HOW I MANAGE THE DYSPEPTIC PATIENT AND NON-ULCER DYSPEPSIA

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Dyspepsia is a common problem, with up to 40% of the population complaining of upper abdominal symptoms at some time or other.[1,2] Clinical diagnostic accuracy in dyspeptic patients is only about 50%[3] and significant diagnoses with important consequences such as peptic ulcer disease and gastric cancer must be excluded. With the easy availability of fibre-optic endoscopy, the question arises as to who should be investigated early. This article will address these issues, and also deal with non-ulcer dyspepsia (NUD) as a distinct clinical entity.

DEFINITION OF DYSPEPSIA

The features of 'dyspepsia' are legion. One all-embracing definition of it is episodic, recurrent or persistent upper-abdominal or lower-chest discomfort or pain, related to eating, which may be accompanied by other gastrointestinal symptoms over a period (arbitrarily at least two weeks).[4] Patients tend to include almost any abdominal discomfort such as heartburn, flatulence, regurgitation, vomiting, nausea, post-prandial fullness, bloating, belching, early satiety or anorexia.[4,5]

EPIDEMIOLOGY OF DYSPEPSIA

In population studies, the prevalence of dyspepsia is from 20% to 40%.[1,2] Endoscopy performed for dyspepsia reveals that the number of significant diagnoses rises with age (Table 1).[6,7] Overall, an organic cause for dyspepsia is found in about 40% of patients.[8] The prevalence of dyspepsia and associated endoscopic findings is fairly consistent worldwide, but it should be noted that gastro-oesophageal reflux disease is rather uncommon in Orientals and is much less prevalent, for example in Singapore, than in western populations.[9]

WHO SHOULD BE INVESTIGATED EARLY?

It is important to elicit a full clinical history, including medication and physical signs that may point towards possible organic diseases, such as those listed in Table 2. Several groups of patients deserve closer attention:[11-14]

- Patients who were previously uncomplaining and who present with newly-developed dyspepsia.
- Patients older than 55 years of age.
- Patients with a history of smoking or use of non-steroidal anti-inflammatory analgesics (NSAIDs) or a history of heavy alcohol consumption.
- Patients with the 'alarm features' in their history and examination, as given in Table 3.
- Patients (or relatives of patients) whose true agenda is exclusion of malignancy.[15]
- Patients with a strong family history of malignancy, especially gastrointestinal malignancy.
- Patients with severe, long-standing symptoms which were not investigated previously.
- Patients with psychological problems.
- Patients whose symptoms are very typical of either peptic ulcer disease or gastro-oesophageal reflux disease.

TABLE 1
Endoscopic diagnosis of dyspepsia.

Diagnosis	Forbat *et al*. 1987 (≥25 years old)[6]	Lockhart *et al*. 1985 (≥70 years old)[7]
Normal	38%	20%
Reflux	24%	13%
Gastroduodenitis	13%	22%
Ulcer	51%	58%
Cancer	0%	33%

TABLE 2
Common organic diseases causing dyspepsia.[10]

Structural disorders of the gastrointestinal system
Gastric and duodenal ulcers
Gastro-oesophageal reflux
Biliary tract disease
Gastritis and duodenitis
Pancreatitis
Carcinoma – stomach, pancreas, colon
Malabsorption syndromes
Other infiltrative diseases of the stomach, e.g. lymphoma

Metabolic disorders
Diabetes mellitus
Hyper- and hypo-thyroidism
Hyperparathyroidism
Electrolyte imbalance including renal failure

Drugs
Non-steroidal anti-inflammatory agents
Oral antibiotics
Theophylline
Digitalis
Iron or potassium supplements
Alcohol

Miscellaneous
Ischemic heart disease
Autoimmune diseases such as atrophic gastritis

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TABLE 3
'Alarm features' mandating urgent investigation.

Weight loss
Dysphagia
Persistent vomiting
Severe pain
Bleeding (including occult bleeding)
Anaemia
Jaundice
Palpable mass

INVESTIGATING THE DYSPEPTIC PATIENT

The objectives of investigating a dyspeptic patient are first to determine whether there is a demonstrable lesion in the upper gastrointestinal tract, and second to exclude extra-gastrointestinal diseases.

First-line tests would include:

- blood count and differential count,
- ESR,
- simple biochemistry (urea, electrolytes),
- liver function tests,
- faecal occult blood test,
- upper gastrointestinal endoscopy and biopsies, or a barium meal,
- ultrasound examination of the abdomen, especially the hepatobiliary system, if endoscopy is normal.

Gastric emptying studies, oesophageal manometry and pH monitoring are at present research tools, and their place in the clinical management of dyspepsia is yet to be fully established.

THE ISSUE OF THERAPEUTIC TRIALS BEFORE ENDOSCOPY

Therapeutic trials for dyspepsic patients with neither alarm features nor positive screening tests are controversial. The arguments in favour are:[16]

- endoscopy is expensive and may be dangerous,
- most patients have functional disease and would be treated with anti-secretory medication anyway,
- peptic diseases also respond to anti-secretory agents,
- gastric malignancy is a rare cause of dyspepsia whose prognosis will not change significantly with a few weeks' delay in diagnosis.

As dyspepsia becomes managed more and more by primary care physicians, it is increasingly tempting for them to use therapeutic trials to decide which patients need specialist attention.[17]

A refinement to the use of therapeutic trials is possible through the growing availability to primary care physicians of breath tests for *Helicobacter pylori* (*H. pylori*).[18] There is a growing tendency to regard the absence of *H. pylori* in a young patient as evidence of absence of serious disease; it is often assumed in a young patient that it represents, at worst, benign peptic ulcer disease and a therapeutic trial of proton pump inhibitors and *H. pylori* eradication therapy is given. Patients are sent for further investigation only if symptoms persist or relapse.

However, therapeutic trials have been condemned because:

- it is impossible to be sure what drug to give (apart from an attempt to eradicate *H. pylori*) and, whatever is chosen, the outcome provides no diagnosis because of placebo and common initial responses of several conditions to antisecretory or motility agents;
- many patients would be assigned diagnoses baselessly, and inappropriate and expensive medication may have to be prescribed for a long time;
- endoscopy is nowadays safe and easily available in many countries. There remains the chance that the prognosis of a serious disease could be changed by delay in diagnosis and treatment, a worry that is uppermost in many patients' minds;[19]
- it is not necessarily more economical to give therapeutic trials.[20]

If there is a problem of access to endoscopy and the patient is young, the presentation very innocuous and there is some resistance to investigations, an empirical therapeutic trial can be given, but rapid relapse or anything less than total remission would mandate further investigations.[11] Where endoscopy is easily available and acceptable to the patient, it is prudent to remove doubt and uncertainty as early as possible. A negative endoscopy itself may prove therapeutic for a patient with non-ulcer dyspepsia worrying about underlying illness.[19,20]

In practice, of course, by the time a patient is referred to a gastroenterologist for endoscopy, he is likely to have had one or more courses of empirical therapy, if for no better reason than as a temporising measure while waiting for a specialist appointment.

NON-ULCER DYSPEPSIA

A significant proportion of patients with dyspepsia are found to have no organic disease after investigations. These patients are labelled as suffering from non-ulcer dyspepsia (NUD), sometimes also known as 'functional dyspepsia'. NUD patients present an extremely difficult management challenge.

DEFINITION OF NON-ULCER DYSPEPSIA

Patients with NUD may exhibit any or all dyspeptic symptoms. Pointers to NUD are young patients with a long history of symptoms but otherwise good health and appetite, previous negative investigations for the same symptoms and severity of symptoms which vary with levels of background emotional stress. The Rome criteria[4] define NUD as:

- chronic or recurrent upper abdominal pain or discomfort, the duration of which is less than one month, with symptoms present more than 25% of the time;
- no clinical, biochemical, endoscopic or ultrasonographic evidence of any known organic disease likely to explain the symptoms is found and
- features suggesting sub-categories of ulcer-, reflux-, or dysmotility-like dyspepsia.

Other descriptions include aerophagia and non-specific dyspepsia. The attempt to identify sub-classes of patients with particular symptoms was made in the hope that

therapy can be rationalised. However, the considerable overlap that exists limits the clinical usefulness of such a classification.[1,22]

Symptoms suggestive of gastro-oesophageal reflux, such as heartburn or acid regurgitation, are particularly difficult to evaluate, as they are neither sensitive nor specific. Up to half of patients with typical symptoms have no demonstrable reflux disease and an equal number with confirmed reflux report other non-specific symptoms.[22,23] Patients with reflux symptoms but without endoscopic oesophagitis are often labelled NUD without further investigations such as oesophageal manometry or 24-hour pH measurement, which are not routinely available. Genuine reflux may therefore be misdiagnosed as NUD. On the other hand, if reflux is demonstrated, it should not be labelled as NUD. This problem is the root of the difficulty in comparing therapies, since reflux is variably included in NUD.

It should also be noted that irritable bowel syndrome (IBS) occurs quite commonly in patients with NUD either simultaneously or on different occasions.[24,25] A good history will establish if irritable bowel syndrome is present.[26]

EPIDEMIOLOGY OF NON-ULCER DYSPEPSIA

The prevalence of NUD varies according to the definitions used, the populations studied (population-based studies give higher prevalences than hospital-based studies),[9,27] the intensity of investigations and the length of follow-up. Reported prevalence from various countries ranges from half to two-thirds of patients with dyspepsia.[9,28-30] Unlike irritable bowel syndrome, more men have NUD than women.

PATHOPHYSIOLOGY OF NON-ULCER DYSPEPSIA

The pathophysiologic processes involved in NUD are poorly elucidated and understood with no good and reproducible correlation between symptoms of NUD and the pathophysiological basis for these symptoms.[31,32]

Abnormal upper gastrointestinal motility has been found in some NUD patients, but the relationship between detected abnormalities and symptoms is complex and indirect.[33,34] Biliary dyskinesia may also cause the symptoms of NUD, but the manometric studies needed to exclude this are not routine.[35] It is possible that abnormal visceral perception is a factor in NUD. Patients have been demonstrated to have a lower threshold to gastric distension but increased sensitivity to gastric acid has not been shown.[36,37] Psychological factors have also been implicated. NUD patients have been found to have higher levels of anxiety, neuroticism and depression than duodenal ulcer patients or controls,[38,39] but these may reflect health-care seeking behaviour rather than be causes of symptoms. NUD patients also had more perceived stressful life events, higher scores in somatization and hysterical personality traits as compared with healthy controls.[38,40] Psychological factors have been shown to affect gastrointestinal motility by altering autonomic activity or by reduction in visceral pain threshold.[41]

The role of *Helicobacter pylori* in NUD is unclear. Although *H. pylori*-associated gastritis and duodenitis are found in up to half of NUD patients, correlation has not been proven in studies of either *H. pylori* prevalence in NUD or eradication of *H. pylori* in NUD patients. With the current state of evidence, NUD should not be regarded as being curable by erradication of *H. pylori*.[42-47]

DRUG TREATMENT FOR NON-ULCER DYSPEPSIA

The lack of an established clear pathogenesis renders the treatment of NUD difficult. Therapeutic benefits are not easy to measure objectively. Trials classify patients and assess symptoms differently, and it is often unclear if gastro-oesophageal reflux has been excluded. There is also a large placebo response of 30% to 60%.[31,48]

Prokinetic drugs

The rationale for the use of prokinetic drugs is to improve gastric emptying. The dopamine agonist metoclopramide blocks receptors in the proximal gut, stimulates upper gastrointestinal motility and increases lower oesophageal sphincter tone.[49] Unfortunately, metoclopramide crosses the blood/brain barrier and central nervous system toxicity, such as tardive dyskinesia, is seen in up to 20% of patients. Domperidone is another dopamine agonist that enhances antral peristalsis and has been shown to be better than placebo in NUD.[50] Side-effects are rare as this does not cross the blood/brain barrier. Cisapride is a substituted piperidinyl benzamide related to metoclopramide, and is a 5-hydroxytrypamine type-4 agonist. It enhances motility along the entire gastrointestinal tract and increases lower oesphageal sphincter pressure and motility by 20% to 50%. Figures of 60-90% good-to-excellent response in patients treated with cisapride compared to placebo have been cited.[51,52] However results have not been consistent.[53,54] Nonetheless, a meta-analysis of trials of cisapride, domperidone and metoclopramide for NUD suggests a 46% therapeutic gain of these agents over placebo.[55,56] Recently, cisapride has been associated with cardiac conduction disorders leading to 38 fatalities in the US between 1993 and 1998 when used in combination with azole antifungals, macrolide antibiotics, protease inhibitors and selective serotonin reuptake inhibitor antidepressants.[57] The overall risk is very low and with awareness of the potential drug interactions, cisapride remains one of the most popular drugs for NUD.

Anti-ulcer drugs in NUD

Controlled studies of antacids in NUD have shown no benefit.[48,50,58,59] The results with H2 receptor antagonists are inconsistent, with half of all studies showing no benefit. However, a meta-analysis shows that there may be a 20% better response than placebo, although there is a possibility that the inclusion of some reflux patients may have made the difference.[55,57] The place of proton pump inhibitors in NUD remains unclear.[60,61] Any benefit shown may have been due to treating existing gastro-oesophageal reflux labelled NUD.

The use of psychotropic medicines, such as tricyclic antidepressants, anxiolytic agents and selective serotonin reuptake inhibitors, remains empirical. There are no data from controlled studies, but it might be expected that some patients would respond favourably, as they do in irritable bowel syndrome.[62]

Other drugs

Numerous agents have been used, none showing any evidence of efficacy.[48] They include pirenzepine[63] (a selective muscarinic blocking agent), misoprostol,[64] pancreatic supplements, ursodeoxycholic acid, antispasmodic drugs and sucralfate.[65,66] Drugs that reduce visceral sensation, such as fedotozine, a peripheral kappa

opioid agonist that reduces visceral nociceptive thresholds,[67] serotonin receptor antagonists such as ondansetron and granisetron, and somatostatin analogues such as octreotide have also been studied.

Empirical drug treatment

Drug treatment for NUD is not always required. Often, reassurance that there is no serious disease is sufficient. Drugs should be reserved for those who are bothered enough by their symptoms to want treatment. The choice of which drug to use is difficult. The clinician is left with empirical choices based on a 'best guess' of what might achieve the most desirable outcome, and inevitably he has to be guided by symptoms.[55] (Table 4.) Responses are hard to predict. Studies have shown, for example, that cisapride can relieve a broad spectrum of symptoms, not just dysmotility-like symptoms in NUD. Modifying therapy, changing dosages or perhaps combining drugs over a few visits may be necessary to achieve relief.

NATURAL HISTORY OF NON-ULCER DYSPEPSIA

There is evidence that there are as many patients with new-onset dyspepsia as there are those who spontaneously remit.[68] Up to 30% of patients have been known to lose their symptoms upon completion of investigations that demonstrate no serious disease, and this group may contribute to the placebo responders.[69] NUD patients do not appear to be more likely to develop peptic ulcer disease, although it is difficult to be sure that those who have received empirical antisecretory treatment prior to negative endoscopy are not in fact 'in between ulcers', especially those who prove to be *H. pylori* infected.[70,71]

PRINCIPLES OF MANAGEMENT OF NON-ULCER DYSPEPSIA

- Often patients present for consultation only after a long period of symptoms, and it is important to determine the reason for consultation. Fear of cancer must be identified. Doctor-hopping should be detected, as useful investigations may already have been performed recently, and repeating them would be costly and unnecessary.
- It is important to make a positive diagnosis. Investigations, including endoscopy, should be instituted early, especially for patients in the higher risk groups but over-investigation should be avoided. Once a diagnosis of NUD is made, it is important to resist the temptation to re-investigate a patient who does not recover with empirical treatment, unless symptoms change. Giving in to re-opening investigations destroys the confidence of the patient that serious disease has been excluded. The lack of serious disease must be emphasised to the patient. It is equally important to emphasise that NUD is a recognised entity and not 'in the mind'.
- It may help the patient to have the possible pathogenesis of the disorder explained in simple terms, for him to appreciate that there is no 'disease' as such, but that the stomach and intestines are 'misbehaving' a little and only need encouragement to settle down. It is also helpful to introduce concepts like gut dysmotility, heightened visceral sensation and the importance of the brain-gut interaction when relating symptoms to stress.
- It is worthwhile to explore possible psychological factors and, if found, to determine whether counselling or medication for them is appropriate. Often, a mild anti-depressant or anxiolytic drug in combination with other empirical NUD treatment is sufficient. Some patients with severe and multi-system symptoms may benefit from counselling from a specialist in chronic pain syndromes or a psychiatrist.
- Often patients want to know if some foods should be avoided, and they should be told that there is no standard list of things to avoid in NUD, but what they know disturbs them, should logically be avoided. Often these foods include coffee, caffeine-containing foods, alcohol and, in lactase-deficient individuals (many Orientals), milk. It is worth discouraging the casual use of non-steroidal anti-inflammatory drugs.
- Enquire from the patient if medication is desired. Often, reassurance is enough for the patient. There is a large placebo response and a third of NUD patients lose (or forget) their symptoms once they are reassured as to the absence of serious disease. If drugs are to be

TABLE 4
Empirical therapy for non-ulcer dyspepsia.

Predominant symptoms	**Potential therapeutic alternatives**
Ulcer-like symptoms hunger and night pain, relief with food or milk	Antisecretory drugs: H_2 receptor antagonists to start with
Dysmotility symptoms fullness, bloating, nausea, gascousness	Prokinetic drugs: Cisapride Domperidone Metoclopramide
Reflux-like symptoms heartburn, acid reflux and water-brash, but without endoscopic reflux features, and either negative motility / pH studies or not done	Anti-reflux advice Antisecretory drugs Prokinetics
Unspecified dyspepsia symptoms cannot be classified into any of the above classes	H_2 receptor blocker or prokinetic drugs or a combination
Concomitant severe anxiety or depression	Consider adding antidepressants or anxiolytics

prescribed, it is worth emphasising to the patient that the choice of drug from those available is empirical and that it may take time to discover the 'best' treatment for the patient. This advice is especially important in places where patients are able and liable to doctor-hop to find instant cures, leading to frustration, anxiety and demoralisation for both patient and doctors.

- Patients are often anxious about whether they will continue to suffer symptoms, or require medication for life. They should be told that their symptoms may well disappear after a short course of therapy, say in a few months, but that there are patients who appear to need medication indefinitely. It is reasonable to ask the patient to stop medication completely after total symptomatic relief to see if a relapse occurs. Realistic goals should be set. For example, occasional symptom relapses after remission should not be dealt with by chronic drug treatment, but the patient should learn to cope.
- The patient should be followed up at least once to determine the natural history or response to treatment if taken, to provide further reassurances and to modify therapy as required.

Key points

- **Dyspepsia is a common symptom in the community but only 40% of patients have significant diagnoses.**
- **Clinical diagnostic accuracy is poor - only about 50% of patients.**
- **Organic diseases causing dyspepsia should be excluded quickly, especially in older patients with suspicious or 'alarm' features on history and examination.**
- **Initial investigations include blood counts, biochemistry, liver function tests, faecal occult blood, upper gastrointestinal endoscopy and ultrasound of the hepatobiliary system.**
- **Endoscopy should not be deferred in favour of a therapeutic trial as there is no advantage.**
- **Non-ulcer dyspepsia (NUD) is diagnosed when there is no evidence of organic disease after investigations.**
- **It is important to determine a NUD patient's motive for consultation, to make a clear and confident diagnosis of NUD and to emphasise the absence of serious disease.**
- **The pathophysiology of NUD is unclear and there is no correlation with symptoms.**
- **Despite this, empirical treatment when desired by patients is targeted at predominant symptoms, such as ulcer-, dysmotility- or reflux-like dyspepsia.**
- **If a patient has intractable symptoms, psychological factors should be sought.**
- **The main drugs used are antisecretory, prokinetic and psychotropic drugs in various combinations.**
- **Insufficient evidence exists that *H. pylori* causes NUD, nor that its eradication heals NUD.**
- **The natural history of NUD is variable but benign, and reassurance is important.**

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