Seeking Answers for Post-Infectious Irritable Bowel Syndrome
Christopher Chang, MD, PhD

While the observation that irritable bowel syndrome (IBS) can follow an episode of infectious acute gastroenteritis (AGE) was first published more than 40 years ago, efforts to explain the pathophysiology of post-infectious IBS (PI-IBS) have only recently begun in earnest.

Factors predictive for PI-IBS – such as female, younger age and heightened duration or intensity of the antecedent AGE – mirror the condition’s epidemiology. Psychological factors such as hypochondriasis and an increase in major life events are independently predictive of developing PI-IBS. Moreover, higher levels of perceived stress, somatization and anxiety are also associated with PI-IBS.

Studies quantify incidence of PI-IBS
Retrospective and prospective studies published over the past 15 years have revealed incidences of PI-IBS ranging from seven to 31 percent, with follow-up periods of three months to six years following AGE. Of note, these studies spanned multiple continents and involved an array of gut pathogens. A recent meta-analysis calculated a 9.8 percent prevalence of IBS following AGE compared to 1.2 percent in controls; the pooled odds ratio of developing IBS after AGE was 7.3 percent (note 1).

A prospective cohort study took advantage of a 2002 Salmonella enteritidis outbreak in a Catalonian village in Spain that resulted in 1,243 cases of AGE (identified by symptoms, with some cases confirmed by culture). Based on self-administered questionnaires completed every three months, researchers calculated a relative risk of 7.8 percent for developing IBS within one year after Salmonella AGE compared to uninfected controls from a neighboring county (note 2).

In 2000, livestock fecal contamination of the water supply in Walkerton, Ontario resulted in more than 2,000 cases of AGE due primarily to

Continued on Page 4 (see “PI-IBS”)

<table>
<thead>
<tr>
<th>Mechanisms of Post-Infectious Intestinal Changes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune activation or impaired anti-inflammatory responses</td>
<td>C. jejuni infection leads to elevated intra-epithelial T-cells in rectal mucosa months later</td>
</tr>
<tr>
<td>Changes in mucosal function; elevated serotonin release after test meal</td>
<td>Hyperplasia of various cell types, such as Paneth, mucus-producing and serotonin-secreting enteroendocrine cells in the small intestine; elevated serotonin release after test meal</td>
</tr>
<tr>
<td>Persistent changes within the enteric nervous system</td>
<td>Remodeling of damaged nerves and elevated growth factor expression following inflammatory changes post-infection</td>
</tr>
<tr>
<td>Chronic changes in visceral sensitivity</td>
<td>Activation of mast cells alters pain perception and induces motility changes</td>
</tr>
</tbody>
</table>

Figure 1: Mechanisms of post-infectious intestinal changes and examples of each. Observations point to the possibility of multiple, non-mutually exclusive mechanisms for PI-IBS.
Staging of Advanced Esophageal Cancer

Laith H. Jamil, MD

The American Cancer Society estimated that there were 15,560 new U.S. cases and 13,940 deaths from esophageal cancer in 2007. Esophageal cancer is three to four times more common among men, and 50 percent more common among African-Americans. In some countries such as Iran, northern China, India and South Africa, esophageal cancer rates are 10 to 100 times higher than those of the United States. In Western countries, the incidence of esophageal adenocarcinoma in white men has been increasing at a rate of about two percent per year.

Importance of staging
Esophageal cancer staging is guided by the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer and the International Union Against Cancer. Since management decisions are heavily affected by the initial disease staging, accuracy is critical. Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) is the most accurate modality in the initial tumor (T) and node (N) staging of esophageal cancer, while computed tomography (CT) and positron emission tomography (PET) scans are the most useful to detect metastatic disease.

CT and PET for initial staging, detection of metastasis
A CT scan of the chest and upper abdomen is usually performed once a diagnosis of an esophageal cancer is made, both to evaluate the region of the primary tumor and to search for distant metastatic disease. PET scans are even more sensitive than CT for detecting metastatic disease, and are now widely used for preoperative staging in patients who lack evidence of distant disease on CT.

Endoscopic ultrasound becomes standard practice
In recent years, EUS has replaced CT as the standard investigation in the T and N staging of esophageal cancer, and is considered the locoregional staging modality of choice. Using a dedicated radial echoendoscope, the physician captures ultrasound images from within the esophagus that allow assessment of the tumor's size and location. Once a tumor penetrates all the way through the wall of the esophagus (T3) or is node-positive, it is considered to be advanced disease, and long-term survival is uniformly poor. The optimal treatment for these patients is controversial; in many institutions, initial chemo-radiotherapy is preferred over immediate surgery for patients with T3 and/or regional node-positive (N1) disease.

The accuracy of EUS for T staging compared to postsurgical pathological staging ranges from 61 percent to 76 percent, and for N staging from 64.5 percent to 89 percent. EUS can accurately stratify patients into “early” (T0-2 or N0) or “advanced” (T3-4 or N1) disease categories in 83 percent of cases, providing information that is highly predictive of treatment outcome and patient survival.

In fact, EUS changes patient management in about one-third of cases, with the majority (85 percent) moving toward nonsurgical and palliative treatments after identification of advanced disease. To avoid overstaging, EUS-guided FNA of suspicious lymph nodes is critical – since up to 80 percent of N0-pathology staged tumors may be overstaged as N1 by EUS alone.

EUS in multimodality imaging
The strength of EUS in a multimodality staging strategy – used in conjunction with CT and PET – is in identifying patients with locally advanced disease and guiding the need for preoperative neoadjuvant therapy. In a study of 56 patients who concomitantly underwent examination with EUS, CT and PET in a multimodality staging program, EUS was the only imaging test that identified all primary tumors and provided tumor staging (note 1). EUS identified a significantly greater number of patients (58.9 percent) with locoregional nodes than CT (26.8 percent, P = .0006) or PET (37.5 percent).

Esophageal stricture and EUS
Some advanced esophageal tumors are challenging to evaluate using EUS because the tumor creates a stricture of the esophagus too narrow to be traversed by echoendoscopes, which are 12.7 mm in diameter. A non-traversable stricture can significantly decrease the accuracy of standard echoendoscope T-staging.

In such cases, a non-optic esophagoprobe (a slightly narrower instrument used for esophageal imaging) may be used as an alternative to the echoendoscope. The esophagoprobe is comparable in T-staging accuracy to the echoendoscope in patients with traversable tumors. Dilating the esophageal stricture may allow an echoendoscope or esophagoprobe to traverse the constricted segment of the esophagus. Gradual dilation in a series of procedures over several days may be safer than dilating the stricture all at once.

Figure 1: Endoscopic view of the upper margin of a lower esophageal tumor.

Figure 2: Endoscopic ultrasound showing invasion of a tumor beyond the muscularis propria.

Figure 3: Endoscopic ultrasound showing malignant-appearing lymph nodes in the right upper paratracheal area.
cent, P = .02). CT alone identified the need for preoperative neoadjuvant therapy in 15.2 percent of patients, PET alone identified this need in 28.3 percent and EUS – the most effective of the three modalities – identified this need in 34.8 percent.

Laparoscopic staging
Some centers use laparoscopic staging for esophageal cancer given the increasing prevalence of distal esophageal adenocarcinoma. This approach can potentially detect more nodes and distant metastases.

In a study of 125 patients with potentially resectable cancer of the distal esophagus or stomach, laparoscopic staging changed TNM classification in 46 cases (37 percent). This resulted in up-staging of the N-factor (n = 15) and M-factor (n = 28). Downstaging of the T-factor was recorded in three cases (note 2).

Another study compared laparoscopy to EUS for esophageal staging in 47 patients. EUS-FNA was 90 percent accurate compared to laparoscopic staging. Overall, staging accuracy of EUS compared to laparoscopic staging was 72 percent. Accuracy was 76 percent for patients with complete EUS staging compared with 64 percent for patients with incomplete EUS examinations. Staging differences were mostly reflected in distant metastases detected by laparoscopy (17 percent) (note 3).

PET with fluorodeoxyglucose
The role of fluorine-18 fluorodeoxyglucose PET (FDG-PET) in esophageal cancer staging continues to evolve. This technology is not indicated in the staging of superficial esophageal cancer. And while FDG-PET is better at detecting infiltrating lymph nodes and distant metastases than CT, it can lead to some false positive results. For this reason, CT is commonly the first choice for detecting metastatic disease. When CT shows no evidence of distant disease, FDG-PET is then used preoperatively to verify the absence of metastases.

There may be a role for FDG-PET to estimate the tumor metabolic length in untreated esophageal cancer, providing a noninvasive delineation of the superior and inferior extent of viable tumor involvement using computer-generated metabolic length measurements.

Magnetic resonance imaging
The role of magnetic resonance imaging (MRI) in esophageal cancer staging has not been thoroughly evaluated. Riddell et al were able to develop imaging criteria for local staging using high-resolution T2-weighted (T2W) MRI. Their success using this technique in a small group of patients demonstrated the value of continued study of MRI as a possible alternative, non-invasive method of local staging for esophageal cancer.

Future tests on FNA samples
There is growing evidence of the need for new forms of pathological testing of FNA samples. For example, there is reason to suspect the presence of micrometastases in lymph nodes that cannot be detected by standard pathological methods. Furthermore, the addition of methylation analysis to conventional cytology may have resulted in increased sensitivity to the presence of cancer while sacrificing accuracy in identifying the type of cancer.

Digital image analysis (DIA) and fluorescence in situ hybridization (FISH) are two promising new forms of testing. One early study looked at DIA/FISH versus routine cytology (RC) examination on upper EUS-FNA samples, including samples from lymph nodes and esophageal malignancy. The sensitivity, specificity, and accuracy of DIA/FISH versus RC for detecting malignancy were 97 percent, 100 percent and 98 percent, versus 87 percent, 100 percent and 90 percent respectively. In one patient where RC was negative, DIA/FISH diagnosed squamous cell cancer.

Conclusion
For advanced esophageal cancer, locoregional staging is best performed with EUS-FNA, while a CT scan of the thorax and abdomen, and FDG-PET should be used to detect metastatic disease. The role of laparoscopic staging is evolving and seems to complement EUS staging, while the role of MRI in esophageal cancer staging has not been well-studied.

References

Dr. Jamil is Associate Director of Interventional Endoscopy, Pancreatic and Biliary Disease Program at Cedars-Sinai Medical Center. Laith.Jamil@cshs.org

Figure 4: Endoscopic ultrasound-guided fine needle aspiration. Yellow arrow indicates needle.

Figure 5: CT scan showing an esophageal tumor.
Campylobacter jejuni and *E. coli* O157:H7 (note 3). Questionnaires were administered two years later; residents with suspected AGE were 4.8 times more likely to develop IBS than controls (IBS prevalence was 36.2 percent vs. 10.1 percent among controls).

Finally, approximately 300 patients from a Beijing dysentery clinic in 1998 were followed by questionnaire for one to two years and compared to uninfected family members as controls. The rate of IBS in the dysentery group was 8.1 percent compared to only 0.8 percent in the control cohort (note 4).

**Investigating the mechanisms of PI-IBS**

While the epidemiology and risk factors associated with PI-IBS are relatively well established, observed post-infectious intestinal changes point to multiple, non-mutually exclusive mechanisms to account for PI-IBS (see Figure 1; note 5).

Cedars-Sinai researchers are taking an approach that employs animal models of PI-IBS to gain further understanding of the links between motility disturbances and AGE, IBS and small intestine bacterial overgrowth (SIBO). In one such model, rats demonstrate persistent altered stool consistency and increased rectal lymphocytes three months after *Campylobacter jejuni* infection is cleared (Figure 2). Findings are even more pronounced in rats with SIBO (identified by quantitative polymerase chain reaction of bacterial DNA in intestinal contents rather than by breath-testing). More findings on the potential mechanisms behind these changes are forthcoming.

**Few well-studied treatment options**

To the detriment of patients with PI-IBS, there have been few treatment trials specifically addressing this condition. One of the few such trials of PI-IBS-specific therapy is a study of prednisolone that failed to improve IBS symptoms or reduce enteroendocrine cells. The study involved 29 post-*Campylobacter* patients who received 30 mg/day for three weeks in a double-blind, randomized, controlled trial (note 6).

Probiotics, while an intuitive option, have an equivocal track record for relieving IBS symptoms and have not been systematically tested for PI-IBS. Moreover, the multitude of formulations and bacterial species available further complicate probiotic recommendations.

Various therapies directed toward non-PI-IBS, such as SIBO eradication or the use of tricyclic antidepressants and serotonin antagonists, have been suggested, but without convincing studies to match. It is our hope at Cedars-Sinai that greater understanding of the pathophysiology of PI-IBS will provide guidance as to the most promising routes for PI-IBS therapeutic clinical trials in the near future.

Dr. Chang is Associate Director of the GI Motility Program at Cedars-Sinai Medical Center.

**References**


**Figure 2:** Rats demonstrate persistent altered stool consistency and increased rectal lymphocytes three months after *Campylobacter jejuni* infection.