Functional Dyspepsia

TO THE EDITOR: Talley and Ford (Nov. 5 issue)[1] omit chronic abdominal-wall pain, a common disorder that is often attributed to abdominal cutaneous-nerve entrapment,[2] as a possible cause of epigastric pain. Chronic abdominal-wall pain is often localized to the upper abdomen — for example, in 33.9%[3] and 71.4%[4] of patients in two series. Before diagnosis, patients typically have fruitless and costly health care visits, diagnostic tests, and drug therapy.[3,4]

Characteristic features of the pain[2] and physical-examination findings described nearly 90 years ago[2-5] underlie the diagnosis, which can be confirmed by the response to a local anesthetic injection.[2,3] Aware clinicians consider this nonvisceral cause of epigastric pain before applying the authors' recommended treatment algorithm, which includes endoscopy, testing for *Helicobacter pylori*, and empirical acid-suppression therapy.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The authors cite a Cochrane meta-analysis of proton-pump inhibitor (PPI) treatment in 3347 patients with functional dyspepsia, which showed a relative risk of persistent symptoms of 0.87. Would the authors qualify their recommendation that "acid suppression seems to be a worthwhile strategy in most patients"?

PPIs, available over the counter, may be associated with community-acquired infection with *Clostridium difficile*.[1,2] In a recent trial, PPIs led to a dysregulated gastric microbiome in normal volunteers, with significant changes in taxa associated with *C. difficile* and gastrointestinal bacterial overgrowth.[3]

There are also concerns about community-acquired pneumonia. A Johns Hopkins meta-analysis of data from 6,351,656 participants showed an increase by a factor of 1.5, with the highest risk within the 30 days after therapy initiation.[4]

We collected gastroscopy data from 14 patients. In 6 patients whose gastric juice had a pH of 4 or less, bacteria were not cultured. The remaining 8 patients, whose gastric pH was 5 to 8, all had cultures that grew bacteria. This experience would support the view that less acidic gastric juice may favor bacterial growth.

Do the authors have data or comments on potential iatrogenic effects of PPIs in patients with functional dyspepsia?

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TO THE EDITOR: The review of functional dyspepsia neglected the importance of thyroid dysfunction on its causation. Both hypothyroidism and hyperthyroidism have been related to abnormal gastric myoelectrical activity. Gunsar et al. found that patients with hypothyroidism had significantly elevated dyspepsia scores, which were improved after treatment of hypothyroidism. In patients with hyperthyroidism, the dyspepsia scores

were also improved in the euthyroid state after treatment.[1] Kyriacou et al. have described the relationship between thyroid disorders and gastrointestinal dysfunction.[2] Serum thyroid hormone level has also been shown to be related to gastrointestinal activity.[3] Therefore, we suggest that thyroid function be checked in patients with unexplained dyspepsia, including measurement of serum concentrations of thyrotropin and free T_4.

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THE AUTHORS REPLY: Our list of alternative etiologic factors was not designed to be exhaustive, but we agree that chronic abdominal-wall pain is another possible cause of epigastric pain. It is relatively easy to rule this out by performing Carnett's test, in which the patient tenses the abdominal musculature by raising the head and shoulders from the examination table or by raising both legs with knees straight; if localized pain is accentuated on palpation, the test is positive.[1]

All medications carry risks. Evidence for harm from PPIs comes from observational studies,[2] with the inherent issues of confounding and bias. Although the estimates of effect are statistically significant, this does not equate to causality. In addition, reported effect sizes for community-acquired pneumonia and *C. difficile* infection are generally less than 2. A minimum effect size of 2 is recommended for identifying reliable causal associations, and more prudent guidelines advise that effect sizes of less than 3 or 4 be discounted altogether. We conclude that there probably are risks with PPIs, even though published data from randomized, controlled trials raised no safety issues during 5 to 12 years of continuous PPI use.[3] Histamine H_2-receptor antagonists are an alternative in functional dyspepsia.

Before recommending routine thyroid-function screening in functional dyspepsia, we would want to know that the prevalence of abnormal test results is higher among persons with functional dyspepsia than among healthy persons. We are not aware of any such data, and given that the background prevalence of abnormal results of thyroid-function tests is 4%,[4] any overlap between thyroid disorders and functional dyspepsia may relate to chance, rather than an etiologic role of thyroid dysfunction in dyspepsia.

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Since publication of their article, the authors report no further potential conflict of interest.

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Tumor Regression and Allograft Rejection after Administration of Anti–PD-1

TO THE EDITOR: Although antibodies against the programmed death 1 (PD-1) receptor and one of its ligands (PD-L1) have produced tumor regressions in multiple cancer types, these therapies are untested in patients treated with long-term immunosuppressive medications.[1] Here, we re-