GERD – Evolving and Expanding

Gastroesophageal reflux disease (GERD) continues to intrigue both clinicians and researchers alike because of its varied presentation, changing epidemiology, lack of gold standard for diagnosis, and evolving treatment. It affects a major proportion of the adult population in the Western World and appears to be on the increase even in areas such as Southeast Asia, suggesting a role of environmental factors and lifestyle. GERD has different manifestations from simple heartburn to esophageal chest pain, hoarseness of voice or even asthma-like symptoms. Of course, the major impact that this disease has is on the quality of patient's life, particularly in those with nighttime symptoms of reflux disease.

The question of whether the spectrum of GERD is continuous or discontinuous, and whether the entities of endoscopy-negative reflux, esophagitis and Barrett's esophagus are truly distinct or entities in transition from less severe to more severe forms remains a source of contention. It is also unclear if these entities differ greatly with respect to their pathophysiology and natural history but their clinical management is similar – aimed at symptom resolution. Moreover, the classification of GERD, based on endoscopic criteria, really does not help in either diagnosis or treatment given that the majority of GERD patients have a normal endoscopy and that treatment is symptom driven. A substantial proportion of patients with so-called endoscopy-negative reflux disease may actually have lesions which may not be detected by standard endoscopy alone, creating a challenge in the endoscopic recognition of subtle abnormalities. There is also room for identifying new histopathological criteria or biological markers of inflammation for helping in the assessment of nonerosive GERD. The extra-esophageal manifestations of reflux disease appear to be most poorly understood in terms of their pathogenesis as well as treatment, with treatment failure being common in this subgroup of patients.

The role of inflammation and metaplasia in the gastric cardia continues to be a source of debate between two different schools of thoughts where this is related to *Helicobacter pylori* infection vs. reflux-induced disease. However, it is possible that damage in this area may be a result of both etiologies with reflux change leading to more severe consequences such as intestinal metaplasia and carcinogenesis. Barrett's esophagus, the pre-cancerous lesion for esophageal adenocarcinoma, is a known complication of GERD occurring in about 10–15% of the patients. The enigma of why only a small proportion of

GERD patients develop Barrett's esophagus and even fewer develop dysplasia or esophageal adenocarcinoma continues. The role of biomarkers to identify patients at high risk for neoplasia is being explored but not ready for general clinical application.

Although the majority of patients with erosive esophagitis can be healed with acid suppression therapy or with anti-reflux surgery, symptom resolution appears a much more difficult endpoint to achieve. Anti-reflux surgery is similar to medical therapy in the long-term maintenance treatment of patients with reflux disease; however, the continued need for medical therapy in up to a third of the patients as well as its associated complications make it a less desirable option in all GERD patients. Acid suppression treatment appears to be inadequate for making a major impact in progression to neoplasia in Barrett's esophagus, again reflecting major host and disease related factors which cannot be modified with acid suppression alone. Simple chemopreventive agents are being tested and loom in the horizon to prevent the development of neoplasia in Barrett's esophagus patients.

Newer modalities such as endoscopic therapies for reflux disease also represent an endoscopic-based therapeutic approach but it is unclear if they add to our current armamentarium for the treatment of GERD patients. A major advance, however, has been the advent of new endoscopic modalities for the diagnosis of minimal changes in patients with endoscopy-negative reflux disease, detection of neoplasia and dysplasia in patients with Barrett's esophagus as well as therapies for the treatment of early cancer such as mucosal resection and photodynamic therapy.

Future studies will help clarify whether patients diagnosed with reflux disease undergo progression of disease from non-metaplastic to metaplastic to cancerous epithelium and identify specific host or disease factors which predispose certain individuals to complications of the disease versus others who have uncomplicated disease. There are unmet needs also for the therapy in patients with symptomatic GERD.

*Prateek Sharma
Peter Malfertheiner*