Nocturnal Acid Breakthrough on Proton Pump Inhibitor Therapy: To Treat or Not to Treat

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Opinion statement
Nocturnal acid breakthrough is misunderstood and infrequently requires treatment in everyday practice. There are important subgroups of patients in whom esophageal reflux occurs in the presence of nocturnal acid breakthrough in which treatment may be needed.

Introduction
The most common treatment for gastroesophageal reflux disease (GERD) is antisecretory therapy, principally with proton pump inhibitors (PPIs). Delayed-release PPIs are substituted benzimidazoles, weak bases (pH ~ 4.5), acid labile, and require protection from gastric acid. They are absorbed in the duodenum, converted to an active sulfonamide, and transported to the parietal cell, where they block active proton pumps. The onset of action is relatively slow. Although some relief is seen on day 1, it usually takes 5 days to achieve steady state. PPIs block 70% to 80% of active pumps and require pump activation for maximal effect. Thus, the drugs are best administered before meals, as parietal cell activation is maximum in the setting of food (sight, sound, smell, ingestion). Individual variability in pH response is based on multiple factors, including absorption, cytochrome P450 metabolism, and genetic polymorphism, which may make predicting individual dose response difficult. Delayed-release PPIs control pH (acid) best during the daytime, with an almost universal recovery of some acid secretion in the sleeping period. This pharmacologic effect, now termed nocturnal acid breakthrough (NAB), has been a source of much controversy and research over the past 10 years.

NAB is an often-misunderstood concept. When used correctly, NAB describes the pharmacodynamic phenomenon of acid secretion recovery, a decrease in intragastric pH to less than 4 overnight while taking PPIs (Fig. 1). The original description of NAB defines the phenomenon as more than 1 continuous hour with intragastric pH less than 4 overnight on twice-daily PPI. When this definition is used, 70% to 80% of patients on twice-daily PPI will have NAB [1]. The concept has been extended, without supporting data, to include all overnight acid recovery regardless of PPI dose. NAB in and of itself is not clinically important unless there is associated esophageal acid reflux resulting in nocturnal symptoms or esophageal injury. Esophageal reflux occurs in a very small percentage of normal subjects and patients with GERD who do not have Barrett’s esophagus. However, in those with Barrett’s esophagus and/or scleroderma esophagus (a forme fruste of end-stage GERD), it is quite frequent [2]. The unifying feature of those who have esophageal acid reflux during NAB is a decrease in the lower esophageal sphincter (LES) pressure to below normal and ineffective esophageal motility (IEM) [3]. In this article, we review NAB, its potential clinical importance, and its treatment in the rare clinical scenario that requires it.

DEFINITION OF NAB
The term “nocturnal acid breakthrough” was first defined as overnight recovery of gastric acid to a pH less than 4 for at least 1 continuous hour in the overnight period in patients on twice-daily PPI. In the original study, the overnight period was defined as 10 pm to 6 am. Forty-
five patients who underwent intragastric pH monitoring on twice-daily PPI were reviewed [1]. NAB as previously defined was seen in 70% of these patients. This pharmacologic phenomenon was seen with equal frequency with omeprazole, lansoprazole, pantoprazole, and rabeprazole and seen in normal subjects and patients with GERD. Early observations with twice-daily esomeprazole demonstrated a decrease in NAB frequency and an improvement in intragastric pH control compared with lansoprazole. This difference has not been studied [4•,5].

The authors of the original paper found that NAB onset depends on the timing of the evening PPI dose. In general, NAB onset is approximately 6 to 7 hours after the evening dose [1]. In patients taking a once-daily dose of a PPI before breakfast, “NAB” onset is much earlier, usually occurring before midnight [6]. NAB is in part related to *Helicobacter pylori* infection. Studies have documented that patients on PPI who are *H. pylori* positive have a much lower NAB frequency and superior control of intragastric pH overall compared with *H. pylori*-negative subjects [7–9]. This observation’s clinical importance is also unknown.

**CLINICAL IMPORTANCE OF NAB**

Much controversy surrounds the clinical importance of NAB; in many cases, it has been overestimated. There is tremendous variability and little predictability of the presence of esophageal acid exposure (reflux) during periods of NAB. Reflux depends on GERD’s severity, LES pressure, and esophageal clearance. At least 50% of patients with Barrett’s esophagus and/or scleroderma and GERD will have some overnight esophageal acid exposure during NAB, compared with only 10% to 15% of those with GERD and no Barrett’s, and only 2% of normal subjects. In fact, few have abnormal amounts of overnight acid exposure [2]. Patients with below normal LES pressure and/or IEM were up to eight times more likely to reflux during NAB than those without these motility abnormalities [3]. Studies attempting to correlate the presence of NAB and esophageal acid exposure have been incon-