

Total Acid Suppression and Its Effect on Barrett's Esophagus

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Presentation Summary

Barrett's esophagus is a complication of gastroesophageal reflux disease (GERD) and may result from prolonged acid exposure in the esophagus. As a result, clinicians are investigating a possible relationship between acid suppression and a decrease in the risk of Barrett's esophagus progression. Some studies suggest that the length of Barrett's esophagus may be reduced with total acid suppression therapy. Other studies indicate that patients with Barrett's esophagus are less sensitive to acid-induced symptoms (eg, heartburn). While these patients may feel better symptomatically, the acid may not be sufficiently reduced to prohibit further damage. Acid suppression, even on high-dose pharmacotherapy, does not always eliminate the nocturnal acid breakthroughs. The contrasting study results on this issue are discussed.

Barrett's esophagus, which is characterized by specialized intestinal metaplasia in the lower esophagus, is a complication of gastroesophageal reflux disease (GERD), resulting from chronic exposure of the esophagus to acid refluxate. Some studies suggest that ameliorating acid exposure should reduce or eliminate Barrett's esophagus and possibly the malignant potential. However, no consensus has been reached.

Medical—acid-suppressing medications such as proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H₂RAs)—or surgical approaches are effective ways to treat GERD. Although acid suppression therapy has been shown to adequately control symptoms and heal esophagitis in patients with GERD, neither medica-

tion nor surgery has been shown to definitively eliminate the cancer risk. Recent studies indicate the level of acid suppression proven effective for treating typical GERD is not high enough for patients with Barrett's esophagus.

Patients With Barrett's Esophagus Are Less Sensitive to Acid Exposure

More than 10 years ago, Johnson and associates reported on decreased sensitivity to acid exposure in Barrett's esophagus patients and a need for more aggressive treatment to affect this condition.¹ Fifteen patients with Barrett's esophagus and 15 patients with GERD were tested for sensitivity to acid perfusion. Sensitivity (via the Bernstein test) occurred in 100% of the GERD

patients, but in only 66% of the Barrett's esophagus patients. Barrett's esophagus patients also took longer to develop pain during acid perfusion than did the patients with GERD (6 versus 2 minutes). Symptoms for patients with Barrett's esophagus were also less frequent and less severe. As a consequence, such patients may be less able to recognize acid reflux. These observations have since been replicated.

Controlled symptoms alone are not an indicator of effective therapy because such patients are less sensitive to the refluxate. As a result, clinicians have used pH monitoring to investigate whether reflux is controlled in a Barrett's esophagus patient.

Nocturnal Acid Breakthrough

Current data suggest that breakthrough acid secretion occurs despite PPI therapy. One 24-hour pH monitoring study compared GERD patients, Barrett's esophagus patients, and healthy volunteers, all taking omeprazole twice daily. Study results indicated recovery of acid overnight, with esophageal acid exposure in a significant portion of the GERD and Barrett's esophagus patients.²

In another 24-hour pH monitoring study, 5 patients with Barrett's esophagus were given omeprazole (20 to 60 mg/day) until they were asymptomatic. The results showed that the pH was well above 4 for most of the day but dropped to an acidic level with accompanying reflux before the next dose of omeprazole, particularly occurring during the night in 4 of the 5 patients.³

Effect of High-Dose PPI Therapy on Barrett's Esophagus

Some studies indicate that acid suppressive therapy must be powerful enough and administered for the necessary duration to abolish the nocturnal acid pulses and to successfully treat patients with Barrett's esophagus.

One of the first studies to examine the effect of high-dose PPI therapy on acid control in patients with Barrett's esophagus suggested that acid control was not sufficient to decrease the length of the disease.⁴ However, the investigators' conclusions are questionable because of inadequate control of the acid exposure and the use of standards for normal acid exposure in untreated normal subjects. Thirteen patients were given lansoprazole 60 mg each morning for an average of 6 years. All patients were followed for the duration of the study. Symptoms improved, and the esophagitis was healed in all patients. However, 5 of the study participants did not have normal 24-hour pH readings, and the 8 patients who were "normalized" were still having considerable reflux but were less sensitive to it. Increased numbers of squamous islands appeared in 62.5% of the normal pH group and in 80% of the abnormal pH group. This is an ongoing investigation to determine whether the appearance of squamous islands is necessarily indicative of Barrett's esophagus regression because glandular tissue may be present underneath.

In a recent study, 14 patients with Barrett's esophagus were given 60 mg of omeprazole each morning for 12 months and followed during that time. A decrease in Barrett's esophagus length from 4.5 ± 1.9 cm to 2.1 ± 1.6 cm ($P < 0.005$) was documented. The 24-hour pH monitoring results showed normal pH ranges but continuing acid secretion, although the 24-hour mean percentage of time with the pH less than 4.0 decreased from 29.4% at entry to 4.9% at 12 months.⁵

A 6-year follow-up study of 47 patients who were given 20 mg of omeprazole indicated that all symptoms for all of the 47 patients were controlled. There was no decrease in Barrett's esophagus length, and squamous islands appeared in some of the patients.⁶

These results prompted further exploration of cellular changes with

minimal acid exposure in Barrett's esophagus patients. Biopsies from normal and Barrett's esophagi were grown in organ culture with acidic media, either continuously or with 1-hour acid pulses, and compared with cells grown in pH 7.4 media for up to 24 hours. Enhanced cell proliferation and a delay in the maturation were noted in cells grown in 1-hour acid pulses. Continuous acid exposure blocked cell proliferation in Barrett's esophagus, suggesting that the diverse patterns of acid exposure in individual Barrett's esophagus patients may explain the unpredictable progression from Barrett's esophagus to neoplasia.⁷

A study published in 1999 observed 42 patients with Barrett's esophagus who were given lansoprazole for symptom control: 24 patients had "normalized" acid exposure based on 24-hour pH monitoring (group A); 18 had continuing abnormal reflux (group B). Villin, a measure of differentiation, and proliferating cell nuclear antigen (PCNA), a marker for proliferation, were measured. At baseline, an inverse relationship existed between villin and PCNA expression. In group A, a substantial increase in differentiation and a decrease in proliferation were observed; in group B, no change from baseline in differentiation or proliferation was observed.⁸

Another study published in 1999 supports the theory of total acid suppression for Barrett's esophagus regression. Fifty-three patients with Barrett's esophagus were prospectively randomized into 2 groups: 27 who received the H₂RA ranitidine 150 mg twice a day and 26 who received the PPI omeprazole 40 mg twice a day. Symptoms were controlled in both groups. After 24 months, endoscopy showed that omeprazole produced a small but statistically significant decrease in the length and area of Barrett's esophagus compared with the ranitidine group. The pH recording

showed almost total control of acid reflux in the omeprazole group.⁹

Conflicting study results abound, leading clinicians to question how patients with Barrett's esophagus

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should be managed. One suggested approach is to initially start the patient on PPI therapy twice a day before meals to control his or her symptoms and to heal the esophagitis. After 1 month, 24-hour dual-electrode pH monitoring should be performed to ascertain the exact extent of acid suppression and healing. The treatment can be adjusted, if necessary, based on pH monitoring results. At that time, endoscopy with biopsy can be performed to determine dysplastic changes.

Summary

Presently, there is neither unequivocal evidence nor consensus about the most appropriate treatment for Barrett's esophagus. However, current studies may provide additional data on the role of continued acid exposure and Barrett's esophagus development, and the data presented here suggest that complete acid suppression may have an effect on the length and area of Barrett's esophagus.

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