Gastroenterology 2018;154:263–266

INTRODUCTION

Esophageal Diseases

Rebecca C. Fitzgerald[1] Michael F. Vaezi[2]

[1]MRC Cancer Unit, University of Cambridge, Cambridge, United Kingdom and [2]Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, Tennessee

This special issue of *Gastroenterology* provides in depth discussions of esophageal diseases with significant public health interest for which there have been substantial advances in recent years, including gastro-esophageal reflux disease, eosinophilic esophagitis, and esophageal cancer. These disorders could be considered "bread and butter" areas for GI clinicians and yet, like so many areas of medical practice, these subjects have become increasingly specialized as we gain a better understanding of their underlying pathogenesis and as new technologies emerge for their diagnosis and therapy.

The importance of esophageal disease is highlighted when one considers the striking epidemiological trends of these diseases. In the Western world it is estimated that one in ten adults complains of reflux symptoms; this is becoming a global problem with the obesity epidemic and the global adoption of western dietary patterns[1,2] (see article by Drs Joel E. Richter and Joel H. Rubenstein on pages 267–276).[3] There has also been a stark increase in incidence of esophageal adenocarcinoma over the past forty years which has led to a hitherto uncommon cancer type pre-occupying GI oncologists in the western world[4,5] (see article by Drs Helen G. Coleman, Shao-Hua Xie, and Jesper Lagergren on pages 390–405).[6] Many reviews focus on esophageal adenocarcinoma, given its surge in incidence; however, esophageal squamous cell carcinoma still accounts for 90% of esophageal cancers globally, including a significant part of clinical practice in the West (see article by Drs Christian C. Abnet, Melina Arnold, and Wen-Qiang Wei on pages 360–373).[7] Eosinophilic esophagitis (EoE) is also an emergent disease, which was probably overlooked as a cause of bolus obstruction in the past.[8,9] The prevalence rates of EoE are now estimated to be as high as 1 in 1000 and it accounts for a substantial part of the endoscopic workload in the US[10,11] (see article by Drs Evan S. Dellon and Ikuo Hirano on pages 319–332).[12]

Some common themes emerge from this collection of articles. There is a growing appreciation of the microbiome and the immune micro-environment in the pathophysiology of these disorders. The importance of the microbiome in colonic disease is well established; however, it is now observed that there is a complex but conserved bacterial population resident in the normal esophagus, with an estimated 140 bacterial species, of which 95 are identified. The diversity and composition of these florae may alter in the context of esophageal disease —although a causal relationship is more difficult to establish.[13–15] Another common theme is improved sub-classification of esophageal disease. This progress is in part due to sequencing technologies which can now be applied to a single cell resolution. This enables us to classify esophageal diseases more precisely as to etiology, thereby potentially allowing precision diagnosis and therapy – this is most prominent in the area of cancer but it is also becoming relevant across inflammatory disorders. There is also progress towards less invasive and more sensitive diagnostic tools. For example, reflux disease can be assessed using ambulatory tools and devices, in some cases linked to laboratory tests. These have the potential for application in primary care, for assessment of mucosal inflammation and diagnosis of Barrett's esophagus.[16] Whichever methods gain widespread adoption in the future, it is clear that in order to identify patients at risk for esophageal cancer we need to overcome the barriers to investigation which includes improving public awareness about symptoms and bringing diagnostic technologies nearer to the patient.[17]

The first section evaluates GERD; a key theme for its articles is the overlap between acid reflux, gastroparesis, functional dyspepsia and EoE, leading to frequent misdiagnosis. This is important from an epidemiological perspective (see article by Drs Joel E. Richter and Joel H. Rubenstein[3] on pages 267–276), as well as in terms of pathophysiology (see article by Drs Jan Tack and John E. Pandolfino[18] on pages 277–288), diagnosis (see article by Drs Michael F. Vaezi and Daniel Sifrim[19] on pages 289–301) and therapy (see article by Drs C. Prakash Gyawali and

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2017.12.017

Ronnie Fass[20] on pages 302–318). New diagnostic strategies for GERD and EoE in the developmental phase will likely lead to more accurate diagnostic strategies. In the past, therapy for GERD has focused on either acid suppression or mechanical anti-reflux therapy (endoscopic or surgical) across the whole spectrum of conditions. Proton pump inhibitors are now one of the most widely prescribed medications available without a medical consultation. In the long-term, their over-use can lead to complications and to overlooking underlying conditions such as EoE or Barrett's esophagus. However, with improved understanding of pathophysiology more tailored treatment approaches are evolving with the possibility of adding neuromodulators, psychological interventions and electrical sphincter stimulation into the armamentarium.[21,22] Therefore, diagnostic modalities are required which can differentiate between the different phenotypes of reflux disease, including non-erosive reflux disease, which can lead to atypical manifestations including ENT and respiratory manifestations. Advances in impedance testing and biomarkers such as salivary pepsin are interesting approaches that have been evaluated recently and are discussed by Vaezi et al.[19] It should be remembered that whether or not the refluxate will cause epithelial damage depends on the balance between aggressive (degree of refluxate) and defensive forces (eg, epithelial resistance). The sensory mechanisms will then determine the relationship between reflux exposure and symptom generation and here other factors such as stress and psycho-social co-morbidities will also play a role, as discussed by Drs Jan Tack and John E. Pandolfino[18] (pages 277–288).

The second section focuses on eosinophilic esophagitis. The cause for this newly defined disease seems closely related to an allergic-type reaction, which promotes eosinophil mediated inflammation. In some cases, there is expression of a unique set of genes, which probably relates to underlying genetic susceptibility and interactions with environmental exposures in early life. The microbiome may also play a role, although details of this are not yet fully understood (see article by Drs Kelly M. O'Shea, Seema S. Aceves, Evan S. Dellon, Sandeep K. Gupta, Jonathan M. Spergel, Glenn T. Furuta, and Marc E. Rothenberg on pages 333–345).[23] Currently, treatment hinges on dampening down the inflammatory response including through the use of topical steroids and dietary manipulation. Long-term topical steroid use is a concern in patients diagnosed as children who may have long duration of disease. However, as our understanding of the pathogenesis increases this may inform specific therapeutic strategies, including disruption of allergic inflammatory and T- helper type 2 cytokine-mediated responses. The duration of untreated disease is the best predictor of stricture risk; this highlights the importance of early diagnosis and therapy. Prospective long-term outcome studies, focused on multiple aspects of disease activity, are needed to fully understand the disease pathogenesis and to develop new therapeutic strategies. Such studies would be aided by less invasive, bedside diagnostic tools that avoid reliance on repeated endoscopy and biopsy (see article by Drs Alex Straumann and David A. Katzka on pages 346–359).[24]

The third section focuses on esophageal cancer. Each article discusses the two histological subtypes (squamous and adenocarcinoma) separately or together as seemed most logical, to avoid repetition whilst highlighting distinctions when required.

The etiology of esophageal squamous cell carcinoma is linked to smoking, alcohol, polycyclic aromatic hydrocarbons exposure from a variety of sources and high temperature ingestion. Despite initial reports of a potential etiologic link between human papilloma virus and esophageal squamous cell carcinoma (ESCC), the number of cases caused by these viruses appears to be very low (see article by Drs De-Chen Lin, Ming-Rong Wang, and H. Phillip Koeffler on pages 374–389).[25] In contrast, reflux disease, obesity and tobacco smoking (to some extent) have been established as the primary risk factors for esophageal adenocarcinoma, although it is not yet clear whether interventions to reduce these risk factors can reduce the risk of progression to cancer.[26] More speculative is the suggestion that the microbiome may also be relevant to the pathogenesis of this disease and it is provocative to consider how the widespread introduction of antibiotics may have altered the gastrointestinal flora with untold effects on disease susceptibility.

The cellular and molecular pathogenesis of Barrett's esophagus has been an active topic of research over many years and the precise mechanisms are still under debate. Drs Michael Quante, Trevor A. Graham and Marnix Jansen[27] (pages 406–420) suggest that Barrett's can be seen as a successful adaptation to esophageal damage.[26] In carcinogenesis, this evolutionary process continues as an interaction between the inflammatory microenvironment on the one hand and the acquisition of somatic genomic alterations in evolving stem cell populations on the other. In this article the various model frameworks for understanding the origin of Barrett's esophagus are discussed in favor of the development from a stem cell, such as a gastric cardia stem cell, or a submucosal stem cell (squamous gland duct cells).[28] Although there are a number of unanswered questions about the development of Barrett's, what is clear is that the resulting metaplasia and its risk for cancer result in a complex and heterogeneous landscape which makes the development of predictive biomarkers challenging.

The revolution in sequencing technology has enabled us to study the esophageal genome at an unprecedented level of detail and the The Cancer Genome Atlas (TCGA)[28] and International Cancer Genome Consortium (ICGC) efforts[29–31] have rendered a vehicle for standardized datasets available to the wider research community.[10,29] The initial hopes that this new understanding would result in a paradigm shift for therapeutic approaches have not materialized. However, a new era of trials are starting to emerge in which; a) histological subtypes are considered as distinct entities; b) the imaging assessments and surgical management are standardized; and c) molecular targeted therapies are introduced to the relevant patient groups following stratification. It is vital that we continue to refine the trial designs to be more adaptive as new information is gleaned and as new agents become available. To make the