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AMERICAN COLLEGE OF GASTROENTEROLOGY

# EVIDENCE-BASED GI

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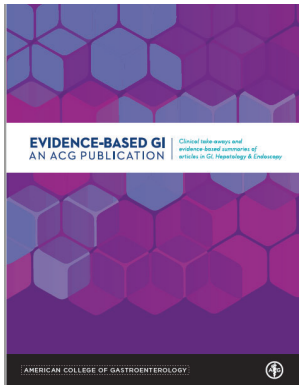


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***October 2024***

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## INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

## IMPORTANT SAFETY INFORMATION

**WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**

**IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.**

### CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

### WARNINGS AND PRECAUTIONS

#### Risk of Serious Dehydration in Pediatric Patients

- IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).
- Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

#### Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

### MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

**Reference:** IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.; 2022.

**Please see Brief Summary of full Prescribing Information on the following page.**

ardelyx

**IBSRELA (tenapanor) tablets, for oral use**

**Brief Summary of Full Prescribing Information**

**WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

## 1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

## 4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

### 5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

**Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)**

| Adverse Reactions | IBSRELA N=293 % | Placebo N=300 % |
|---|---|---|
| Diarrhea | 16 | 4 |
| Abdominal Distension | 3 | <1 |
| Flatulence | 3 | 1 |
| Dizziness | 2 | <1 |

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

*Adverse Reaction of Special Interest – Severe Diarrhea*

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m$^2$). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

*Hyperkalemia*

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m$^2$) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

## 7 DRUG INTERACTIONS

### 7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure ($C_{max}$) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

*Animal Data*

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

**8.2 Lactation**

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

**8.4 Pediatric Use**

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

*Juvenile Animal Toxicity Data*

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

**8.5 Geriatric Use**

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**10 OVERDOSAGE**

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

**17 PATIENT COUNSELING INFORMATION**

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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GUIDELINES

# ACG Guideline on Treatment of *Helicobacter pylori*: New Recommendations… Will Practice Change?

Dr Philip Schoenfeld
*Editor-in-Chief*

**Philip Schoenfeld, MD, MSEd, MSc (Epi)**

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This summary reviews Chey W, Howden C, Moss S, et al. ACG Clinical Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2024;119:1730-53.

*Correspondence to Philip Schoenfeld, MD, MSEd, MSc. Editor-in-Chief. Email: EBGI@gi.org*

**Keywords:** *Helicobacter pylori,* guideline, vonoprazan

## STRUCTURED ABSTRACT

**Question:** What is the optimal approach to treatment of *Helicobacter pylori* infection in North America?

**Design**: The Patient Intervention Comparison and Outcomes (PICO) format was used to develop key questions of clinical relevance to be addressed in the guideline. A health services librarian performed literature searches of PubMed (MEDLINE), EMBASE, and the Cochrane Library. GRADE methodology was used to assess benefits and risks of therapies in a North American population. For clinically relevant topics that were not amenable to formal evidence-based recommendations, key concepts based on expert consensus were presented.

**Patients**: Adults (≥18 years old) with *H. pylori* infection

**Interventions/Exposure**: Proton pump inhibitor (PPI)-clarithromycin triple therapy, bismuth quadruple therapy (BQT), concomitant therapy, rifabutin-

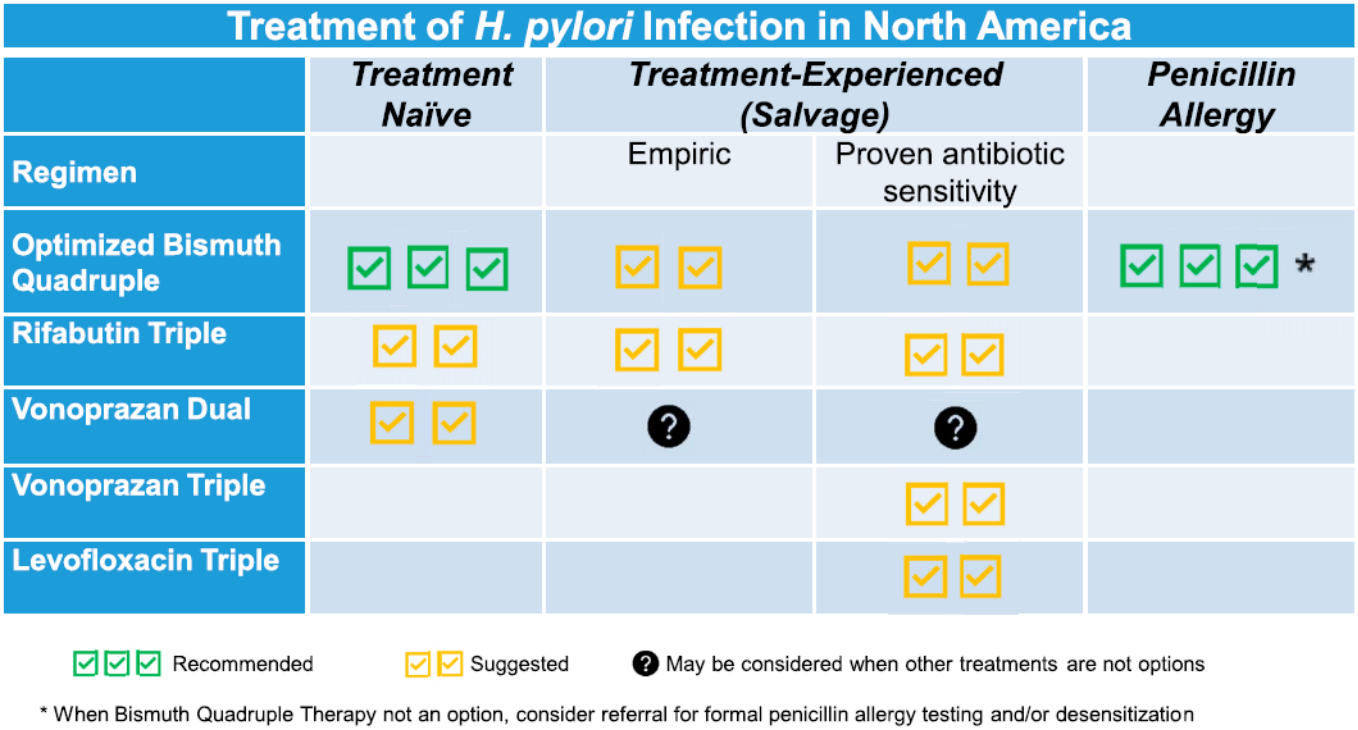


**Figure 1**. ACG Clinical Guideline on the treatment of *Helicobacter pylori.*

triple therapy, potassium-competitive acid blocker (PCAB) dual therapy, PCAB triple therapy, quinolone-based therapy, high-dose PPI dual therapy, susceptibility-guided therapy, and probiotics. Comparators included PPI-clarithromycin triple therapy, BQT, and empiric (i.e., non–susceptibility-guided) therapy. Respective dosing and frequency of each regimen was also recorded.

**Outcome:** *H. pylori* eradication rates in intention-to-treat (ITT) analyses and per-protocol analyses, compliance with treatment, and rates of adverse events.

**Data Analysis**: Guideline methodologists performed meta-analysis when appropriate with RevMan software and the Cochrane Risk of Bias tool to assess risk of biased results based on use of concealment of allocation, blinding, incomplete outcome data reporting, selective reporting and other potential biases. The GRADE process[1] uses 2 types of guideline recommendations based on the quality of evidence, risks vs benefits, feasibility, and costs while taking into account patient-based and population-based factors.

*Strong Recommendation:* Providers should recommend this intervention for most patients. A strong recommendation is usually accompanied by "High" or "Moderate" level of evidence from well-designed randomized controlled trials (RCTs), or RCTs with mild methodologic limitations.

*Conditional Recommendation/Suggestion*: Many providers might suggest this therapy, while other providers would consider other therapy in similar patients. Conditional recommendations/suggestions are usually accompanied by "Low" or "Very Low" quality of evidence.

The quality of evidence is categorized based upon an assessment of study methodology, including risk of bias, evidence of publication bias, heterogeneity among studies, and precision of the estimate of eradication rates. High quality evidence rating infers that the guideline authors are confident in the accuracy of research data to support a particular recommendation and further research is unlikely to change this recommendation. Low or Very Low quality evidence infers that the guideline authors have less confidence in the accuracy of research data to support a particular recommendation and future research may alter this recommendation.

**Funding:** The American College of Gastroenterology.

**Results:** Optimized bismuth-based quadruple therapy (BQT) for 14-days is the recommended therapy for treatment-naïve patients **(Figure 1, Table 1**) as well as treatment-experienced patients who failed to eradicate *H. pylori* with an initial course of PPI-clarithromycin triple therapy. Optimized BQT consists of PPI twice daily, tetracyclince 500 mg 4 times daily, metronidazole 500 mg 3 or 4 times daily, and bismuth subcitrate or bismuth subsalicylate 4 times daily for 14 days. Rifabutin-based triple therapy and vonoprazan-amoxicillin dual therapy are alternative suggested regimens. The guideline specifically recommends against using PPI-clarithromycin triple therapy unless antibiotic sensitivity has been performed and clarithromycin-sensitivity has been proven.

In the key concepts section, the guideline authors' note that clarithromycin-resistance and levofloxacin-resistance has risen precipitously, which greatly reduces the efficacy of these clarithromycin-based and levofloxacin-based regimens when used as empiric therapies. This is particularly important since PPI-clarithromycin triple therapy (i.e., PrevPac; Takeda Pharmaceuticals, Bannockburn, IL) remains the most commonly prescribed *H. pylori* infection treatment, although eradication rates drop to approximately 30% in clarithromycin-resistant strains of *H. pylori*.

The key concepts section also emphasizes that proof of *H. pylori* eradication is required in all patients after treatment by obtaining a fecal antigen test, urea breath testing, or gastric biopsy. Importantly, this testing should not be done until at least

4 weeks after the patient has completed antibiotics and after the patient has been off PPIs/PCABs for at least 2 weeks, although the patient can be bridged with H2 receptor antagonists and antacids during that period.

Finally, the authors recommend expanding the indications for testing and treating *H. pylori* to include individuals at increased risk of gastic cancer, individuals with atrophic gastritis, gastric intestinal metaplasia, and household members of adults with *H. pylori* infection based on non-serologic testing. This expanded list of indications reflects recognition of *H. pylori's* role in increasing the risk of gastric cancer as well as being classified by the World Health Organization as a Class I carcinogen due to its causative role in the development of mucosa-associated lymphoid tissue (MALT) lymphoma.

| Regimen | Drugs (doses) | Dosing frequency | FDA Approval | Recommendation |
|---|---|---|---|---|
| Optimized bismuth quadruple | PPI (standard dose) | b.i.d. | No | Strong (moderate quality of evidence) |
| | Bismuth subcitrate (120 - 300 mg) or subsalicylate (300 mg) | q.i.d. | | |
| | Tetracycline (500 mg) | q.i.d. | | |
| | Metronidazole (500 mg) | t.i.d. or q.i.d. | | |
| Rifabutin triple (Talicia) | Omeprazole (10 mg) | 4 capsules t.i.d. | Yes | Conditional (low quality of evidence) |
| | Amoxicillin (250 mg) | | | |
| | Rifabutin (12.5 mg) | | | |
| PCAB dual (Voquezna DualPak) | Vonoprazan (20 mg) | b.i.d | Yes | Conditional (moderate quality of evidence) |
| | Amoxicillin (1,000 mg) | t.i.d | | |
| PCAB triple (Voquezna TriplePak) | Vonoprazan (20 mg) | b.i.d | Yes | Conditional (moderate quality of evidence) |
| | Clarithromycin (500 mg) | | | |
| | Amoxicillin (1,000 mg) | | | |

**Table 1.** Recommended regimens for treatment-naïve patients with *H.pylori* infection.

b.i.d., twice daily; PCAB, potassium channel acid blocker; PPI, proton pump inhibitor; q.i.d., 4-times daily; t.i.d., 3-times daily.

## COMMENTARY

### *Why Is This Important?*

This guideline makes substantial changes from the 2017 guideline recommendations[2] because of rising resistance rates to clarithromycin and levofloxacin, which reduces the efficacy of commonly-used regimens, and also because of the publication of RCTs since 2017 that demonstrated the efficacy of rifabutin-based triple therapy and vonoprazan-amoxicillin dual therapy. I commend the authors for the huge effort required to produce this well-designed guideline.

### *Key Study Findings*

Optimized bismuth-based quadruple therapy for 14 days is the recommended therapy for treatment-naïve patients **(Figure 1, Table 1**) as well as treatment -experienced patients who failed to eradicate *H. pylori* with PPI-clarithromycin triple therapy. PPI-clarithromycin triple therapy should not be used unless antibiotic sensitivity has been performed and demonstrated clarithromycin-sensitivity.

### *Caution*

The GRADE methodology provides transparency about how recommendations were made, although the authors' subjective opinions may influence assessments about the strength of recommendations and quality of evidence. For example, given that the prevalence of amoxicillin-resistant *H. pylori* strains is approximately 1%, I might have provided a Strong recommendation based on moderate quality of evidence for vonoprazan-amoxicillin duel therapy among treatment-naïve patients without penicillin allergies. However, I also understand the authors' rationale for only providing a Conditional recommendation here.

### *My Practice*

I agree that optimized BQT should be the preferred *H. pylori* treatment regimen in the compliant patient. Unfortunately, I've found that my patients at the VA have difficulty complying with this regimen because of its complexity (4 medications taken up to 4 times per day while obtaining tablets from 4 different pill bottles) and the potential for dyspepsia and altered bowel habits. Also, there have been intermittent shortages of tetracycline, and the guideline recommends against substituting doxycycline. Therefore, I prefer to use PCAB-based dual therapy with vonoprazan and amoxicillin, which enhances compliance with its blister packaging and is well-tolerated, despite the additional cost to our pharmacy. Shared decision-making with individual patients may be particularly helpful here.

For patients who were previously treated with clarithromycin-based triple therapy or in treatment-naïve patients with a penicillin allergy, I prefer to use

optimized BQT. My personal tips are to proactively educate the patient about potential side effects (change in stool color, mild dyspepsia), emphasize the importance of compliance, engage a family member to help if possible, and help the patient set an alarm or even use a phone application to remember to take their medications. There is simply no substitute for spending extra time with the patient to educate them.

With my GI fellows, I emphasize the basics: don't order a *H. pylori* test unless you intend to treat, don't use PPI-clarithromycin based triple therapy, always plan to confirm eradication 4 weeks after antibiotic therapy has been completed, but, remember that the patient has to be off PPIs/PCABs for 2 weeks prior to testing.

### *For Future Research*

As noted by the guideline authors, comparative RCTs performed in North America of optimized BQT versus rifabutin-based triple therapy and vonoprazan-based dual/triple therapy in both treatment-naïve and treatment-experienced patients would be helpful. I'd also emphasize the importance of implementation research to minimize the continued use of PPI-clarithromycin triple therapy. Again, this is by far the most commonly prescribed *H. pylori* treatment regimen, although the guideline explicitly states that it should only be used when the specific strain of *H. pylori* has demonstrated susceptibility to clarithromycin (which is quite rare).

### *Conflict of Interest*

Dr. Schoenfeld reports serving on advisory boards, consultant and speakers bureau for Phathom Pharmaceuticals.

**Note:** The authors of this ACG Guideline are active on social media. Tag them to discuss their work and this EBGI summary.

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# Risankizumab Is Superior to Placebo for Induction and Maintenance of Moderate-Severe Ulcerative Colitis (UC): Assessing the UC Treatment Paradigm

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*Associate Editor*

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IBD

This summary reviews Louis E, Schreiber S, Panaccione R, et al. Risankizumab for ulcerative colitis: Two randomized clinical trials. JAMA. 2024:e2412414.

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**Keywords**: Ulcerative colitis, risankizumab, randomized controlled trial

## STRUCTURED ABSTRACT

**Question:** Is risankizumab (Skyrizi; AbbVie Pharmaceuticals, San Francisco, CA), a p19 subunit-specific interleukin (IL)-23 monoclonal antibody, superior to placebo for induction of remission and maintenance of remission of moderate-severe ulcerative colitis (UC)?

**Design**: INSPIRE and COMMAND were phase 3, double-blind, placebo-controlled, randomized clinical trials (RCT) of risankizumab for moderate to severe UC. In the 12-week induction trial (INSPIRE), patients were randomized 2:1 (risankizumab:placebo) to 1,200 mg risankizumab or placebo administered intravenously at 0, 4, and 8 weeks. Patients who had clinical response or clinical remission to risankizumab induction were included in the maintenance trial (COMMAND) conducted from week 12 to week 52, in which patients were randomized 1:1:1 to

180 mg risankizumab, 360 mg risankizumab, or placebo administered subcutaneously every 8 weeks.

**Setting:** INSPIRE, the induction of remission RCT, was conducted in 261 centers in 41 countries from November 2020 through August 2022. The maintenance of remission RCT, COMMAND, was conducted in 238 centers in 37 countries.

**Patients**: Inclusion criteria included: 18-80 years old; moderate-severe ulcerative colitis based on adapted Mayo score ≥5 (0-9 scale) which consists of rectal bleeding score (0-3), stool frequency score (0-3), endoscopy subscore (0-3); endoscopic subscore of 2-3 based on central review of endoscopic images; prior history of inadequate response, loss of response, or intolerant of conventional therapy (glucocorticoids or immunomodulators) or biologic therapy. Exclusion criteria included prior exposure to ustekinumab, mirikizumab, or risankizumab.

**Interventions:** For the induction of remission RCT, INSPIRE, 1,200 mg risankizumab or placebo was administered intravenously at 0, 4, and 8 weeks. For the maintenance of remission RCT, COMMAND, 180 mg risankizumab, 360 mg risankizumab, or placebo were administered subcutaneously every 8 weeks.

**Outcomes:** For the induction trial, the primary outcome was clinical remission at week 12. For the maintenance trial, the primary outcome was clinical remission at week 52. Clinical remission was defined as a stool frequency score ≤1 and not higher than baseline, rectal bleeding score of 0, and endoscopic subscore ≤1 without friability. Secondary outcomes included endoscopic and histologic improvement as well as endoscopic remission, among others.

**Data Analysis**: Intention to treat (ITT) analysis. Categorical outcomes were analyzed using the Cochran-Mantel-Haenszel test. Continuous outcomes were analyzed using mixed-effect models with a repeated-measures method or analysis of covariance.

**Funding:** AbbVie Pharmaceuticals, manufacturer of risankizumab.

**Results:** Of 975 UC patients in the induction of remission trial, 60% were male, mean age was 42 years, 70% were White, mean disease duration of 7 years, and mean adapted Mayo score of 7. Clinical remission rates at week 12 were 20.3% (132/650) for 1,200 mg risankizumab vs 6.2% (20/325) for placebo ($P < 0.01$).

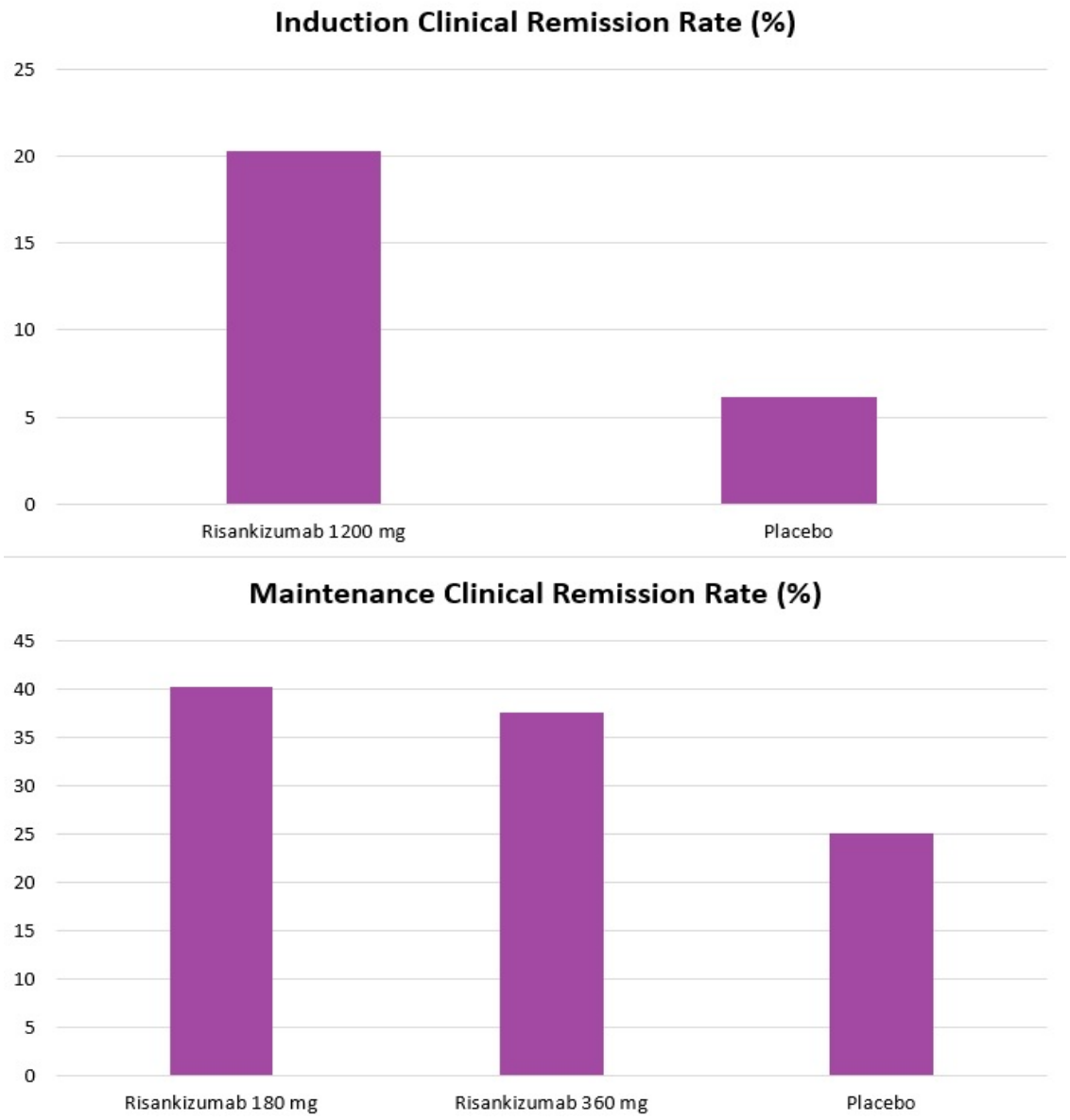


**Figure 1.** Results of induction and maintenance risankizumab compared to placebo.

**(Figure 1)** Endoscopic improvement was observed in 36.5% for risankizumab vs 12.1% for placebo ($P<0.01$). UC patients that were treatment-naïve to biologic therapy demonstrated numerically higher remission rates compared to treatment-experienced patients who had a history of inadequate response to biologic therapy. Specifically, in treatment-naïve patients, clinical remission rates for risankizumab and placebo were 29.7% vs 8.4%, respectively, while clinical remission rates in treatment-experienced patients were 11.4% vs 4.3%, respectively.

Of 548 UC patients in the maintenance of remission trial, 57% were male, mean age was 41 years, 74% were White, mean disease duration of 8-9 years, and mean adapted Mayo score of 7. Clinical remission rates at week 52 were 40.2% (72/179) for 180 mg risankizumab vs 37.6% (70/186) for 360 mg risankizumab vs 25.1% (46/183) for placebo ($P < 0.01$). **(Figure 1)** Endoscopic improvement was observed in 50.8% for 180 risankizumab vs 48.3% for 360 mg risankizumab vs

31.7% for placebo. Again, UC patients that were treatment-naïve to biologic therapy demonstrated numerically higher maintenance of remission rates compared to treatment-experienced patients who had a history of inadequate response to biologic therapy. Specifically, in treatment-naïve patients, maintenance of remission rates were 50.9% for 180 risankizumab vs 61.7% for 360 mg risankizumab vs 31.1% for placebo, while maintenance of remission rates were 36.6% vs 29.5% vs 23.2%, respectively, in treatment-experienced patients.

A post-hoc analysis demonstrated significantly suppressed levels of IL-22 (a downstream cytokine of the IL-23 pathway) in the risankizumab treatment group compared to placebo. Incidence of adverse events were similar in the risankizumab and placebo group. Rates of both herpes zoster and serious infection were similar between risankizumab and placebo groups during induction and maintenance of remission.

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***Note***

*Although these trials used a classic double-blind, placebo-controlled, randomized study design with modified ITT analysis, study methodology and results are too detailed to summarize comprehensively. Readers are encouraged to review the full study publication.*

## COMMENTARY

### *Why Is This Important?*

Risankizumab is the first p19 subunit-specific interleukin (IL)-23 monoclonal antibody approved for the treatment of inflammatory bowel disease, and the second p19 subunit-specific interleukin (IL)-23 monoclonal antibody approved specifically for ulcerative colitis (UC) in the United States.[1,2] While anti-tumor necrosis factor (anti-TNF) agents have an established role as first-line therapy for moderate-to-severe UC, approximately one-third of patients fail to respond and up to 50% lose clinical response to anti-TNFs over time.[3] The introduction of p19 subunit-specific interleukin (IL)-23 monoclonal antibodies offers a new mechanistic option with subcutaneous administration to treat UC effectively with a favorable safety profile that may be appealing to many patients and providers. In Crohn's disease, risankizumab has been shown to have greater efficacy than ustekinumab, an inhibitor of both IL-12 and 23, though it is unclear how a p19 subunit-specific interleukin (IL)-23 monoclonal antibody will compare to ustekinumab for the treatment of UC.[4]

Ultimately, clinicians now have an expanded menu of options to treat

moderate-severe UC, including oral sphingosine 1-phosphate (S1P) receptor modulators (e.g., etrasimod), oral Janus kinase 1 (JAK1) inhibitors (e.g., upadacitinib), intravenous (IV)/ subcutaneous (subq) anti-integrin monoclonal antibodies (e.g., vedolizumab), IV/subq anti-TNF agents (e.g., infliximab), as well as the anti-interleukin-12/23 monoclonal antibodies. Given this expanding menu of therapies, new algorithms are needed to help gastroenterologists choose preferred treatment for individual UC patients by accounting for the strengths and limitations of individual agents.

### *Key Study Findings*

For the induction trial, clinical remission rates at week 12 were 20.3% (132/650) for 1,200 mg risankizumab vs 6.2% (20/325) for placebo ($P < 0.01$). For the maintenance trial, clinical remission rates at week 52 were 40.2% (72/179) for 180 mg risankizumab vs 37.6% (70/186) for 360 mg risankizumab vs 25.1% (46/183) for placebo ($P < 0.01$).

### *Caution*

Patients with prior treatment with ustekinumab were excluded from this trial. Therefore, it is difficult to extrapolate these results to patients with previous exposure to ustekinumab.

### *My Practice*

In my practice, I commonly prescribe risankizumab as a first-line therapy for moderate-to-severe UC. I will consider this therapy in older adults in whom a more favorable safety profile is needed (e.g. as compared to anti-TNF agents) or in those who prefer a subcutaneous option. Due to the results of the SEQUENCE trial in Crohn's disease, I typically favor prescribing risankizumab over ustekinumab for UC as well, though comparative data in UC are lacking. I also counsel my patients that dose intensification of risankizumab (i.e. reduction of the maintenance dosing interval to more frequent than every 8 weeks) could be needed for loss of response or partial response, similar to ustekinumab.[5]

With respect to other UC therapies, I may consider oral S1P receptor modulators in patients with moderate UC that prefer an oral option. Due to FDA requirements, I usually limit JAK1 inhibitors to UC patients that have failed anti-TNF agents. For older UC patients with multiple co-morbidities, vedolizumab may be a good option because of its safety profile, although I don't limit vedolizumab just to this population. Finally, infliximab is still a very good option, especially in patients with extra-intestinal symptoms, and is now available in subq formulations.

### *For Future Research*

Randomized comparator trials are needed to compare the effectiveness of risankizumab to other advanced therapies for UC, particularly ustekinumab,

vedolizumab, and JAK1 inhibitors. Large cohort studies are needed to explore long-term outcomes of risankizumab for UC beyond 52 weeks and the effectiveness of p19 subunit-specific IL-23 monoclonal antibody in those with prior ustekinumab exposure. Since we have multiple approved treatments for UC with different mechanisms of action, studies of biologic markers that predict response to specific therapies would be helpful to guide treatment. Also, since monotherapy of UC with biologic agents fails to achieve remission in many patients, further research about combination biologic therapy will be helpful to assess the benefits and potential risks of different combinations of treatment.

### *Conflict of Interest*

Dr. Dalal has research grant support from Janssen and Pfizer and has served as a consultant for Janssen, Takeda, and Centaur Labs.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

# Standardized Training for Endoscopic Mucosal Resection of Large Polyps: Does it Reduce Recurrence?



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This summary reviews Meulen LWT, Bogie RMM, Siersema PD, et al. Standardised training for endoscopic mucosal resection of large non-pedunculated colorectal polyps to reduce recurrence (*STAR-LNPCP study): a multicentre cluster randomised trial. Gut. 2024; 73(5):741-750.

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**Keywords:** Colorectal adenoma; colorectal neoplasia; endoscopic polypectomy; endoscopic procedures; therapeutic endoscopy

## STRUCTURED ABSTRACT

**Question:** Does standardized endoscopic mucosal resection (EMR) training reduce the recurrence rates of large non-pedunculated colorectal polyps (LNPCPs)?

**Design**: Multicenter cluster randomized trial. Each community hospital nominated ≥1 endoscopist dedicated to EMR of LNPCPs at their institution. Randomization was performed based on hospital (i.e., all endoscopists from each hospital participated exclusively in the intervention group or control group).

**Setting:** Thirty Dutch community hospitals between April 2019 and August 2021.

**Patients**: From April 2019 through August 2021, consecutive EMR-treated LNPCPs were included. All patients above age 18 with LNPCP suitable for EMR were included.

**Intervention**: The endoscopists were divided into an intervention group, which received e-learning and a 2-day hands-on training session and a control group. The 2 -day hands-on training consisted of lectures, case-based discussions, and hands-on sessions. E-learning modules covered all aspects of EMR, including injection fluids (colloid, dye, epinephrine), types of snares, techniques of piecemeal and en bloc resection, performance of margin thermal ablation, and identification and management of residual tissue after snaring. All study endoscopists completed e-learning modules on identification of post-EMR scar and protocol for obtaining biopsies from the post-EMR scar.

**Outcomes:** Primary outcome was recurrence rate after 6 months. A standardized protocol, including assessment of EMR scar with multiple images of scar obtained with white light, zoom focus, narrow band imaging, virtual chromoendoscopy or blue-light imaging was followed. Recurrence, which was defined as visible neoplastic tissue in or within 5 mm of scar, was determined by independent reviewers blinded to treatment allocation. If visible neoplastic tissue was present, then this was removed endoscopically and reported. If there were no signs of recurrence, then the EMR scar was biopsied per standardized protocol at the center and each peripheral quadrant.

Secondary aims included comparison of recurrence rates stratified by LNPCP size (20-29 mm, 30-39 mm, $\geq$ 40 mm), EMR techniques (e.g., lifting fluid used, number of pieces, use of adjunctive treatments or margin thermal ablation), and complication rates between the 2 groups.

**Data Analysis**: Intention to treat analysis. All consecutive non-invasive LNPCPs, suitable for EMR, were included in the study.

**Funding:** Dutch Cancer Society.

**Results:** Among 30 community hospitals, a total of 59 endoscopists participated. From April 2019 through August 2021, 1,412 large non-pedunculated colorectal polyps (699 in the intervention group, 713 in the control group) were study eligible with 98% undergoing EMR. A total of 1,277 lesions (90%) underwent 6-month repeat colonoscopy to assess for recurrence with post-EMR scar identified in 1,215 lesions, which were then utilized for primary outcome assessment. For these 1,215

post-EMR lesions/scars, the initial median polyp size was 30 mm, and both groups had similar distributions in terms of size, morphology, site, and access scores.

There were significant differences in EMR technique among the intervention group versus the control group. The intervention group was more likely to add epinephrine to the lifting fluid (73% vs 41%, respectively, $P > 0.001$), use colloid lifting fluid instead of normal saline (87% vs 63%, respectively, $P < 0.001$), identify residual tissue after snaring (24% vs 18%, respectively, $P = 0.003$), and perform margin thermal ablation (92% vs 75%, respectively, $P < 0.001$).

There was a significantly lower recurrence rate in the intervention group compared to the control group: 13% vs 25%, respectively; odds ratio (OR) 0.43; 95% confidence interval (CI) 0.23-0.78, $P = 0.005$. Recurrence was more often unifocal in the intervention group (92% vs 76%, $P = 0.006$). The largest benefit of the intervention was for polyps 20-29 mm (5% vs 20%, respectively; OR 0.20; 95% CI 0.08-0.52) and 30-39 mm (10% vs 21%, respectively; OR 0.36; 95% CI 0.16-0.81), but there was no significant difference for lesions >40 mm (24% vs 31%, respectively, $P = 0.151$).

Intraprocedural adverse events (e.g., intraprocedural bleeding or damage to muscularis propria) was similar between groups (29% vs 35%, $P = 0.258$) and were also similar for complication rates requiring hospitalization or emergency treatments/evaluations (8% vs 9%) with 1 perforation occurring in 1% of cases in both

## COMMENTARY

### *Why Is This Important?*

EMR is a safe and effective modality for resecting LNPCPs ≥20 mm where invasion is not suspected. However, recurrence after EMR of LNPCPs is common (up to 30%) but can be reduced significantly in expert centers to less than 5% by utilizing various techniques depending on the primary resection modality.[1,2] This study shows how a standardized 2-day course with hands-on training and e-learning modules can significantly impact recurrence rates among community practicing gastroenterologists.

### *Key Study Findings*

Standardized EMR training among community gastroenterologists significantly reduced recurrence rates at 6 months by 50% in this study that included 1,412 polyps.

This is substantial improvement given the low intensity of the 2-day training course. Largest effect was seen among polyps 20-40 mm where a recurrence reduction for lesions size 20-29 mm (5% vs 20%, OR 0.20; 95% CI 0.08-0.52, $P = 0.001$) and 30-39 mm (10% vs 21%, OR 0.36; 95% CI 0.16-0.81, $P = 0.013$)

whereas for polyps ≥40 mm (24% vs 31%, OR 0.61; 95% CI 0.31-1.20; $P$ = 0.151).

### *Caution*

It is unclear which items in the training course contributed most to the significant decrease in recurrence rate as the course delved into multiple aspects of performing an EMR as well identifying residual tissue and recurrent polyps. There was also variation in recurrence rate between centers where the highest recurrence rates were noted in centers with lower volumes. In addition, it is possible that simply attending the course led those endoscopists to become more enthusiastic about honing their resection skills.

### *My Practice*

While I can't employ the specific 2-day hands-on training and e-learning modules used in this trial, the study methodology is similar to the approach of my GI group. First, similar to study endoscopists, I'm designated as the primary endoscopist for complex EMR in my group. Although I didn't complete an advanced endoscopy fellowship, I actively sought hands-on training in my GI fellowship to maximize my volume of complex EMR. If you didn't get enough of this hands-on training, then the American Society for Gastrointestinal Endoscopy (ASGE) offers this in multiple settings, including in the hands-on workshops at the American College of Gastroenterology Annual Meeting and at Digestive Disease Week. I also studied multiple ASGE website videos on optimal performance of EMR. These educational videos seem similar to this study's e-learning modules. For example, I learned to mix epinephrine with a colloid injection fluid to lift LNPCPs. This is especially important to minimize bleeding when doing piecemeal cold snare. Before I do any injection, I carefully identify the margins of the polyp using zoom focus, high-definition white light, and narrow band imaging. This is crucial to facilitate identification of residual tissue both centrally and at polyp margins after beginning resection. I also routinely use soft-tip coagulation for thermal ablation of polyp margins among other tips to minimize recurrence.

Finally, allowing adequate time for complex EMR and optimizing procedure volume minimizes recurrence when doing EMR of large non-pedunculated colorectal polyps. Since my schedule includes extended endoscopy slots for complex EMR, my colleagues frequently refer patients with LNPCPs after obtaining a pinch biopsy of the lesion and injecting dye 2 folds distal (i.e., closer to the rectum) from the lesion to facilitate polyp location on repeat colonoscopy. This is certainly preferable to initiating EMR but failing to complete it. Incomplete EMR may produce sub-mucosal fibrosis that makes future EMR technically difficult.

### *For Future Research*

It would be helpful to pinpoint which

elements in a training course provide the largest impact on recurrence rates after EMR. Future research might focus on comparing e-learning modules to hands-on training sessions. At a minimum, specific aspects of hands-on training and learning modules should be described sufficiently to facilitate dissemination of these educational tools.

### *Conflict of Interest*

Dr. Abu-Heija reports no potential conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION



# Diagnostic Yield of Prolonged Wireless pH vs 24-hour pH-Impedance Monitoring for Evaluation of Chronic Laryngeal Symptoms

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Dr Swathi Eluri
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This summary reviews Krause AJ, Greytak M, Kaizer MA, et al. Diagnostic yield of ambulatory reflux monitoring systems for evaluation of chronic laryngeal symptoms. Am J Gastroenterol. 2024 1;119(4):627-634.

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Keywords: Laryngopharyngeal reflux, GERD, Bravo, 24-hr impedance monitoring

## STRUCTURED ABSTRACT

**Question:** Is the diagnostic yield for abnormal gastroesophageal reflux comparable between ambulatory reflux monitoring systems in patients with chronic laryngeal symptoms?

**Design**: Multicenter, international, cross-sectional study (**Figure 1)**.

**Setting:** Five laryngopharygeal reflux (LPR) referral centers (4 centers in the United States and 1 center in Taiwan) between March 2018-May 2023.

**Patients**: Adult patients with chronic laryngeal symptoms, including cough, globus, dysphonia, throat clearing, and sore throat, who had undergone ambula-

tory reflux monitoring off proton pump inhibitor (PPI) therapy, with or without concomitant esophageal symptoms such as heartburn, regurgitation, or noncardiac chest pain. Patients with prior foregut surgery were excluded.

**Interventions/Exposure**: The intervention was ambulatory reflux monitoring systems in 1 of 2 24-hour pH-impedance monitoring configurations: 1) prolonged wireless single pH capsule (Bravo; Medtronic, Minneapolic, MS) or 2) multichannel intraluminal impedance with a single distal pH catheter (MII-pH) and hypopharyngeal-esophageal multichannel intraluminal impedance-pH (HEMII-pH) (Medtronic or Diversatek Healthcare, Milwaukee, WI) .

**Outcome**: The primary outcome was presence or absence of abnormal gastroesophageal reflux (GER+ or GER-) as defined per Lyon consensus criteria. For multichannel intraluminal impedance with a single distal pH catheter, GER+ was total distal esophageal acid exposure time (AET) of at least 6% with esophageal pH < 4.0 and/or at least 80 reflux events/24 hour period. For prolonged wireless reflux monitoring, GER+ was defined as 2 days or more of AET of at least 6% with esophageal pH < 4.0. Those not meeting gastroesophageal reflux disease (GERD) criteria per these definitions were categorized as GER-.

**Data Analysis**: Demographic and clinical data were compared between subjects undergoing 24-hour pH-impedance and wireless monitoring. Secondary analyses were performed to assess diagnostic agreement/disagreement between the 2 pH monitoring systems for the 15 patients who underwent both tests and to compare patients with and without concomitant esophageal symptoms.

**Funding:** National Institutes of Health.

**Results:** Among 813 study patients, demographic data included mean age 53 (SD-16 years); 37% male; 36% with hiatal hernia; 72% with concurrent GERD symptoms (in addition to laryngeal symptoms), and mean body mass index-27. Among study patients, the most common laryngeal symptoms were throat clearing (69%), cough (67%), globus sensation (67%), voice hoarseness (57%), and sore throat (28%). Demographic data were similar between groups getting wireless pH monitoring and 24-hour impedance monitoring except patients getting 24-hour pH impedance monitoring were significantly older (54.0 vs 50.6 years, $P < 0.01$).

Overall, diagnostic yield for GER+ was significantly higher for wireless pH monitoring compared with 24-hour impedance monitoring: 50% (148/296) vs 27%

(145/532); $P < 0.01$. Total AET was significantly higher on wireless pH monitoring compared with 24-hour pH-impedance monitoring (6.4% [SD 4.9] vs 3.6% [SD 5.3]; $P < 0.01$). The first day of AET on wireless pH monitoring was significantly higher than total AET on 24-hour pH-impedance monitoring (6.7 [SD 6.6] vs 3.6 [SD 5.3], $P < 0.01$), with 45% being GER+ on day 1 of wireless monitoring compared to 20% on 24-hour pH-impedance testing when strictly using the criteria of AET of at least 6%. When adding at least 80 reflux events per 24 hours on pH-impedance testing, the diagnostic yield increased from 20% to 27% for wireless monitoring.

Among the 15 patients who underwent both wireless pH vs 24-hour pH-impedance monitoring, there was diagnostic agreement between studies for only 6 (40%) patients. Among 5 patients with a positive wireless pH monitoring study but negative or inconclusive 24-hour pH-impedance study, AET was abnormal on 2 or more days of wireless pH monitoring.

Only 28% (226/813) of the sample had isolated laryngeal symptoms. For patients with isolated laryngeal symptoms, the diagnostic yield of GER+ remained higher

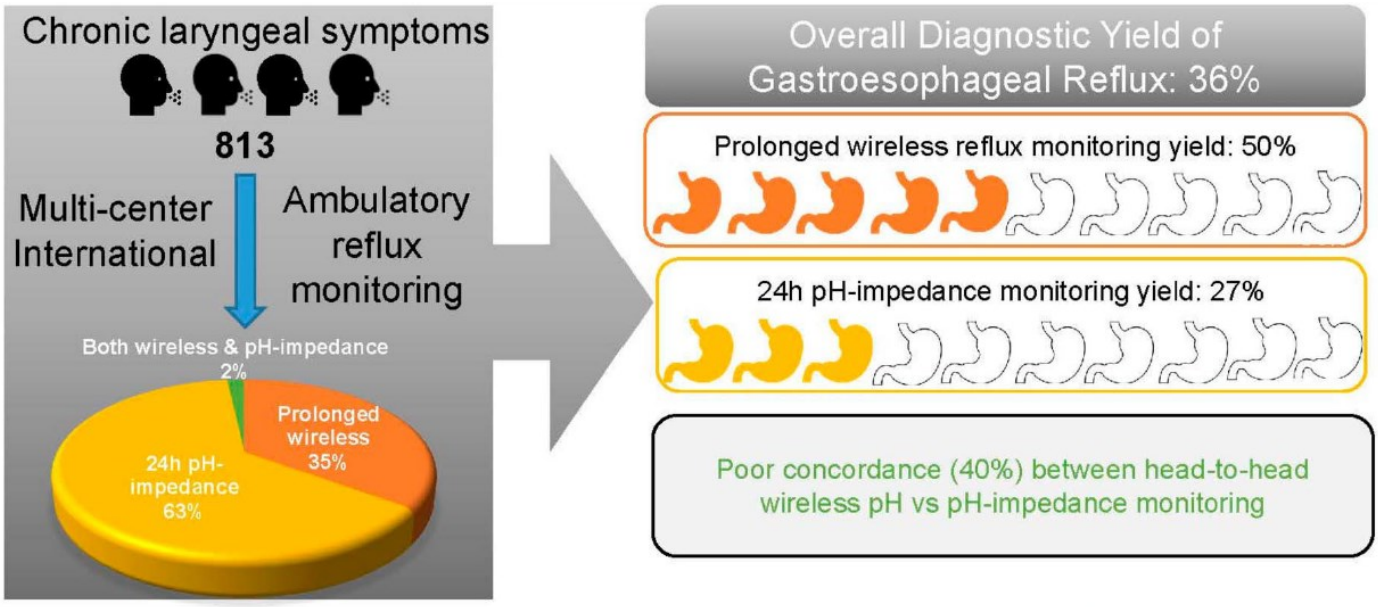


**Figure 1.** Visual abstract showing the multicenter, international, cross-sectional study.

## COMMENTARY

### *Why Is This Important?*

LPR is a common condition leading to GI referrals. Historically, LPR has been diagnosed based on clinical symptoms of chronic cough, hoarseness, or throat clearing, and most gastroenterologists are quite familiar with patients referred by otolaryngologists who have reported seeing erythema or edema on laryngoscopy among patients with these symptoms and then told patients that their symptoms are due to acid reflux. Two important points should be emphasized here. First, we've known for over 20 years that the inter-rater reliability of this assessment is quite poor (i.e., multiple otolaryngologists can look at the same images of laryngeal folds and provide quite variable assessments about presence or severity of edema and erythema).[1] Second, more than 60% of LPR patients do not have pathologic acid reflux on objective pH monitoring. Therefore, when patients with chronic cough, hoarseness, or throat clearing, etc., but without GERD symptoms are referred for LPR treatment based on laryngoscopic images, we must educate the patient that their symptoms may not be due to acid reflux, especially if they have already failed to improve with PPIs. Given this dilemma, recent guidelines have moved towards endorsing ambulatory reflux monitoring in those with isolated chronic laryngeal symptoms to measure pathologic acid exposure, abnormal reflux events, and correlation between patient symptoms and reflux events. However, it is unclear if the diagnostic yield between the 2 ambulatory reflux monitoring systems that are available are comparable, specifically in those with chronic laryngeal symptoms. Understanding whether one method of ambulatory pH monitoring provides results that are more diagnostic in this specific population can have significant clinical utility and implications.

### *Key Study Points*

Diagnostic yield for GER+ was significantly higher for wireless pH monitoring compared with 24-hour impedance monitoring: 50% (148/296) vs 27% (145/532); $P < 0.01$.

### *Caution*

Given that this study was performed at expert LPR referral centers, there are likely some limitations in the generalizability of these results. Data regarding PPI response is also not available and may have provided some nuances to results regarding the yield between the 2 modalities. Most importantly, when comparing the diagnostic yield of 2 different tests, then all patients should undergo both diagnostic tests and the results should be compared to an appropriate "gold standard." Unfortunately, only a handful of patients had both modalities of testing performed and no potential gold standard that included information about PPI response was provided.

### *My Practice*

In my clinical practice, in those presenting with chronic laryngeal symptoms, I almost always perform upfront pH testing off PPI therapy. However, there may be some situations such as patient preference to not pursue pH testing or lack of access to pH testing that may warrant an empiric trial of acid suppression to see if there is a symptom response. Recent studies have also shown significant response with potassium competitive acid blockers (PCABs) in patients with non-erosive reflux disease,[2] and is a potential alternative in those who have previously failed PPI therapy and do not want to pursue objective pH testing. Alternately an empiric trial with a PCAB as the first line could also be considered, given that it is a more potent acid suppressor than PPIs.

It's surprising that the diagnostic yield for gastroesophageal reflux was so much lower with 24-hour impedance monitoring versus wireless pH monitoring even when just looking at the first 24 hours of results. This is one possible hypothesis: patients undergoing 24-hour pH impedance monitoring may systematically alter their diet and activity leading to fewer reflux events. Certainly, many of our patients undergoing 24-hour pH impedance monitoring report eating smaller meals, being less active, or even sleeping in a semi-recumbent position because of the discomfort associated with having a catheter running from their nostril through their oropharynx and into the esophagus.

Ultimately, these study results will change my practice. Previously, I typically preferred 24-hour pH impedance monitoring over wireless pH monitoring, given the lack of data supporting one testing modality over the other. The reason for this is the ability for the 24-hour pH impedance monitoring to provide information regarding reflux events in the proximal esophagus.[3] However, as outlined in this article, some studies have shown no difference in proximal reflux between those with esophageal symptoms and those with chronic laryngeal symptoms.[4] Data is also limited on the significance of non-acid reflux and distal mean nocturnal baseline impedance (2 parameters with increased diagnostic yield using 24-hour pH impedance testing) in those with extraesophageal and atypical GERD symptoms. Since the findings from this study suggest that wireless pH monitoring is the preferred testing method for GERD in patients with chronic reflux symptoms, I will likely adopt this diagnostic method into my practice when seeing patients with laryngeal symptoms.

### *For Future Research*

Future prospective studies comparing both pH monitoring modalities in a head-to-head manner would be valuable. Further assessment of additional reflux monitoring metrics such as proximal acid exposure and reflux, nonacidic reflux events, and mean nocturnal baseline impedance in patients with chronic laryngeal symptoms will also add to the limited literature in this area and help

guide diagnostic and therapeutic pathways in this group.

### *Conflict of Interest*

No potential conflict of interest

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