

## PPI Efficacy in Different Manifestations of GERD

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Proton pump inhibitors (PPIs) are the most effective drug for gastroesophageal reflux disease (GERD). However, the therapeutic response varies among different subgroups of patients and depends on measurements of outcome. For example, an 8-week of PPIs treatment may heal more than 80% of esophagitis, but the response rate of symptoms resolution is about 60-70%. The symptomatic response to PPIs therapy is even lower as estimated by 40-50%, in patients with endoscopy negative reflux disease (NERD), which unfortunately comprises two third of patients with GERD symptoms, resulting in a large number of patients refractory to PPIs therapy. However, using reflux monitoring tests to exclude functional heartburn, the response rate of true NERD is comparable to that of esophagitis. The response rate of extraesophageal reflux disease (EERD) is more unpredictable because many other non-GERD causes may contribute to the airway symptoms, resulting in a significant challenge in managing such patients.

Although pathophysiological studies suggest that motility disorder, sensory impairment, mucosal inflammation accompanied by noxious compositions of refluxate may contribute to the clinical symptoms and signs of reflux, clinical predictors or objective biomarkers for treatment response are scarce in patients with NERD or EERD. Ambulatory pH or impedance-pH monitoring performed off PPI may provide objective evidence of reflux which is able to predict PPI treatment response of typical reflux symptoms. However, for extraesophageal symptoms, GERD can be an inducer, a cofactor, or a bystander. Given both laryngitis and GERD are prevalent diseases, we recently found that pH parameters off PPI is able to predict symptomatic response to PPIs therapy in patients with chronic laryngeal symptoms and without concomitant typical reflux symptoms. In contrast, the parameters of pH-impedance on PPI to predict treatment response in outcome research remains lacking despite the pathogenic evidence of non-acid reflux in the symptom generation.

Due to the lack of objective biomarkers in NERD and EERD, the treatment response of empirical anti-secretory drugs largely relies on the patient subjective report. Disease-specific patient-reported outcome (PRO) instrument thus can be helpful in the evaluation of treatment response in clinical practice and can be used as the primary outcome measurement in clinical trials. In 2009, the US FDA proposed a PRO guidance for medical products to support labeling claims and recommends an a priori responder definition on the PRO score change which can be derived from an empirical responder criterion for conceptually linking the clinical relevance. We recently found that the Reflux Symptom Index scores reduction for at least 6 points from baseline after PPI treatment predicts an empiric criterion, i.e., 50% or more reduction of the primary laryngeal symptom in patients with suspected laryngopharyngeal reflux at a sensitivity of 0.79 and a specificity of 0.70. The results may potentially be applied in future clinical trials and clinical practices.