EVIDENCE-BASED GI
AN ACG PUBLICATION

Clinical take-aways and evidence-based summaries of articles in GI, Hepatology & Endoscopy

AMERICAN COLLEGE OF GASTROENTEROLOGY

EVIDENCE-BASED GI

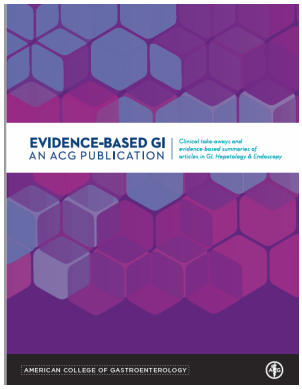
An ACG Publication

EDITORIAL BOARD

CONTACT

We'd love to hear from you!
Send comments and feedback to the editorial office at ebgi@gi.org.

Full issue archives available at gi.org/ebgi



The American College of Gastroenterology (ACG) is an international organization with more than 14,000 physician members representing some 85 countries. The College's vision is to be the pre-eminent professional organization that champions the evolving needs of clinicians in the delivery of high-quality, evidence-based and compassionate health care to advance world-class care for patients with gastrointestinal disorders through excellence, innovation, and advocacy in the areas of scientific investigation, education, prevention, and treatment. *Evidence-Based GI* is a member publication of the American College of Gastroenterology.

TABLE OF CONTENTS

1//IBD

Therapeutic Drug Monitoring of Maintenance Infliximab Is Beneficial for Patients with Immune-Mediated Inflammatory Diseases

Rahul Dalal, MD and Jessica Allegretti, MD, MPH

6// Endoscopy

Endoscopic Eradication Therapy for Neoplastic Barrett's Esophagus Demonstrates 94% Treatment Success and Long-Term Durability

Jennifer Kolb, MD, MS; Sachin Wani, MD

12//CRC Screening

The Pursuit of Excellence in Colonoscopy: Audit and Feedback Improves Polyp Detection in Low-Performers

Philip Okafor, MD, MPH; Uri Ladabaum, MD, MSc

17//Liver

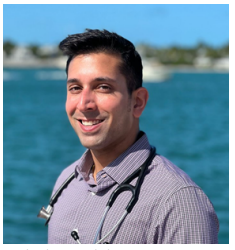
Hepatic Decompensation Rate Is 0.05 per 100 person-years in NAFLD with F0-F2 Fibrosis Score, but Rises to 1 per 100 person-years with F3 Score

Philip Schoenfeld, MD, MSEd, MSc (Epi); Sonali Paul, MD, MS

EVIDENCE-BASED GI
AN ACG PUBLICATION

IBD

Therapeutic Drug Monitoring of Maintenance Infliximab Is Beneficial for Patients with Immune-mediated Inflammatory Diseases



Rahul S. Dalal, MD
Guest Contributor

Jessica R. Allegretti, MD, MPH
Associate Editor

Rahul S. Dalal, MD[1] and Jessica R. Allegretti, MD, MPH[2]

[1]*Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*

[2] *Associate Director, Crohn's and Colitis Center, Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

This article reviews Syversen SW, Jørgensen KK, Goll GL, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA 2021; 326(23):2375-2384. doi: 10.1001/jama.2021.21316. PMID: 34932077

Correspondence to Jessica R. Allegretti, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is proactive therapeutic drug monitoring (TDM) of infliximab levels and anti-infliximab antibodies beneficial during maintenance therapy for patients with stable immune-mediated inflammatory diseases?
Design: Randomized, parallel-group, open-label clinical trial.
Setting: Twenty hospitals in Norway.
Patients: A total of 454 adults with stable psoriasis, psoriatic arthritis, rheumatoid arthritis, spondyloarthritis, Crohn's disease, or ulcerative colitis receiving maintenance infliximab therapy were enrolled between June 2017 and December 2019. Patients were followed through December 2020.
Interventions: All patients were randomized 1:1 to TDM with associated infliximab dose or dose interval changes based on trough infliximab levels and antibodies or standard therapy without infliximab level or antibody monitoring.
Outcome: The primary outcome was sustained disease control (i.e. without a flare requiring change in treatment, change in infliximab dose/interval, or addition of immunosuppressive therapies such as corticosteroids) for 52 weeks. Secondary outcomes included time to disease worsening, patient/physician global assessments of disease activity, remission status, adverse events, and inflammatory markers, among other outcomes.

Data Analysis: Logistic regression was used to analyze the primary outcome with treatment group and stratification factors as covariates. Secondary outcomes were assessed using Cox proportional hazards regression (for time-to-event endpoints), mixed-effects logistic regression (for binary outcomes), and linear regression (for continuous outcomes).
Funding: The study was funded by the Norwegian Regional Health Authorities.
Results: Sustained disease control without disease worsening (primary outcome) at 52 weeks was observed in 73.6% in the TDM group and 55.9% in the standard therapy group, with an estimated adjusted difference of 17.6% (95% CI 9.0%-26.2%, p<0.001). A stratified analysis by use of concomitant immunomodulators showed similar results. The hazard ratio for disease worsening with standard therapy compared to proactive TDM was 2.1 (95% CI 1.5-2.9). Disease activity, remission status, and adverse event rates were similar between intervention arms.

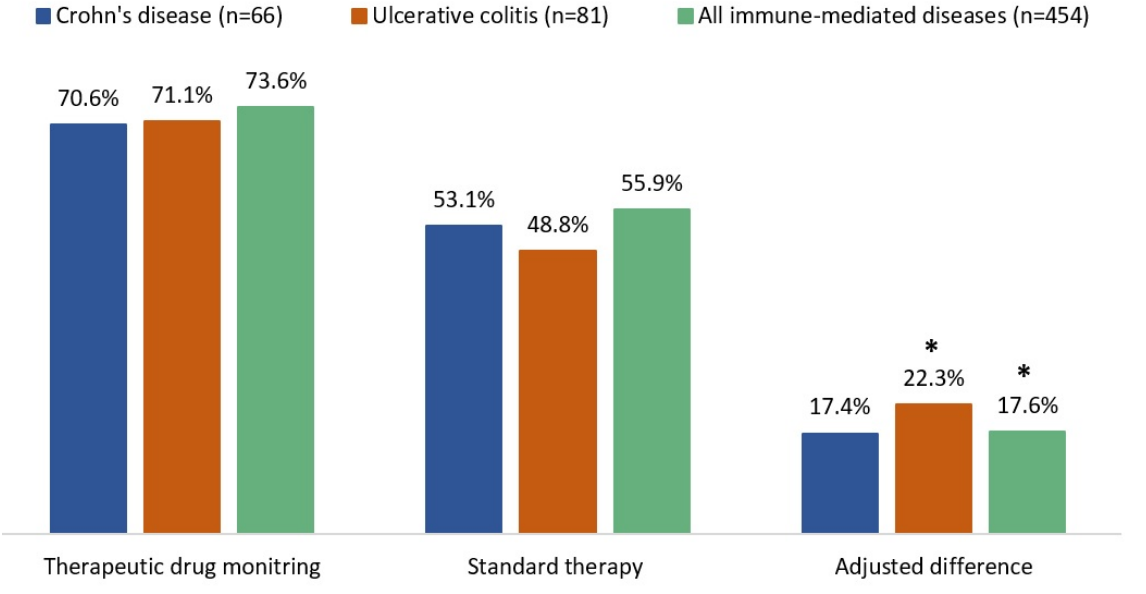


Figure 1. Sustained disease control without worsening.
*Statistically significant results

COMMENTARY

Why Is This Important?

Anti-tumor necrosis factor alpha (TNF) agents such as infliximab are needed to reduce the risk of disease exacerbations and improve quality of life among patients with moderate-to-severe inflammatory bowel diseases (IBD). However, up to 50% of patients with IBD who initially respond to anti-TNF agents lose their clinical response over time.[1] Observational studies have demonstrated that subtherapeutic serum infliximab levels and development of neutralizing anti-infliximab antibodies have been associated with loss of clinical response in this population.[2,3]

Prior clinical trials assessing proactive TDM for infliximab include the TAILORIX (122 Crohn's disease patients) and TAXIT (263 IBD patients) trials, both of which did not demonstrate a statistically significant benefit of TDM for their primary outcome of clinical remission.[4,5] However, TDM was associated with fewer disease flares during the course of therapy in the TAXIT trial.[4] Therefore, additional RCT data is needed to determine if there may be a benefit of proactive TDM for infliximab.

Key Study Findings

In this RCT of 454 patients with stable immune-mediate inflammatory diseases treated with maintenance infliximab, Syversen et al. found that proactive TDM was associated with a lower risk of disease worsening and less anti-infliximab antibody formation over 52 weeks of follow-up compared to standard care. The efficacy of proactive TDM persisted after stratification by immunomodulator use and in sensitivity analyses that varied the definition of disease worsening, strengthening the study's primary findings. These data support the use of a treat-to-target approach using trough drug concentrations and anti-drug antibody levels during maintenance infliximab therapy for autoimmune diseases.

Caution

The study assessed multiple autoimmune diseases, among which IBD represented 147/454 (32.4%) patients. While a statistically significant

favoring TDM was found for ulcerative colitis, the same result was not statistically significant for Crohn's disease, though the overall effect was similar and lack of statistical significance likely reflects that only 61 study patients had Crohn's disease. Larger randomized trials of proactive TDM are therefore needed for the IBD population.

My Practice

I utilize proactive TDM to guide my therapeutic decisions for all of my patients receiving infliximab treatment. I monitor trough infliximab concentrations and anti-infliximab antibody levels immediately prior to the first maintenance infusion and prior to subsequent infusions that follow a change in dose. For low infliximab trough concentrations without antibodies, I typically increase the dose in 2.5 mg/kg intervals to a maximum of 10 mg/kg. If there is a low infliximab concentration with low levels of antibodies present, I will often increase the dose and consider the addition of an immunomodulator. If there is absent drug with high levels of antibodies, I will switch to a new agent. Even though there is limited data for other anti-TNF agents, I still practice more proactive TDM for therapies such as adalimumab.

For Future Research

It remains unclear if the efficacy of proactive TDM is unique to infliximab therapy or if similar effects are present with other anti-TNF agents. Additionally, Syverson et al. did not demonstrate a significant benefit of proactive TDM for Crohn's disease, likely due to the sample size reductions when assessing individual diseases. Larger randomized trials in IBD and cost effectiveness analyses comparing proactive to reactive TDM would be helpful to justify the proactive approach for anti-TNF therapies in the IBD population.

Conflicts of Interest

Jessica R. Allegretti, MD, MPH is a consultant for Baccain, Janssen, Merck, Morphic, Pandion, Pfizer, Salix, Servatus, and Takeda; serves on the advisory boards for Artugen, Finch Therapeutics, and Iterative Scopes; and has received research support from Finch Therapeutics, and Merck.

Rahul S. Dalal, MD has received grant funding from Pfizer.

REFERENCES

1. Roda G, Jharap B, Neeraj N, Colombel J-F. Loss of response to anti-TNFs: Definition, epidemiology, and management. Clin Trans Gastroenterol 2016;7(1):e135.
2. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147(6):1296-1307.e5.
3. Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015;64(10):1539-45. doi:10.1136/gutjnl-2014-307883.
4. Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148(7):1320-9.e3.
5. D'Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. Gastroenterology 2018;154(5):1343-1351.e1.

EVIDENCE-BASED GI
AN ACG PUBLICATION

ENDOSCOPY

Endoscopic Eradication Therapy for Neoplastic Barrett's Esophagus Demonstrates 94% Treatment Success and Long-term Durability

Jennifer M. Kolb, MD, MS
Associate Editor

Sachin Wani, MD
Guest Contributor

Jennifer M Kolb MD, MS[1] and Sachin Wani, MD[2]

[1]*Assistant Professor of Medicine, Division of Gastroenterology, Hepatology and Parenteral Nutrition, VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, Los Angeles, California*
[2]*Professor of Medicine, Division of Gastroenterology and Hepatology, University of Colorado Anschutz School of Medicine, Aurora, Colorado*

This article reviews Sanne van Munster, Esther Nieuwenhuis, Bas L A M Weusten, et al. Long-term Outcomes after Endoscopic Treatment for Barrett's Neoplasia with Radiofrequency Ablation ± Endoscopic Resection: Results from the National Dutch Database in a 10-year Period. Gut 2022; 71: 265-76. PMID: 33753417. http://www.doi.org/10.1136/gutjnl-2020-322615.

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

STRUCTURED ABSTRACT

Question: What are the short- and long-term outcomes of endoscopic eradication therapy (ablation ± resection) for patients with Barrett's esophagus (BE) related neoplasia?

Design: Nine centralized, expert centers in the Netherlands where endoscopists and pathologists adhere to a standardized protocol for BE care.

Patients: The study included 1,386 patients with BE and confirmed low-grade dysplasia (LGD), high-grade dysplasia (HGD), or low-risk esophageal cancer (EAC; mucosal or superficial submucosal sm1, well-moderately differentiated, no lymphovascular invasion, R0 resection) who underwent at least 1 radiofrequency ablation (RFA) between January 1, 2008, and December 31, 2018 in the RFA treatment cohort. There were 1,154 patients in the RFA durability cohort who had successful endoscopic eradication therapy and achieved complete eradication of BE with at least 1-year of follow up.

Interventions/Outcomes: Patients in the RFA treatment cohort underwent endoscopic resection of any visible lesions followed by RFA at 3-4 month intervals (or straight to ablation if all flat dysplasia). This was followed by touch up for residual non-neoplastic BE that persisted with resection, argon plasma coagulation, or RFA of the gastroesophageal junction. The RFA

durability cohort underwent endoscopic surveillance every 3 months in year 1, followed by annual endoscopy in years 2-5, and then endoscopy every 2-3 years. However, after 2015, the protocol was changed to 1 endoscopy in the first year. Surveillance biopsies were taken from the cardia and the neosquamous epithelium, according to the Seattle protocol from 2008-2013, but both were abandoned (neosquamous in 2013, cardia 2016) and replaced with close examination and only targeted biopsies.
Outcome: Rate of complete eradication of intestinal metaplasia (CE-IM) after treatment, rate of sustained eradication of LGD/HGD/EAC during long-term follow up, rate of progression to advanced EAC not amenable to endoscopic resection, and complications. Additional outcomes included diagnostic yield of surveillance endoscopy and random biopsies.
Data Analysis: Durability of dysplasia eradication was estimated using Kaplan-Meir, Hazard Ratio for recurrence dysplasia using Cox proportional hazards model.
Funding: None.
Results: A total of 1,386 patients were in the RFA treatment cohort (62% underwent resection of a visible lesion), and 1,270 achieved complete eradication of intestinal metaplasia (94%, 95% CI 93-95). Treatment failure occurred in only 6% of the cohort. Of the 1,154 patients in the RFA durability cohort (median follow-up 43 months, 4 endoscopies), recurrence of LGD/HGD/EAC occurred in 3% of patients (annual risk 1%, 95% CI 0.8-1.4) and of HGD/EAC in 2% (annual risk 0.7%; **Figure 1)**. Recurrences occurred in 38 patients at a median of 31 months. Most were associated with visible lesions and amenable to endoscopic eradication therapy although 5 were advanced EAC that could not be managed endoscopically. Complications included stenosis requiring dilation (15%), bleeding (2%), and perforation after endoscopic resection or dilation (1%). The less frequent surveillance strategy post complete eradication of intestinal metaplasia (after 2015, annually compared to every 3 months the first year) had similar rates of dysplasia recurrence and progression to advanced neoplasia. Additionally, outcomes were the same after abandoning random sampling from the neosquamous epithelium (post-2013) and random cardia biopsies (post-2016).

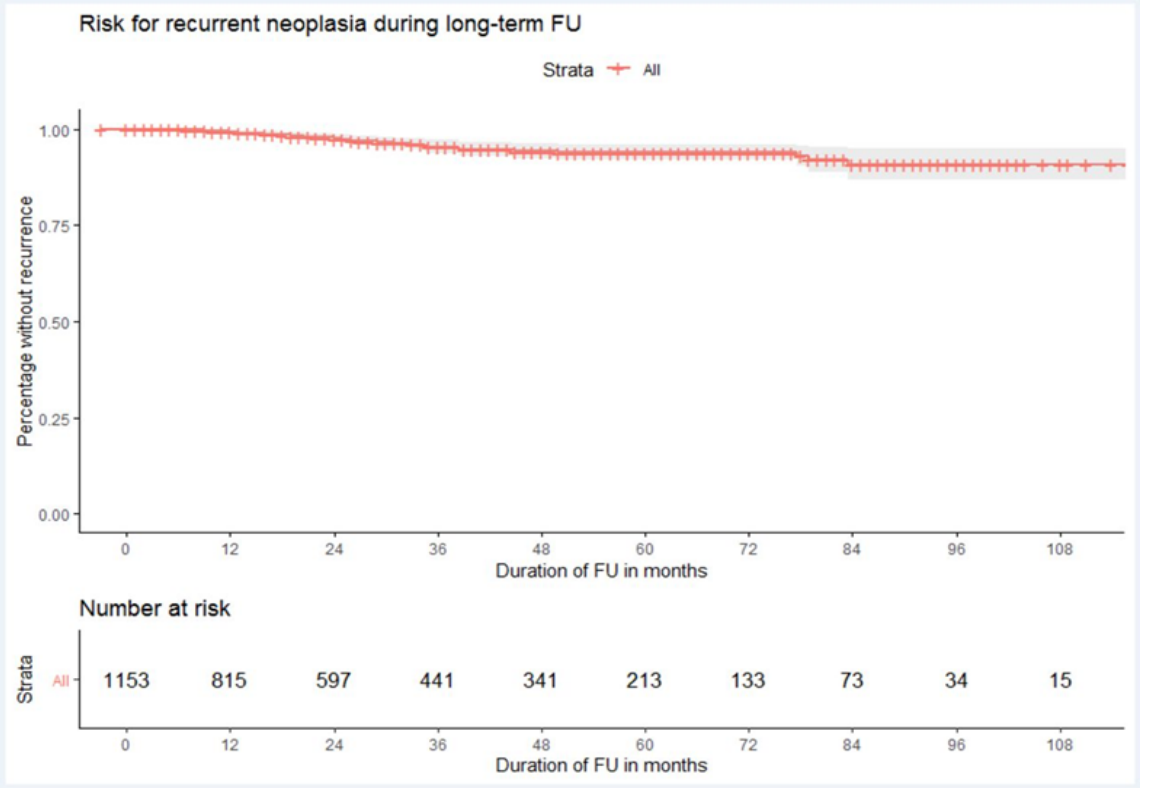


Figure 1. Long-term outcomes. Kaplan-Meier curve for the risk for recurrent dysplasia during follow-up (FU) based on the RFA durability cohort. Recurrence of LGD/HGD/EAC occurred in 3% of patients (annual risk 1%, 95%CI 0.8-1.4) and of HGD/EAC in 2% (annual risk 0.7%).
Figure from van Munster et al. CC BY 4.0 license.

COMMENTARY

Why Is This Important?

Professional society guidelines worldwide recommend endoscopic eradication therapy for BE-related neoplasia with endoscopic resection of visible lesions followed by ablation of the residual flat BE segment over repeated sessions until complete eradication of intestinal metaplasia is reached. Landmark studies such as AIM dysplasia[1] and the SURF trial[2] demonstrate the effectiveness of RFA in achieving complete eradication of intestinal metaplasia in 77-88% of patients. Despite innovation in ablative technologies and meaningful progress creating optimal treatment algorithms, the long-term durability of endoscopic eradication therapy is unknown.

This is the first study to characterize long-term outcomes after RFA in a large cohort and provides important updates to our understanding of the timing and detection of recurrence. Endoscopic therapy was highly effective with low rates of recurrence when performed at centralized care centers by expert endoscopists and pathologists utilizing a standardized protocol. These results emphasize the importance of a high-quality examination as was performed at these Barrett expert centers- use of high-definition endoscopy, standardized reporting systems (Prague C&M criteria), and documentation of any visible lesions.

Additionally, results have been mixed regarding the timing of BE and dysplasia recurrence after eradicating the BE, which impacts surveillance strategies.[3] In this large cohort with long-term follow up, recurrence was rare and typically did not occur until after the first year. In fact, the authors were able to show that more frequent endoscopy every 3 months in the first year after complete eradication of intestinal metaplasia had no benefit over annual surveillance in years 1-5, suggesting less frequent surveillance in year one may be appropriate. Finally, this study addresses 2 key issues related to sampling strategy during surveillance. The current accepted method is 4 quadrant biopsies every 1-2 cm of the neosquamous epithelium (Seattle protocol) during surveillance. However, the investigators abandoned this strategy in 2013 due to presumed low diagnostic yield and indeed found no difference in dysplasia. This underscores the point that most recurrences are visible and can and should be identified with careful inspection. Furthermore, although random biopsies from the cardia showed non-dysplastic IM in 14% of patients, most could not be reproduced and none progressed to neoplasia, suggesting this practice is clinically useless.

Key Study Findings

Endoscopic eradication therapy is highly effective with 1,270/1,348 (94%) of patients achieving complete eradication of intestinal metaplasia. In 1,154 patients with long-term follow up, recurrence was uncommon and occurred in 38 patients (3%) for an annual recurrence risk of 1%. After achieving complete eradication of intestinal metaplasia, surveillance annually versus every 3 months for the first year was equivalent, and random sampling of the neosquamous epithelium and cardia provided no additional value.

Caution

This study was performed in expert high-volume centers in the Netherlands with centralized care. Therefore, results may not be generalizable to general practice settings in the US. The study design may have been selected for patients who were likely to be most successful with endoscopic eradication therapy as they did not enroll those who underwent resection alone without RFA or those who had limited life expectancy.

My Practice

We adhere to a 10-step approach to performing a high-quality endoscopic examination for all patients with BE[4] which includes careful inspection with a distal attachment cap, use of virtual chromoendoscopy, and description of the Barrett's segment and any lesions using standardized reporting systems (Prague, Paris). Any visible lesion, no matter how subtle, should be removed using endoscopic mucosal resection or endoscopic submucosal dissection. RFA is used for flat dysplasia or to eradicate the rest of the flat BE after resection. Although the present results suggest lengthening the surveillance interval to annually in the first year, we remain skeptical about whether these results can be applied to a US population where care is not always standardized or centralized and believe these results will need validation here. We continue to follow ASGE[5] and AGA[6] guidelines for surveillance endoscopies after complete eradication of intestinal metaplasia that suggests surveillance at 1 and 3 years for baseline LGD and 3, 6, and 12 months then annually for HGD based on modeling analyses.[7] We also continue to perform surveillance biopsies of the neosquamous epithelium using the Seattle biopsy protocol, typically focused on the gastroesphageal junction and distal 2cm of the esophagus. Abandoning random biopsies altogether is aspirational but should only be considered in expert hands with well-trained eyes to detect dysplasia.

For Future Research

More research is needed to determine the optimal surveillance interval after achieving complete eradication of intestinal metaplasia and whether results of this study should be incorporated into updated guidelines. Future studies

should develop risk prediction models to identify which individuals are most likely to have BE recurrence and whether surveillance schedules can be tailored to the individual. Additionally, more data is needed before we completely abandon random biopsies of the neosquamous epithelium post-ablation.

Conflict of Interest

The authors report no potential conflicts of interest.

REFERENCES

1. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277-88.
2. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209-17.
3. Kolb JM, Davis C, Wani S. Durability of Endoscopic Eradication Therapy for Barrett's Esophagus-Related Neoplasia: A Call for Centralized Care. Gastroenterology 2022;162:343-345.
4. Kolb JM, Wani S. Barrett's esophagus: current standards in advanced imaging. Transl Gastroenterol Hepatol 2021;6:14.
5. Wani S, Qumseya B, Sultan S, et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. Gastrointest Endosc 2018;87:907-931.e9.
6. Sharma P, Shaheen NJ, Katzka D, et al. AGA Clinical Practice Update on Endoscopic Treatment of Barrett's Esophagus With Dysplasia and/or Early Cancer: Expert Review. Gastroenterology 2020;158:760-769.
7. Cotton CC, Haidry R, Thrift AP, et al. Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus. Gastroenterology 2018;155:316-326 e6.

EVIDENCE-BASED GI
AN ACG PUBLICATION

The Pursuit of Excellence in Colonoscopy: Audit and Feedback Improves Polyp Detection in Low-Performers

Philip Okafor, MD, MPH
Associate Editor

Uri Ladabaum, MD, MSc
Guest Contributor

Philip Okafor, MD, MPH[1] and
Uri Ladabaum, MD, MSc[2]

[1]*Senior Associate Consultant, Department of Gastroenterology, Mayo Clinic, Jacksonville, Florida*
[2]*Professor of Medicine and Senior Vice-Chief, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Standford, California*

This article reviews Tinmouth J, Sutradhar R, Li Q, et al. A Pragmatic Randomized Controlled Trial of an Endoscopist Audit and Feedback Report for Colonoscopy. Am J Gastroenterol 2021; 116: 2042-51. https://doi.org/10.14309/ajg.0000000000001498 PMID: 34515669

Correspondence to Philip Okafor, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does endoscopist audit and feedback (A&F) improve colonoscopy performance?

Setting: Endoscopists in Ontario province, Canada.

Participants: Study included 881 endoscopists; >50% were surgeons, 80% male, and median annual colonoscopy volume >400. Endoscopists who were no longer practicing and those with less than 6 colonoscopies in each study period were excluded.

Intervention/Exposure: Endoscopists were randomly assigned (1:1) to either A&F and a resource sheet (intervention group, n=417) vs no A&F/usual practice (control group, n=416). A&F report included endoscopist's performance using 9 quality indicators along with the endoscopist's rank relative to others (top, middle, bottom tier), and indicator definitions generated for a 1-year pre-report period (January 1, 2014 to December 31, 2014) after which colonoscopy performance was measured over a 12-month period (post-report period). Along with the report, a cover letter, list of resources, and incentives to help improve colonoscopy practice was provided. Although the control group did not receive A&F, they did realize that their performance was being monitored and compared to A&F group during 12-month observation periods.

Outcomes: The primary outcome was polypectomy rate (PR) because adenoma pathology data was not available for the entire study period. However,

the impact of A&F on adenoma detection rate (ADR) was investigated in a *post hoc* analysis. Secondary outcomes included cecal intubation rate, rate of "poor" bowel preparation, and premature repeat after normal colonoscopy (i.e., percent of outpatient colonoscopies performed in individuals 53 years old or older and had a complete normal colonoscopy within past 3 years).

Data Analysis: The principal analysis considered all endoscopists who completed 6 or more colonoscopies in the pre-report and post-report periods. A subgroup analysis in lower-performing endoscopists, defined as endoscopists with PR <25%, was also performed. Primary and secondary outcomes were assessed using crude analysis and adjusted Poisson regression analysis.

Funding: Canadian Cancer Society Research Institute.

Results: Among all endoscopists, mean PR improved from the pre-report to the post-report period in both groups. The increase was not significantly higher in A&F group vs control group. (**Table 1**) However, among lower-performing endoscopists with PR <25%, there was significantly more improvement in polypectomy rate for the A&F arm (17.9% to 23.8%) vs controls (19.4% to 23.3%) [RR: 1.34 vs 1.11, *P*=0.02]. Among low-performing endoscopists, mean ADR also improved more in the A&F group vs controls, though the difference was not significant (RR: 1.12 vs. 1.04, *P*=0.12). No differences were found in A&F effectiveness by specialty or annual colonoscopy volume. No significant differences were found in any secondary endpoints.

COMMENTARY

Why Is This Important?

The ADR has become one of the most widely used and validated quality measures and key performance indicators for screening colonoscopies.[1] Despite its widespread recognition and the inverse association with interval colorectal cancer risk, there still exists significant variation in ADR among endoscopists.[2] Research into endoscopist characteristics and their impact on ADR have yielded mixed results. For instance, a recent study showed no significant differences in ADR based on endoscopist's specialty, sex, location of medical school, practice setting or presence of trainee during colonoscopy.[3] As such, interventions to enhance ADR such as the optimization of withdrawal times,

Outcome	Pre-Report, mean (SD)	Post-Report, mean (SD)	Rate Ratio (95% CI)	*P*-value
Polypectomy rate (all endoscopists)				
Intervention group	39.9 ± 14.8	42.4 ±15.1	1.07 (1.05-1.09)	0.09
Control group	40.0 ± 14.1	41.8 ± 14.2	1.05 (1.04-1.07)	
Polypectomy rate (lower performing endoscopists, i.e. PR <25%)				
Intervention group	17.9 ±6.2	23.8 ± 10.8	1.34 (1.16-1.54)	0.02
Control group	19.4 ± 4.7	23.3 ± 8.5	1.11 (1.06-1.17)	
Adenoma detection rate (all endoscopists)				
Intervention group	28.6 ± 10.8	29.3 ± 10.5	1.03 (1.01-1.05)	0.83
Control group	28.4 ± 11.3	29.1 ± 10.4	1.03 (1.01-1.04)	
Adenoma detection rate (lower performing endoscopists, i.e. PR <25%)				
Intervention group	18.6 ± 7.8	20.3 ± 9.4	1.12 (1.04-1.20)	0.12
Control group	19.2 ± 9.6	19.6 ± 8.7	1.04 (0.98-1.10)	

Table 1. Study Results. Mean PR showed no significant increase in audit and feedback group vs the control group. CI, confidence interval; PR, polypectomy rate; SD, standard deviation.

adoption of artificial intelligence, and utilization of technology-assisted colonoscopy are gaining traction.[4]

With current national ADR benchmarks set at greater than or equal to 25%, the need for sustainable interventions to improve this quality metric, particularly in low-performing endoscopists, has become essential. While artificial intelligence and technology-assisted colonoscopy sound promising, they are yet to reach primetime, underscoring the need for cheap, pragmatic, and scalable interventions. A&F have been shown to improve provider performance and this study by Tinmouth et al. provides evidence that it may also improve polyp detection among endoscopists with low ADRs.

Key Study Findings

Among low-performing endoscopists (i.e., endoscopists with polypectomy rate <25%), A&F led to a statistically greater improvement in polypectomy rate compared to control. A similar improvement was observed among all endoscopists, but this did not meet statistical significance. Adenoma detection rates also improved but this was not statistically different

between the intervention and control arms, though the study might have been underpowered to detect this difference.

Caution

This study provides some evidence that endoscopy performance can be improved with A&F, however, the sustainability of any impact particularly in the long-term, has not been reliably demonstrated. In addition, the authors in this study measured PR and ADR across all indications for colonoscopy, and not specifically for screening colonoscopies. As such, factors like case-mix and indication for the procedure could impact results. It is also essential to highlight that the impact of A&F on ADR was studied as a subgroup analysis and thus might have lacked the necessary power needed to detect a true change in ADR.

My Practice

Our institution (Division of Gastroenterology, Stanford University) has developed a reliable and easy mechanism to collect polyp data not just for ADR, but also serrated lesion detection rates (SLDR), advanced adenomas detection rate (AADR), and advanced serrated lesion detection rate (ASLDR) across the entire gastroenterology division over the past 7 years. This has relied on the buy-in of all endoscopists as the integrity of data collection relies heavily on the input of the group. This effort has grown to become collaborative and every quarter each endoscopist receives an email summary of their colonoscopy performance including data on the extent of exam, Boston Bowel Prep Score, withdrawal time, and indication for the colonoscopy. These data are collected for screening colonoscopies, surveillance colonoscopies, and diagnostic colonoscopies (performed for positive fecal immunochemical or multi-target stool DNA tests). Endoscopist data is compared to department averages for ADR, AADR, SLDR, and ASLDR.

We also receive feedback based on our consistency of providing surveillance recommendations to the referring provider. The ability to historically compare my performance with that of my peers has served as an internal drive that motivates me to consistently monitor the integrity and duration of my withdrawal. Personally, I (PO) use a counter on the screen in the

endoscopy suite to ensure that an adequate amount of time is spent in each colonoscopy segment. Over time, this has led to my ADR improvement, which now approaches the highest in the division.

The main distinguishing features between our program and the A&F intervention tested by Tinmouth et al. are the socialization efforts and the frequency and context of feedback. We have been able to develop, institute and sustain our processes as a group, with multiple touch points at faculty meetings and individualized communications. This was not feasible in the province-wide effort by Tinmouth et al. This probably makes a big difference.

Our experience over the past 7 years, though anecdotal, suggests that the improvement from A&F in the context of a group effort to build a culture focused on high-quality care can lead to behavior changes, but we still maintain that the sustainability of any increase in colonoscopy key performance indicators from A&F needs to be studied in a prospective and rigorous manner.

For Future Research

This randomized control trial by Tinmouth et al. was adequately powered to demonstrate the impact of A&F on polyp detection. However, the impact on ADR was studied post hoc. Further studies that are powered to investigate the impact of A&F on ADR specifically (and AADR, SLDR, ASLDR) would provide needed high-quality evidence because some endoscopists can have a high polyp detection rate but have lower rates of detecting predominantly right-sided lesions such as serrated and advanced serrated lesions. There will also soon be a need for comparative effectiveness studies investigating the impact of technology-assisted colonoscopy versus or in combination with A&F on colonoscopy key performance indicators while quantifying the risk reduction on interval colorectal cancers.

Conflict of Interest

The authors report no potential conflict of interest.

REFERENCES

1. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Am J Gastroenterol 2015;110:72-90.
2. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-306.
3. Sarvepalli S, Garber A, Rothberg MB, et al. Association of Adenoma and Proximal Sessile Serrated Polyp Detection Rates With Endoscopist Characteristics. JAMA Surg 2019;154:627-635.
4. Brand EC, Wallace MB. Strategies to Increase Adenoma Detection Rates. Curr Treat Options Gastroenterol 2017;15:184-212.

EVIDENCE-BASED GI
AN ACG PUBLICATION

LIVER

Hepatic Decompensation Rate Is 0.05 per 100 person-years in NAFLD with Stage F0-F2 Fibrosis, but Rises to 1 per 100 person-years with Stage F3

Philip Schoenfeld, MD, MSED, MSc (Epi)[1] and Sonali Paul, MD, MS[2]

[1]*Chief (Emeritus)-Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, Michigan*

[2]*Assistant Professor of Medicine, Center for Liver Disease, Division of Gastroenterology, Hepatology & Nutrition, University of Chicago School of Medicine, Chicago, Illinois*

Philip Schoenfeld, MD, MSED, MSc (Epi), *Editor-in-Chief*
Sonali Paul, MD MS, *Associate Editor*

This article reviews Sanyal AJ, Van Natta ML, Clark J, et al. Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. N Engl J Med 2021; 385: 1559-69. DOI: 10.1056/NEJMoa2029349. PMID: 34670043

Correspondence to Philip Schoenfeld, MD, MSed, MSc (Epi), Editor-in-Chief. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: What is the risk of hepatic decompensation, hepatocellular carcinoma (HCC), liver-related mortality and all-cause mortality among patients diagnosed with non-alcoholic fatty liver disease (NAFLD) after stratification by fibrosis score?

Design: Prospective, noninterventionregistry.

Setting: Nonalcoholic Steatohepatitis (NASH) Clinical Research Network which consists of multiple US academic medical centers.

Patients: Overall, 1,773 adults (mean age 52; 64% women; 85% White and European ancestry; 42% diabetic) with biopsy-proven NAFLD and at least 1 follow-up visit 48 weeks after liver biopsy. Fibrosis score was determined from liver biopsy: F0-no fibrosis; F1-sinusoidal fibrosis; F2-sinusoidal and portal fibrosis; F3-bridging fibrosis; F4-cirrhosis, and 30% had F3/F4 fibrosis score. Study patients had minimal or no alcohol consumption based on answers to the Alcohol Use Disorders Identification Test questionnaire. Patients received standard of care at their NASH Clinical Research Network center.

Interventions/Exposure: All patients completed protocol-mandated

laboratory data and specific case-record forms at baseline (after liver-biopsy) and at 48-week intervals.

Outcome: Rate of hepatic decompensation (defined as clinically apparent ascites, overt encephalopathy, or variceal hemorrhage), HCC, mortality from any cause, non-hepatic cancer, cardiovascular event, cerebrovascular event, and development of Model for End-Stage Liver Disease (MELD) score of 15 or higher. Outcomes were adjudicated centrally.

Data Analysis: Rates of new-onset events per 100 person-years were calculated using only the first decompensating event. These events were then stratified by fibrosis score. Hazard ratios with 95% confidence intervals were derived from regression models that were further stratified for age, race, sex, diabetes status, and length of biopsy specimen. Investigators noted that the widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive associations.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Results: Among 1,773 study patients, median follow-up was 4.0 years (interquartile range: 2.1-7.4) and total follow-up was 8,210 person-years. Among NAFLD patients with stage F0-F2 fibrosis, the rate of hepatic decompensation is 0.05 per 100 person-years of follow-up (**Table 1**). This rises to 0.99 among patients with stage F3 (bridging fibrosis) with crude hazard ratio = 18.3; 95% confidence interval (CI): 5.4-62.6. This suggests that one-stage regression from stage F3 to stage F2 may be a beneficial target for NAFLD treatments. In a multivariate regression model adjusted for multiple factors, new hepatic decompensation was the only factor associated with higher mortality: hazard ratio = 6.8; 95% CI: 2.2-21.3. Rate of HCC was numerically higher in stage F3 vs stage F4: 0.34 vs 0.14 per 100 person-years.

Fibrosis Stage	*Hepatic Decompensation	HCC	Liver-Related Death	All Cause Mortality
F0-F2	0.05	0.04	0.04	0.32
F3	0.99	0.34	0.28	0.89
F4	2.69	0.14	0.68	1.76

Table 1. Rates of hepatic and non-hepatic outcomes in NASH patients (per 100 person-years of follow-up)
*Hepatic decompensation: clinically apparent ascites, overt encephalopathy, or variceal hemorrhage

COMMENTARY

Why Is This Important?

NAFLD, which is a complex metabolic disorder closely linked to obesity and type 2 diabetes mellitus, is present in more than a quarter of the adult population.[1] NASH, the progressive form of NAFLD, has surpassed hepatitis C as the primary cause of cirrhosis and is present in 5% of the US population.[2] With the ongoing epidemic of obesity in the US, the prevalence of NASH will continue to grow.

Management of patients with NAFLD includes education about the incidence of hepatic decompensation and HCC. Previously, these estimates came from retrospective analyses. Data from the NASH Clinical Research Network and this specific study are prospective, utilize liver histology to determine fibrosis score, and adhere to STROBE guidelines for optimal design and reporting about prospective cohort studies.[3] Thus, this study provides precise data about prognosis and supplements the most recent guidelines about NAFLD management.[4]

Key Study Findings

In multivariate logistic regression models, new hepatic decompensation was the only factor associated with increased risk of all-cause mortality. Rates of hepatic decompensation are very small among patients with stage F0-F2 fibrosis (0.05 per 100 person-years), but increase significantly with stage F3 fibrosis (0.99 per 100 person-years, crude hazard ratio = 18.6; 95% CI: 5.4-62.6.

Caution

Study patients were primarily White and of European descent (85%), so it's unclear if outcomes are different in African-Americans. Fibrosis stage was determined by liver biopsy in study patients while non-invasive tools are more commonly used to define fibrosis stage. Ultimately, there were only 37 hepatic decompensation events and 9 cases of HCC during the 8,210 person-years of follow-up, so confidence intervals around study estimates are quite wide.

My Practice

When I (SP) see a new patient for nonalcoholic fatty liver disease (usually seen on some imaging tests), one of my priorities as a hepatologist is to risk stratify their liver disease, i.e do they have fibrosis. I do this with the use of transient

elastography (TE), which is commonly referred to as FibroScan, and which uses shear wave imaging to estimate liver stiffness.

TE can accurately diagnose cirrhosis and is useful in determining advanced fibrosis (F3/F4) from minimal or no fibrosis.[5] If TE is unavailable, a FIB-4 index (that uses platelet count, ALT, AST, and age; online calculator https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis) that has good predictive accuracy for advanced fibrosis.[6] Should the TE or FIB-4 index be elevated or indeterminate, then MR elastography can be used, which examines the entire liver and can determine both fibrosis and fat fractions. However, it is not available everywhere and in those cases a liver biopsy may be warranted. Liver biopsy may also be done if the patient's liver tests are elevated to help differentiate nonalcoholic steatohepatitis (NASH) from other liver diseases (such as autoimmune hepatitis, depending on serological markers).

If the patient is at low risk (TE < 8 kPa or FIB-4 index < 1.3), it is reasonable to continue to encourage dietary changes and weight loss with repeat testing in 2-3 years if everything has remained stable. Those at indeterminate (TE 8-12 kPa, Fib-4 1.3-2.67) or high risk (TE > 12 kPa, FIB-4 > 2.67, or liver biopsy with F2-F4) would benefit from more intensive and structured weight loss programs, weight management medications, or bariatric surgery with close hepatology follow up.[4]

For Future Research

Larger cohorts followed for longer durations are still needed to provide precise prognostic data. Future studies of NAFLD therapies will need to demonstrate that regression from stage F3 fibrosis to stage F1-F2 translates into reduced risk of hepatic decompensation events.

Conflicts of Interest

The authors report no potential conflicts of interest.

REFERENCES

1. Garcia-Tsao G. Nonalcoholic Steatohepatitis-Opportunities and Challenges. N Engl J Med 2021; 385; 17: 1615-17.
2. cotter TG, Rinella M. NAFLD 2020: The State of the Disease. Gastroenterology 2020; 158(7): 1851-54.
3. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007; 147: 573-7.
4. Kanwal F, Shubrook JH, Adams LA, et al.. Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2021;161(5):1657-1669.
5. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005 Feb;128(2):343-50.
6. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009 Oct;7(10):1104-12.