 6FED (animal milk, egg, wheat, soy, fish and shellfish, and peanut and tree nut elimination) for 6 weeks followed by EGD with biopsy. Individuals with treatment response (histological remission; peak eosinophil count < 15 eos/hpf) completed the study at phase 1.

Phase 2: Individuals without histological response had the option to continue into either 6FED (if failed 1FED) or topical swallowed corticosteroids (fluticasone propionate) if failed 6FED. Repeat EGD was done after 6 weeks.

Outcomes: The primary outcome was histological remission at 6 weeks, defined as peak eosinophil count <15 eos/hpf. Secondary outcomes included proportion of participants with complete remission (peak eosinophil count ≤ 1 eos/hpf), partial remission (peak eosinophil count ≤ 10 eos/hpf and ≥ 6 eos/hpf) and change from baseline in peak eosinophil count. Additional secondary outcomes were histologic

remission for those who completed phase 2 of the study. Additional outcomes were change in symptoms with the Eosinophilic Esophagitis Activity Index (EEsAI) and endoscopic and histologic outcomes using two validated instruments: Eosinophilic Esophagitis Endoscopic Reference Score (EREFS) and Eosinophilic Esophagitis Histology Scoring System (EoEHSS).

Data Analysis: Intention-to-treat (ITT) analysis was used to calculate the primary and key secondary endpoints. The sample size of 120 patients was calculated assuming 45% remission rates in the 1FED vs 70% remission in the 6FED. Subjects who withdrew from the study were considered non-responders and missing data was imputed with the last observation carried forward.

Funding: National Institute of Health.

Results: Between May 23, 2016, and March 6, 2019, 129 patients (mean age 37 years, 54% male) were randomly assigned to 1FED (n = 67) or 6FED (n = 62). Peak eosinophil count at baseline was higher in the 1FED vs 6FED: 50.3 vs 38.4. At 6 weeks, histologic remission was similar in the 6FED and 1FED groups (40% vs 34%, $P = 0.58$) (Figure 1). Similarly, there was no significant difference between the groups at stricter thresholds for histologic remission of $\leq$ 6 eos/hpf (32% vs 18%, $P = 0.07$), although rates of complete histologic remission of $\leq$ 1 eos/hpf were higher in the 6FED vs 1FED (19% vs 6%, $P = 0.03$). Self-reported adherence to dietary therapy was high (1FED 98%, 6FED 97%). Both groups showed improvement in endoscopic fibrostenotic measures with EREFS scores (6FED mean change –1.0 vs 1FED mean change –0.6, $P = 0.28$) and clinical symptoms with EEsAI (6FED mean change –8.2 vs 1FED mean change –3.0, $P = 0.09$).

COMMENTARY

Why Is This Important?

EoE is a chronic inflammatory and fibrostenotic condition driven by a food-antigen-triggered T-helper type 2 allergic immune response. Treatments include PPI, topical swallowed corticosteroids using oral inhalers approved for asthma, and more recently targeted biologic therapy with dupilumab, an interleukin-4 receptor alpha antagonist.

An alternative approach is dietary therapy, which focuses on elimination of specific food exposures thereby preventing the initiation of the inflammatory cascade. Traditionally, empiric food

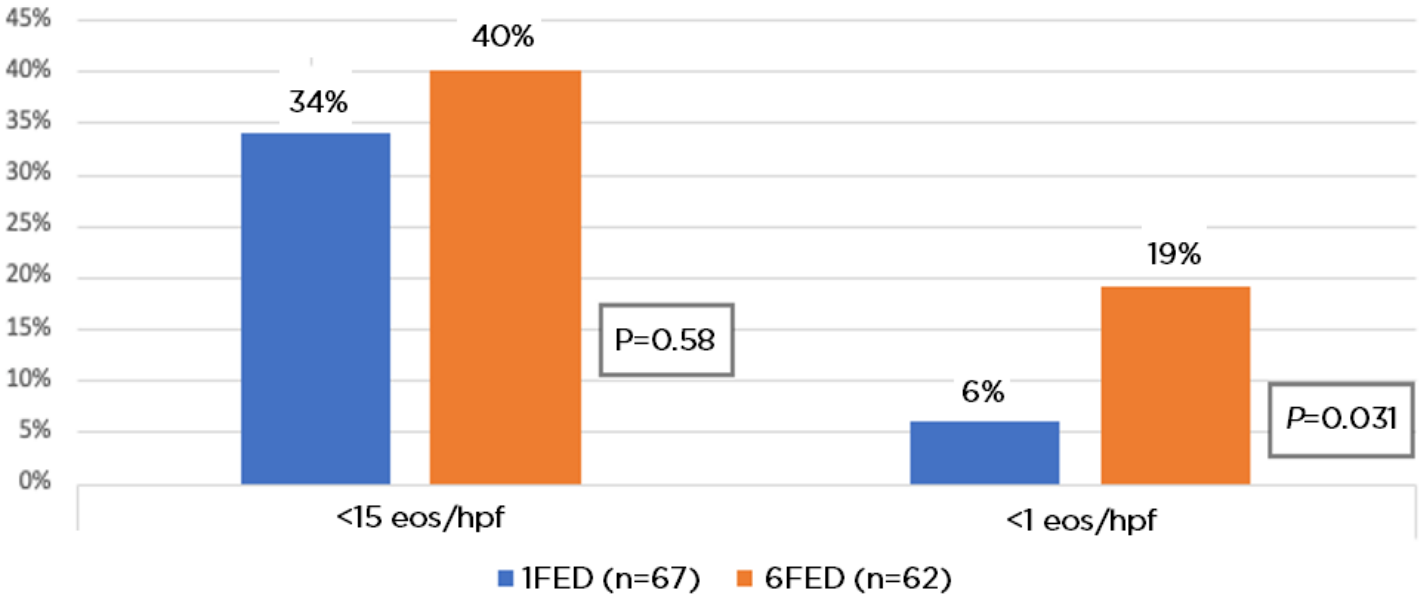

Figure 1: Primary and secondary endpoint outcomes. Proportion of patients in histological remission (<15 eos/hpf) and complete remission (<1 eos/hpf) at week 6.

elimination therapy takes a top-down approach by starting with restriction of multiple food groups followed by a gradual reintroduction. There is growing interest in a step-up approach that is less restrictive and instead starts with the most allergenic food groups (animal milk) given that most patients with EoE tend to have just one or two trigger foods.[3] **(Figure 2).**

Previous non-randomized studies have demonstrated that almost 70% of pediatric and adult patients can achieve histologic remission with an empiric 6FED[1]. However, 6FED poses several practical concerns that limit its utilization for treatment of EoE, including the need for frequent repeated endoscopies after a burdensome re-introduction process as well as poor patient acceptance of these long-term restrictive diets that require avoidance of commonly consumed foods.[2] There have been several single-arm studies evaluating the impact of different levels of restriction with dietary elimination therapy, however comparative data is limited. This is the first randomized trial to compare 1FED to 6FED in adults with EoE.

Key Study Findings

In adults with EoE who were non-responders to PPI, histologic remission (defined as <15 eos/hpf) at 6 weeks was similar in 1FED vs 6FED: 34-40%, P = 0.58.

Improvements in both histologic and endoscopic features using validated scoring systems were similar between both groups. For 1FED non-responders,

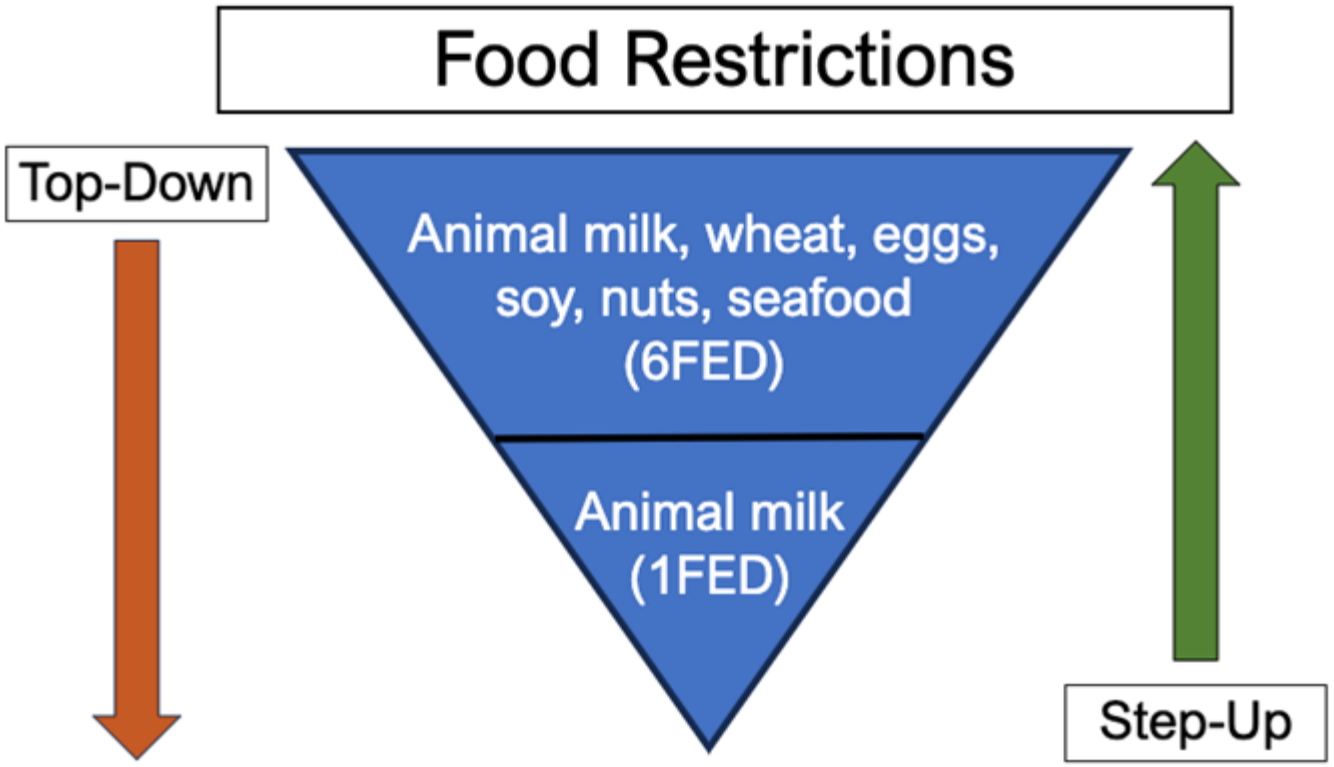

Figure 2: Initial approaches to empiric elimination diets.

6FED was effective in 43%. In 6FED non-responders, swallowed topical steroids was effective in 82%. These findings suggest that elimination of animal milk alone is an acceptable initial dietary therapy for EoE.

Caution

Exclusion of patients who responded to PPI therapy limits generalizability of findings to a subset of the EoE population. The sample size may have been too small to identify differences in clinical symptoms and improvement in endoscopic findings with 1FED vs 6FED. Additionally, the peak eosinophil count at baseline was higher in the 1FED group (50.3) vs the 6FED group (38.4), which could have made it more difficult to achieve histologic remission in the 1FED group.

My Practice

Generally, I try to follow guidelines for management of EoE, including obtaining 6 biopsies from 2 different levels of the esophagus when screening for EoE, obtaining biopsies to check for EoE if I'm performing an EGD to manage a food impaction, and performing repeat EGD about 8-12 weeks after changing EoE treatments since improvement in dysphagia symptoms don't always correlate with histologic remission.[1-2,5]

Generally, PPIs taken twice a day are my initial therapy, although I focus on shared decision making with patients and emphasize that EoE treatment is long-term and should be maintained even after dysphagia symptoms improve. For some patients, an elimination diet may be a preferred first line therapy, but strict adherence to 6FED with gradual reintroduction of potential trigger foods followed by frequent repeat EGD can be onerous for the patient. For this reason, I always explain to patients what the entire process will look like and encourage them to consider whether they will be able to follow all the recommendations. The study findings provide reassurance about starting with a 1FED, which is preferable for patients. If patients don't achieve remission with PPIs/food elimination diets or can't be adherent with food elimination, the decision about whether to proceed with swallowed corticosteroids or dupilumab[5] should reflect the patient's values and wishes through shared decision making.

For Future Research

More data are needed to inform the optimal duration of diet elimination therapy given the uncertainty of long-term nutritional and psychological effects. Future studies should evaluate if the current findings are relevant beyond the US since food triggers may vary geographically.

Conflict of Interest

Dr. Kolb and Dr. Patel report no potential conflicts of interest.

Note: The authors of the article published in the Lancet Gastro Hepatol are active on social media. Tag the to discuss their work and this EBGI summary:

@EvanDellon @IkuoHirano @ngonsalvesMD

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Kiwifruit-A Specific Food to Improve Stool Frequency in Patients With Mild Constipation

FUNCTIONAL

Dr Philip Schoenfeld
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

Chief (Emeritus), Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI.

This summary reviews Gearry R, Fukudo S, Barbara G, et al. Consumption of 2 Green Kiwifruits Daily Improves Constipation and Abdominal Comfort-Results of an International Multicenter Randomized Controlled Trial. Am J Gastroenterol 2023; 118: 1058-68.

STRUCTURED ABSTRACT

Question: Do 2 green kiwifruit (without skin) per day significantly increase complete spontaneous bowel movements in patients with mild functional constipation or irritable bowel syndrome with constipation (IBS-C)?

Design: This is a multicenter, randomized cross-over trial comparing kiwifruit and psyllium. After a 2-week screening period to establish baseline symptoms, study participants were randomized to eat 2 green kiwifruits or to consume 7.5 grams of psyllium for 4 weeks. After an additional 4-week washout period, each patient crossed-over and completed a 4-week trial of the other treatment (**Figure 1**).

Setting: New Zealand, Japan, and Italy from 2014-2017.

Patients: Patients meeting Rome III criteria at initial screening for functional constipation (FC) (n = 60), IBS-C (n =61), and healthy controls (n=63).

Interventions/Exposure: Two green kiwifruits, without skin, vs 7.5 grams of psyllium husk daily. Two green kiwifruits and 7.5 grams of psyllium both contain approximately 6 gm of dietary fiber. It is important to note that approximately 2 teaspoons of brand name psyllium can contain approximately 6-7 mg

of psyllium and 5 gm of dietary fiber.

Outcome: Primary endpoint was number of complete spontaneous bowel movements (CSBMs) per week. Although a specific definition of CSBM was not reported, it's frequently defined as a spontaneous bowel movement with a complete sense of evacuation, which may or may not require absence of straining, too. Key secondary endpoints included gastrointestinal (GI) comfort based on GI Symptom Rating Scale (GSRS), stool consistency based on Bristol stool scale, and straining severity.

Data Analysis: Sample size was calculated to detect a CSBM increase of 1.5 per week in each constipated group (FC and IBS-C) compared to baseline. Intention-to-treat analyses were performed. Categorical endpoints were assessed with Chi-square test and continuous variables were assessed with a mixed models approach to repeated measures of analysis of variance. A hierarchical approach was used to deal with multiple secondary endpoints.

Funding: Zespri International, the world's largest marketer of kiwifruit.

Results: In the combined FC/IBS-C group, study patients were primarily female (82%), European (60%) with mean age = 39 +/-15 and mean body mass index (BMI) = 23 +/- 4. Although the study did not specifically report baseline CSBM, the combined FC/IBS-C group appeared to have almost 4 CSBMs per week at baseline (**Figure 2**). Patients with FC increased their mean CSBMs per week with kiwifruit (1.53) and psyllium (0.67). In IBS-C patients, mean CSBMs per week increased with kiwifruit (1.73) and psyllium (1.25). When evaluating the combined FC/IBS-C group, kiwifruit produced significantly higher increases in mean CSBMs/ week vs psyllium (1.69 vs 0.90, $P = 0.038$) (**Figure 2**). Total GSRS scores were significantly lower after kiwifruit compared to psyllium in the combined FC/IBS-C group.

COMMENTARY

Why Is This Important?

Although we have multiple over-the-counter (OTC) and prescription therapies for chronic idiopathic constipation (CIC) with demonstrated efficacy[1], many patients prefer dietary interventions. Simply suggesting that patients increase their dietary fiber may be too vague and unhelpful for patients, especially since "bran" fiber has not demonstrated efficacy in randomized controlled trials (RCTs).[1] Prior to this research, prunes (or dried plums) contain sorbitol, act as osmotic laxatives, and were the only other specific food that demonstrated efficacy for increasing bowel movements.[2-3] However, since prunes contain sorbitol and are

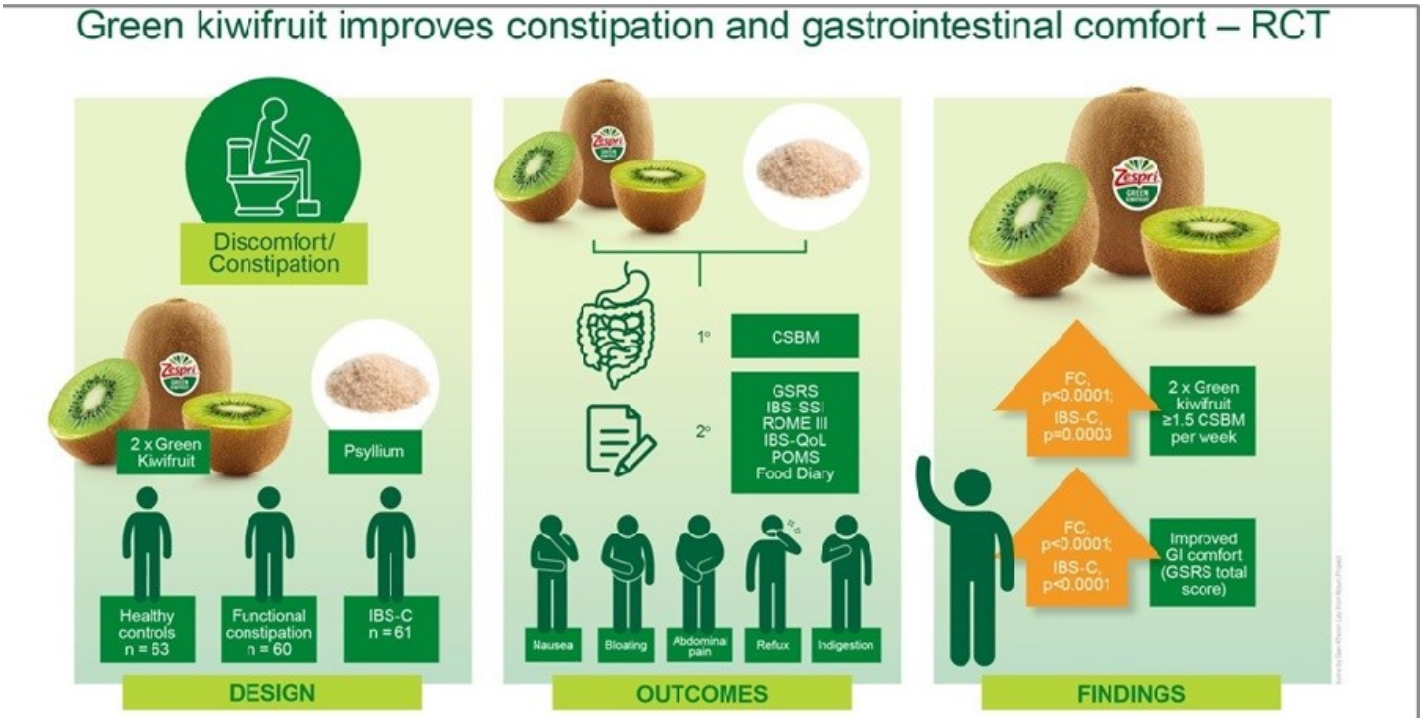

Figure 1. Randomized controlled trial design and results.
Abbreviations: CSBM, complete spontaneous bowel movement; FC, functional constipation; GI, gastrointestinal; GSRS, gastrointestinal symptom rating scale; IBS-C, irritable bowel syndrome with constipation; IBS-QoL, irritable bowel syndrome quality of life; IBS-SSI, irritable bowel syndrome with supplemental security income.

high FODMAP foods, they may also increase bloating and worsen IBS symptoms. Kiwifruits provide an attractive alternative because their cell walls have a particularly pronounced swelling and water-holding capacity in vitro. This facilitates water retention in the lumen of the colon and could improve stool frequency and consistency.

Although this study has important limitations in design (see *Caution* section below), 2 green kiwifruit without skin appears to be effective for increasing CSBMs and this is at least the second RCT to demonstrate this.[4] Therefore, this is an important advance for our patients.

Key Study Findings

When evaluating the combined group of patients with functional constipation or IBS-C, kiwifruit produced significantly higher increases in mean CSBMs/ week vs psyllium (1.69 vs 0.90, $P = 0.038$) (**Figure 2**).

Caution

Although patients met Rome III criteria for functional constipation or IBS-C at the onset of the initial 2-week lead-in/ screening period, study patients appear to have had > 3 CSBMs/week when first randomized to kiwifruit or psyllium (**Figure 2**). This suggests that patients had very mild symptoms at onset of the trial, limits generalizability, and contrasts with the moderate-severe CIC patients

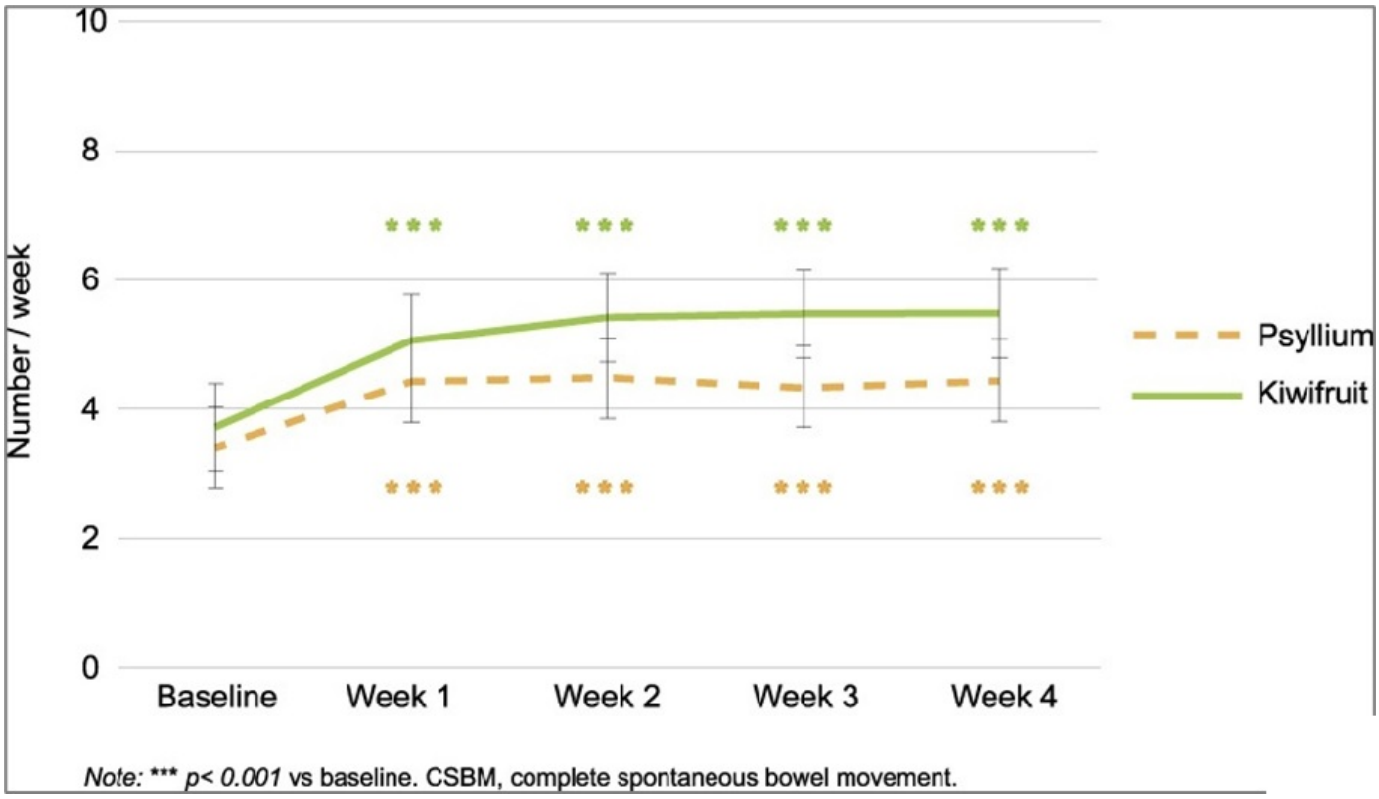

Figure 2. increase in complete spontaneous bowel movements from baseline in combined constipation (functional constipation + irritable bowel syndrome with constipation) patients. Abbreviations: CSBM, complete spontaneous bowel movement; FC, functional constipation; GI, gastrointestinal; GSRS, gastrointestinal symptom rating scale; IBS-C, irritable bowel syndrome with constipation; IBS-QoL, irritable bowel syndrome quality of life; IBS-SSI, irritable bowel syndrome with supplemental security income.

with < 1 CSBM/week that have been enrolled in RCTs of constipation therapies. Also, the study duration is quite short for a chronic condition: 4 weeks in each treatment arm, and patients were unblinded about their treatment.

My Practice

Many of my patients dislike the consistency of psyllium/fiber supplements and desire dietary interventions. For these patients, prunes and kiwifruit are good recommendations, although prunes may increase bloating since it contains sorbitol. I also educate my patients that excessive consumption of water is unlikely to improve constipation symptoms unless it's combined with an agent (e.g., kiwifruit) that facilitates water retention in the colon.

Per my previous commentary[1], the vast majority of my patients have already tried and failed multiple OTC agents, including fiber supplementation, polyethylene glycol (PEG), or stimulant laxatives, prior to my evaluation. Although it's certainly reasonable to discuss dietary modification for constipated patients, we should focus on asking patients what they have tried and failed in the past and then focus on initiating

prescription therapies for moderate-severe symptomatic patients that make it to a gastroenterologist. Of course, shared decision-making is also critical. We must offer treatments that the patient will utilize and can afford. Unfortunately, many of my patients live in inner-city "food deserts" where they have limited access to well-stocked grocery stores with kiwifruit. Finally, don't forget the basics when patients present for evaluation of chronic constipation. Do a digital rectal exam and assess for pelvic floor dysfunction/inappropriate ascent of the pelvic floor when the patient does a Valsalva maneuver. When I suspect pelvic floor dysfunction, especially in women who have had complicated vaginal deliveries and have failed multiple CIC therapies, I'll order anorectal manometry and defecography.

For Future Research

Longer and better designed clinical trials would be helpful, although these studies would be expensive to conduct.

Conflict of Interest

Dr. Schoenfeld reports serving on advisory boards, consultant and speakers bureau for Ironwood Pharmaceuticals, AbbVie Pharmaceuticals, and Ardelyx Pharmaceuticals, and serving as an advisory board member for Salix Pharmaceuticals.

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In Case You Missed It

Albumin Infusions Do Not Improve Outcomes in Hospitalized Patients with Decompensated Cirrhosis: The ATTIRE Trial

LIVER

Nicole Rich, MD, MSCS
Associate Editor

Nicole E. Rich, MD, MSCS

Assistant Professor, Associate Director of the Liver Tumor Program, Harold C. Simmons Comprehensive Cancer Center, Associate Director of Clinical Research, Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas Texas

This article reviews China L, Freemantle N, Forrest E et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. NEJM 2021; 384: 808-817.

Correspondence to Nicole Rich, MD, MSCS, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does administering repeated daily infusions of 20% albumin solution, targeting a serum albumin level of ≥3.0 g/dL, reduce the incidence of infection, renal dysfunction, and death among hospitalized patients with decompensated cirrhosis compared with standard care?

Design: Multicenter, open-label, parallel-group randomized controlled trial (RCT).

Setting: Thirty-five hospitals across England, Scotland and Wales between January 2016 and June 2019.

Patients: Included patients were: (a) age ≥18 years; (b) hospitalized with acute complications of decompensated cirrhosis; (c) had a serum albumin level <3.0 g/dL within 72 hours of hospital admission; and (d) had an anticipated hospital stay of 5 days or longer. Investigators used their clinical judgement to avoid recruiting patients with (a) expected short-term hospitalization and (b) good short-term survival. Exclusion criteria included patients with advanced hepatocellular carcinoma (with life expectancy < 8 weeks) and patients who received palliative care.

Interventions/Exposure: Twenty percent human albumin solution (infused at 100 ml/hr) beginning on day 1 of recruitment into study, with goal to maintain albumin level ≥3.5 g/dL vs standard care. Albumin infusions were continued for a maximum of 14 days post randomization, until discharge, or when patient was deemed fit for discharge, whichever came first. Notably, albumin was *not* withheld in patients in the standard of care group with spontaneous bacterial peritonitis, hepatorenal syndrome, or those who underwent large-volume paracentesis due to ethical concerns (given the established benefit of albumin in these scenarios, as recommended by society guidelines). Patients were evaluated until day 15, at discharge, or when patient was deemed fit for discharge.

Outcome: The primary endpoint was a composite endpoint that included: (a) infection of any cause, which was adjudicated by physician and did not require positive cultures; (b) renal dysfunction defined as serum creatinine >50% higher than level at randomization; or, (c) death between trial day 3 and trial day 15 or date of discharge if occurring before trial day 15. Outcomes were assessed beginning on trial day 3 as a pre-trial feasibility study demonstrated serum albumin levels ≥3.0 g/dL were reached in most patients within 3 days.

Secondary endpoints included: (a) death at 28 days, 3 months, and 6 months; (b) the composite primary endpoint components; (c) total amount of albumin administered; (d) length of hospital stay; (e) days in the intensive care unit (ICU); (f) incidence of other organ dysfunctions; (g) incidence of liver transplantation within 6 months of trial enrollment; (h) model for end-stage liver disease (MELD) score at end of trial; (i) use of terlipressin for kidney dysfunction, hypotension or variceal bleeding; and finally, (j) serious adverse events. Quality of life and cost-effectiveness analyses are also planned.

Data Analysis: Intention-to-treat analysis, time-to event analysis and mixed effects logistic regression model.

Funding: Health Innovation Challenge Fund, a partnership between the Wellcome Trust and the Department of Health and Social Care.

Results: Eight hundred twenty-nine patients were randomized and 777 unique patients ultimately had data that could be evaluated. The albumin and standard care groups were matched at baseline. Mean age was 53.8 (SD 10.6 years), 70.2% were men, and most (89.7%) had alcohol-related liver disease (ALD). The most common reason for hospitalization was new or worsening ascites (67%), followed by hepatic encephalopathy (19%) and variceal hemorrhage (15%). Overall, patients were recruited to the study 1 day post-hospitalization on average, and median length of stay was 8 days (interquartile range [IQR] 6 -15 days) in the albumin group and 9 days (IQR 6 – 15 days) in the standard care group. Mean serum albumin level at time of enrollment was 2.3 (SD .37 g/dL); median 200 g (IQR 140–

280 g) of 20% albumin was administered in the albumin group compared to 20 g (IQR 0-120) in the standard care group; 49.4% of patients in the standard care group received no albumin.

Overall, incidence of the primary composite endpoint was similar in the albumin and standard of care groups: 29.7% vs 30.2%; adjusted odds ratio (OR) = 0.98; 95% confidence interval (CI) 0.78 -1.33. Time-to-event analysis showed no significant difference in infection, kidney dysfunction, or death between the 2 groups: Hazard Ratio (HR) = 1.04; 95% CI: 0.81–1.35. Further, there was no difference in primary endpoint events in the albumin vs standard care group in any of the prespecified subgroup analyses based on MELD, baseline serum albumin level, use of antibiotics, and number of organ dysfunctions, among others. There were no significant differences in secondary outcomes, including death or time to death.

Compared to the standard care group, more adverse events occurred in the albumin group. Specifically, serious adverse events due to pulmonary edema or fluid overload were numerically higher in the albumin group: 6% vs 2%.

COMMENTARY

Why Is This Important?

Patients with decompensated cirrhosis are at high risk of developing infections that can result in renal failure and death. Intravenous albumin has been used for over 70 years in patients with cirrhosis and continues to be widely prescribed for volume expansion in this population of patients with peripheral arterial vasodilation. Societal guidelines recommend albumin infusion in patients with spontaneous bacterial peritonitis, hepatorenal syndrome, and after large-volume paracentesis.[1]

Albumin, the most abundant protein in serum, not only generates oncotic pressure but has several other functions, including antioxidant, ligand binding and endothelial stabilizing effects.[2,3] Preclinical studies suggest albumin also appears to have an anti-inflammatory role which could result in decreased systemic inflammation and fewer infections, resulting in reduced rates of renal dysfunction and improved survival. However, no large-scale RCTs to date have confirmed this hypothesis. Rather, results of clinical trials of albumin use in cirrhosis are conflicting[4, 5], with recent meta-analyses finding no difference between albumin vs other plasma expanders in preventing death after large-volume paracentesis, and no interventions reducing all-cause mortality in patients with hepatorenal syndrome.[5, 6]

This RCT, the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) trial, aimed to clarify the role and potential benefit of targeted albumin infusions (vs standard care) to reduce rates of infection, renal dysfunction and death, among a population of hospitalized patients at high risk of developing infections and subsequent

mortality. Trials, such as this one, involving hospitalized patients with cirrhosis are challenging and the investigators should be commended for their efforts to tackle this important question about a common clinical scenario.

Key Study Findings

There was no benefit to using albumin to reach and maintain a target serum albumin level ≥3.0 g/dL in hospitalized patients with cirrhosis to minimize infection, renal dysfunction or death compared to standard of care with targeted albumin infusion: 29.7% vs 30.2%; adjusted OR= 0.98, 95% CI 0.71 – 1.33, nor any benefit for any secondary endpoints or across prespecified subgroups.

No significant between-group differences were observed in a time-to-event analysis (HR 1.04, 95% CI 0.81 – 1.35). Compared to standard care, the albumin group received 3x-10x the amount of albumin and had more serious adverse events due to pulmonary edema or fluid overload: 6% vs 2%.

Caution

This trial included sicker hospitalized patients compared to prior trials published in 2018[4, 5] and was not blinded due to concerns about harm to patients receiving excess volumes of "non-albumin" fluid, and routine albumin measurements would have unblinded the trial. Investigators assessed the primary endpoint at time of hospital discharge, rather than predefined time point post-randomization, which may lead to misinterpretation of data and difficulty comparing results with other trials. Excess administration of albumin can be harmful and lead to serious adverse events, particularly cardiopulmonary complications (e.g, pulmonary edema) as observed in this study. The incidence and severity of cardiopulmonary complications become of particular concern in clinical scenarios where albumin therapy is used in combination with terlipressin (recently FDA approved in the US). Finally, as 89.7% of patients had cirrhosis due to alcohol use, with a large proportion having acute alcoholic hepatitis, results may not be generalizable to patients with other etiologies of cirrhosis.

My Practice

I follow the American Association for the Study of Liver Diseases (AASLD) 2021 Practice Guidance on the Diagnosis, Evaluation and Management of Ascites, Spontaneous Bacterial Peritonitis, and Hepatorenal Syndrome.[1] I administer IV albumin to hospitalized patients with refractory ascites, those with hepatorenal syndrome, spontaneous bacterial peritonitis, and at time of large volume paracentesis (LVP), as supported by these guidelines. These guidelines acknowledge the results of the ATTIRE trial and do not recommend use of targeted albumin in hospitalized patients with decompensated cirrhosis outside of the aforementioned scenarios.

For patients with spontaneous bacterial peritonitis (SBP), albumin is not just a

volume expander but prevents progression of acute kidney injury and improves survival, with the sickest patients (bilirubin >5 mg/dL or Cr >1.0 mg/dL) deriving most benefit.[7,8] I do administer the dose of albumin (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) that was used in the trial conducted by Sort and colleagues, though it should be acknowledged that this dosage was arbitrarily selected.[7] For patients undergoing LVP, I administer the recommended 6-8 g per liter of ascites removed. In my practice, my colleagues and I also administer 50 g albumin to patients undergoing paracentesis <4 liters. The optimal doses of albumin for patients with SBP as well as at time of LVP has yet to be determined and more prospective studies are needed in this area.

Data regarding the long-term use of albumin in outpatients with cirrhosis and diuretic-responsive ascites remain controversial and its routine use in clinical practice is not currently supported by the guidelines.[1] A study by Angeli and colleagues demonstrated 20-40 g/week albumin was an effective treatment for muscle cramps in patients with cirrhosis[9], and while this is mentioned in the AASLD guideline as a therapy to consider, this is not something I have personally adopted in my clinical practice.

For Future Research

To improve generalizability and allow for cross-study comparison, future randomized trials in hospitalized patients with advanced cirrhosis should ideally define outcomes based on prespecified timepoints rather than ending data collection at time of hospital discharge.

Conflict of Interest

Dr. Rich has served as consultant for AstraZeneca.

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EVIDENCE-BASED GI
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ENDOSCOPY

Surveillance Colonoscopy Recommendations in Older Adults With Limited Life Expectancy– More Work to be Done!

Shria Kumar, MD, MSCE

Assistant Professor, Division of Digestive and Liver Diseases, University of Miami Miller School of Medicine, Miami, FL

Shria Kumar, MD, MSCE
Associate Editor

This article reviews Calderwood AH, Tosteson TD, Wang Q, et al. Association of Life Expectancy With Surveillance Colonoscopy Findings and Follow-up Recommendations in Older Adults. JAMA Intern Med. 2023 May 1;183(5):426-434. doi: 10.1001/jamainternmed.2023.0078.

Correspondence to Shria Kumar, MD, MSCE. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does estimated life expectancy impact recommendations for timing of repeat surveillance colonoscopy in older adults undergoing routine colon polyp surveillance colonoscopy?

Design: A retrospective cohort study.

Setting: New Hampshire, United States.

Patients: Adults > 65 years old who underwent colonoscopy for colon polyp surveillance between April 1, 2009 and December 31, 2018 with results entered into the New Hampshire Colonoscopy Registry (NHCR) and who had Medicare Parts A and B coverage in the year prior to colonoscopy (to ensure data linkages). Exclusion criteria included those undergoing colonoscopy for indications other than surveillance or with a history of colorectal cancer (CRC), inflammatory bowel disease, or genetic CRC syndromes.

Patient data from NHCR was linked with Medicare claims data. The NHCR is a statewide registry that collects data from sites performing colonoscopy throughout New Hampshire. Data collected includes patient demographic data, family history, colonoscopy procedure data including indication, findings (number and size of polyps or cancer), pathology reports, and follow-up recommendations. Outcomes regarding CRC are supplemented by linkage with the New Hampshire State Cancer Registry. The authors also obtained information on comorbidities and cancer diagnoses through linkage to Centers for Medicare & Medicaid Services.

Exposures: Life expectancy was estimated using a validated prediction model using comorbidities from Medicare claims data[1] and categorized as < 5 years, 5-9 years, and ≥ 10 years. The main covariate was endoscopist recommendations for future colonoscopy, whether it was a specific interval, "recommendation pending pathology," "no future colonoscopy indicated," or other – essentially identifying whether the endoscopist recommended to stop screening. Procedures missing a recommendation or with a recommendation of "follow-up recommendation pending pathology report" were excluded from the analysis of follow-up recommendations because of the inability to assess the final recommendation after the pathology report was reviewed.

Other important covariates included patient age, sex, race, ethnicity, educational level, family history of a first-degree relative with CRC, body mass index, self-reported health, completeness of colonoscopy, bowel preparation quality, and endoscopist factors like gender, specialty, years since completion of training, and adenoma detection rate.

Outcomes: The primary outcomes were: 1) clinical findings of polyps on colonoscopy, especially prevalence of advanced adenomas (i.e., adenomas ≥10 mm, adenomas with high-grade dysplasia or villous features, sessile serrated polyps or hyperplastic polyps ≥10 mm, sessile serrated polyps with dysplasia, or traditional serrated adenomas) or CRC; and, 2) recommendation for timing of future colonoscopy and/or recommendation to discontinue further surveillance colonoscopy.

Statistical Analysis: Data were analyzed using multivariable logistic regression models, with adjustment for factors associated with missing recommendations.

Funding: National Cancer Institute.

Results: Nine thousand eight hundred and thirty-one participants met inclusion criteria. Patient demographics included mean age of 73.2 years, 46.2% were female, and 83.5% were White. Life expectancy was < 5 years in 7.5%, 5-9 years in

35%, and ≥ 10 years in 57.5%, Overall, 791 patients (8.0%) had advanced polyps or CRC. Most of the patients (83.3%) had no adenomas or only 1-2 small adenomas or serrated polyps, which are appropriate for up to 10-year interval between surveillance colonoscopies.

Although there were almost 10,000 participants in the cohort, only 5,281 patients (53.7%) had a documented recommendation at the time of colonoscopy to stop or continue colonoscopy, while approximately 12% had no recommendation and approximately 34% stated recommendation for repeat colonoscopy pending review of pathology results. Among the 5281 patients with an available recommendation, only 13.1% received a specific recommendation to discontinue surveillance colonoscopy, regardless of limited life expectancy or lack of adenomas on colonoscopy.

Although study results did not specifically report on adherence to guidelines about timing of repeat surveillance colonoscopy, several findings stand out. Among 227 patients with life expectancy < 5 years and no adenomas found on colonoscopy, 58% were told to return for repeat surveillance colonoscopy. Among 4622 patients who were recommended to repeat colonoscopy, approximately 70% were told to repeat colonoscopy in 4-5 years. This recommendation was most likely made for patients with 0-2 small adenomas on their colonoscopy, although the interval between colonoscopies could have been lengthened to 10 years. Most importantly, this was recommended in 61.3% of patients with life expectancy <5 years and 69.0% of patients with life expectancy of 5-9 years.

COMMENTARY

Why Is This Important?

Colonoscopy use in older adults is a hot topic, the US has an aging population and we want to provide good quality preventative healthcare, but balance it with the risks of invasive procedures (and our burgeoning healthcare costs). Recently, Dr. Philip N. Okafor, Associate Editor of EBGI, wrote about "Screening Colonoscopy in the Elderly Population—Is Less Better?" where he reviewed El Halabi al. Frequency of use and outcomes in individuals older than 75 years from the Journal of the American Medical Association Internal Medicine. In that study, screening colonoscopy in adults >75 years of age was associated with a very low rate (0.2%) of invasive colorectal adenocarcinoma – and in those with invasive cancer and a life expectancy <10 years, only 1 of 9 received treatment for their malignancy. What's more, those with life expectancy <10 years had approximately double the rate of adverse events after colonoscopy.

While that study evaluated screening, the present study evaluates surveillance colonoscopy. Surveillance after prior colon polyps is the most frequent indication for colonoscopy in older adults. While our guidelines recommend indi-

vidualized decision-making regarding colonoscopy in older adults,[2] our tools to do so are frankly limited. We do not have readily available life expectancy calculators or exact guidance on the cut-off for which colonoscopy would no longer have more benefit than risk, and the fragmented nature of care can make conversations difficult (for example, an "open access" colonoscopy with limited documentation). Still, as endoscopists, we have an important role to play in these decisions. The well-known adenoma-to-carcinoma sequence takes 10-15 years, so performing colonoscopy on those with life expectancy under 10 years may not provide sufficient benefit.[3,4] Coupled with the higher rates of adverse events in older adults undergoing colonoscopy, decision-making becomes even more important.[5] Studies like this are essential to identify both the utility of surveillance colonoscopy, and our real-world practice patterns.

Key Study Findings

Only 13.1% of patients > 65 were told to discontinue colonoscopy for colon polyp surveillance, regardless of limited life expectancy or only finding 0-2 small adenomas on colonoscopy. Among the entire cohort of 9831 of older adults undergoing surveillance colonoscopy, only 8.0% had advanced adenomas or CRC, and the proportion was highest among those with shorter life expectancy.

Caution

The authors did an excellent job with available data, but it is important to consider that the cohort only consists of persons who were recommended for and underwent surveillance colonoscopy. Furthermore, the cohort consisted of 9,831 persons but 4,550 (46.3%) did not have a recommendation in their colonoscopy report—73.4% were due to pending pathology results, the other 25.8% simply had no recommendation. This can be a source of misclassification, though it should be noted that recommendations for follow up are considered a Grade 1A recommendation by the American Society for Gastrointestinal Endoscopy: "appropriate recommendation for timing of repeat colonoscopy [should be] documented and provided to the patient after histologic findings are reviewed."[6] Another area of note is that the cohort was overwhelmingly White – there are marked disparities in healthcare delivery across racial and ethnic groups, including receipt of colonoscopy when indicated.[7]

My Practice

My practice in this area tends to depend on the patient situation. Sometimes, I am seeing a patient in clinic and as part of the visit, can discuss screening. In this case, I seek to have a discussion about the utility of screening, which includes evaluating comorbidities and discussing their quality of life and preferences, to come to a shared decision. (While not the focus of the authors' study, I also utilize non-invasive testing for certain situations, which is best for detecting advanced neoplasia.) Other times, I am performing a referred or open-access colonoscopy, either for endoscopic mucosal resection of a

previously identified lesion or for surveillance/screening. In those cases, if I believe further surveillance is not warranted, I have a telephone or in-person visit with the patient on a separate day. Without clear guidance, I have not incorporated a formal calculator of life expectancy into my discussions.

For Future Research

Ideally in the future, we will have guidance and recommendations using a validated life expectancy calculator specific to colonoscopy. This would account for comorbidities, prior findings and risk factors, and allow us to formally assess the benefits of colonoscopy in older adults. This could also help stratify persons as we consider non-invasive or invasive screening/surveillance methods. Finally, as noted above, we need to take the initiative to find ways to ensure equity in healthcare delivery of colonoscopy, so that we can maximize the benefits of colon cancer screening across all groups.

Conflicts of Interest

Dr. Kumar reports no conflicts of interest.

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