

Non-Ulcer Dyspepsia: A Review of the Pathophysiology, Evaluation, and Current Management Strategies

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Abstract

Non-Ulcer-Dyspepsia (NUD) is defined by The Rome III criteria as a chronic or recurrent epigastric pain within the last 3 months and an onset of symptoms at least 6 months prior to presentation. This disease has become a very common and costly condition, for the patient himself, and for the physician to diagnose it. It is not only the complexity of the pathophysiology that makes this disease a challenging diagnosis for the physician, it also the lack of testing strategies to approach a patient with this problem. In this review we will summarize the current universe of information of NUD, we will also cover the pathophysiology and the current guidelines for the evaluation and management, so the physician has a better sense of how to engage this common and difficult type of patients.

Keywords: Pathophysiology; Non-Ulcer-Dyspepsia (NUD); Epigastric pain

Introduction

Dyspepsia is a common problem clinician's see daily in their clinics. When patients have a thorough evaluation and no plausible etiology is found to explain their affliction, a diagnosis of non-ulcer dyspepsia is often assigned to them. Various reports suggest that the percentage of patients with an organic cause of dyspepsia range from 25-33% while 67-75% does not have a clear etiology. In recent years much investigation into the causes and possible treatment algorithms have been studied [1,2]. This paper will review the current definitions of non-ulcer dyspepsia (NUD), pathophysiology, and guidelines for evaluation and management.

Definition

The Rome III criterion for a diagnosis of NUD is chronic or recurrent epigastric pain within the last 3 months and an onset of symptoms at least 6 months prior to presentation. The term functional dyspepsia and idiopathic dyspepsia are often used as well. Symptoms include ulcer-like dyspepsia; gastroparetic-like (nausea, early satiety, and post-prandial pain), and undifferentiated.

Evaluation

It is often said that NUD is a diagnosis of exclusion and in many ways this is true. To declare a diagnosis of NUD one cannot have any anatomical nor structural abnormalities. Organic causes of dyspepsia also include medications, endocrinopathies, and systemic illnesses.

Because NUD is so common with an estimated worldwide prevalence of 10-40% [3], it is imperative that a complete evaluation is performed and a diagnosis be made expeditiously. Delay in diagnosis adds to a patient's misery and escalates healthcare costs as potentially unnecessary testing and empirical treatments are begun. It is suggested that approximately 50% of patients remain symptomatic over a 5 year follow-up period [3]. A paper by Leeds and colleagues reported annual expenditures in excess of £1 billion annually [4].

The initial step in evaluation of dyspepsia is eliminating organic etiologies from the list of potential causes. The differential diagnosis includes peptic ulcers, medications, biliary/pancreatic disease, malignancies (both gastric adenocarcinoma and lymphoma), transverse

colonic disease, Crohn's of the foregut, atypical gastroesophageal reflux disease (GERD), vascular disease, metabolic causes (renal, hypercalcemia, and heavy metal poisoning), thoracic vertebral disease, endocrinopathies (thyroid, hyperglycemia, and adrenal insufficiency), and rarely mucosal diseases such as sarcoidosis, eosinophilic gastritis, and collagenous gastritis [5] (Figure 1).

The initial evaluation needs a complete history that includes systemic illnesses, medication, and a psychosocial history. The latter is significant because anxiety and depressive disorders release neurohormonal factors that can cause foregut symptoms. While performing the abdominal exam it is advisable to search for carnett's sign which correlates well with abdominal wall pain. The rest of the abdominal exam will often be normal (Figure 2).

The complexity of the evaluation is often dependent upon a person's age, symptoms, and index of suspicion of an organic etiology. Generally it is advisable to request a complete blood count (CBC), complete chemistry panel, thyroid panel, and stool for occult blood.

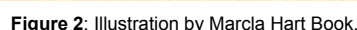
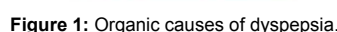
Beyond appropriate laboratory tests, it is often necessary to obtain an imaging study such as ultrasonography (USG) or a computerized tomography scan (CT scan) to visualize intra-abdominal organs. Upper endoscopy is also utilized to look for gastric mucosal injury and neoplasia. If erosions or ulcers are observed or the mucosal integrity is compromised then biopsies may be obtained to look for *Helicobacter pylori*, infiltrative processes, or neoplasia. Recent attempts to correlate endoscopic findings and symptoms resulted in a degree of ambiguity [6] (Figure 3).

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The true pathogenesis of NUD remains unclear but the following discusses the major theories. Most will agree that these patients are not a homogenous group and that many may have more than one contributing factor.

In addition to the classic dysrhythmias, other motility disorders are occasionally seen and include antral hypomotility and impaired gastric accommodation in response to a meal. Gastric emptying studies are often requested during the evaluation of patients with NUD, especially the sub-category with gastroparetic-like symptoms. If these patients have delayed emptying they may falsely be diagnosed with gastroparesis (Figure 4).

Over the years *Helicobacter pylori* (*H. pylori*) has attracted attention in the area of NUD. When peptic ulcers are found as an organic cause, the correlation of symptoms and disease is high. It is less so when only erosions are seen and much less so when there is no visible mucosal injury. A disease process is considered a cause of symptoms only if cure of the disease corresponds to remission of the symptom. If *H. pylori* is found, most clinicians are in favor of treating the infection, but empirical treatment for presumed infection is not advised. In regions where this bacterium is endemic, an endoscopy is recommended, specifically if the prevalence in the community is at least 10% [1].

Visceral hypersensitivity plays a role in many functional illnesses such as irritable bowel syndrome (IBS), irritable esophagus, non-cardiac chest pain syndromes, and NUD. This condition is characterized by a decrease in the threshold for induction of pain with normal gastric compliance. Mertz and associates observed that 87% of NUD patients had a reduction in perceptual threshold as compared to

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Figure 4: Gastric rhythms in electrogastrography.

just 20% in the organic dyspepsia group. In this setting dysfunction of mechanoreceptors and aberrant processing of the afferent fibers on the spinal cord and brain lead to alterations in the brain-gut axis as well as on the local levels [12,13]. Chemosensitivity has also been shown to be increased in many patients with NUD. Samson and his colleagues infused acid into the duodenal bulb of patients with NUD. Compared to controls these patients were more likely to develop nausea [14].

When approaching the patient with NUD one can never overlook the psychosocial aspects. There are clear associations seen with dyspepsia and anxiety disorders, generalized somatiform disorder, and depressive disorders. Patients with NUD, much like their IBS counterparts, have a higher incidence of childhood abuse [15-17].

Food induces many neurohormonal responses and it as well activates mechanoreceptors as the stomach is stretched or distended. This explains why some patients are only symptomatic in the post-prandial state. The majority of patients with NUD have symptom exacerbations following a meal [18].

Kim and his team compared levels of acylated ghrelin, a hormone produced by endocrine cells in oxyntic mucosa of the stomach, in patients with NUD and controls. Ghrelin has several functions that include appetite regulation, acid secretion, and induces migrating motor complexes and gastric emptying. They reported that abnormal levels can relate to discomfort and early satiety [19].

Management

Proton pump inhibitors (PPI's) are often prescribed empirically and without clear data to support their use. Short term benefits have been shown, but it is commonly accepted that most functional disorders enjoy a high placebo response. As mentioned previously, some patients with NUD develop symptoms during acid infusion as compared to controls. Since PPIs are readily available and have good safety profiles, some patients may benefit from their use, keeping in mind that if positive results are not seen following a short course then alternative therapies should be chosen.

Tricyclic antidepressants (TCA's) have been studied extensively in the management of NUD. They have been effective in patients with tachygastria demonstrated by EGG and also patients with normal gastric rhythms [20]. They have anticholinergic activity and affect serotonin pathways as well. These effects thus modulate the enteric nervous system with regard to local motor activity as well as the brain-gut axis. TCA's have been shown to improve patients quality of life [21]. A review of 13 articles comprising 1700 patients found that in 11 of these studies symptoms improved with antidepressants or anxiolytics [22].

Unlike patients with depression, very low doses of TCA are required in NUD therapy. This is probably due to the high number of receptors in the gut. Most TCA have been studied or have vast clinical experience. Since desipramine has fewer side effects among this class of medications it is a popular choice.

The recommended starting dose is 10 mg with increases of 10 mg until a desired effect is seen. Younger patients, especially those in their teens and early twenties, can often tolerate dose adjustments every few days while the elderly may need 2-4 weeks between increases. Most patients achieve benefit between 20 mg and 50 mg. Since fatigue can be an adverse event we recommend dosing the TCA's in the early evening.

Prokinetics have been efficacious in numerous studies [23,24].

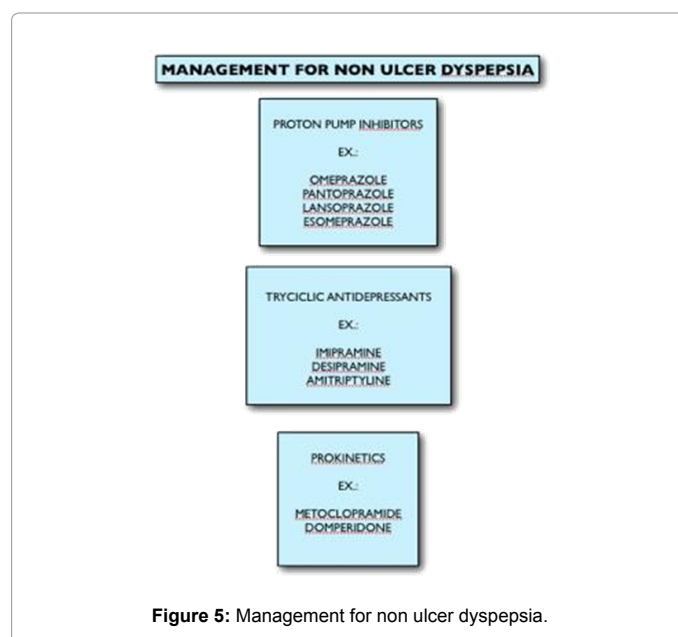


Figure 5: Management for non ulcer dyspepsia.

Their use is generally reserved for those patients in whom an EGG demonstrates tachygastria. Empiric use of motility enhancing agents should be cautious, since the majority of patients with NUD have either tachygastria or a mixed dysrhythmia. Patients with these rhythms may see no improvement or worsen. There are 4 agents that have been evaluated in NUD. These include metoclopramide, cisapride, tegaserod, and domperidone. Metoclopramide, though available through prescription can improve patients with bradygastria, but the potential for neurological events prevents it from receiving even a modest recommendation. Because of potential adverse cardiac events, cisapride and tegaserod have been removed from the US market. Domperidone often is available through compounding pharmacies and is gaining acceptance as the treatment of choice for NUD secondary to bradygastria (Figure 5).

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