

## **Bile and Pepsin – How Relevant Are They in the Management of Gastro-Oesophageal Reflux Disease (GORD)?**

*A report from a meeting of the Primary Care Society for Gastroenterology (PCSG) during the annual conference of the British Society of Gastroenterology (BSG), Glasgow, March 27<sup>th</sup> 2007.*

Many patients experience the typical symptoms of gastro-oesophageal reflux disease (GORD), despite being on long-term acid-suppressing therapy. It may be that the underlying problem is not acid at all, but non-acid factors such as refluxing bile and pepsin.

Professor Pali Hungin, Dean of Medicine at the University of Durham, told yesterday's meeting of the PCSG that as nearly all GORD is treated by general practitioners, the issues surrounding non-acid reflux are an important consideration in terms of the primary care management of patients with what appear to be reflux symptoms.

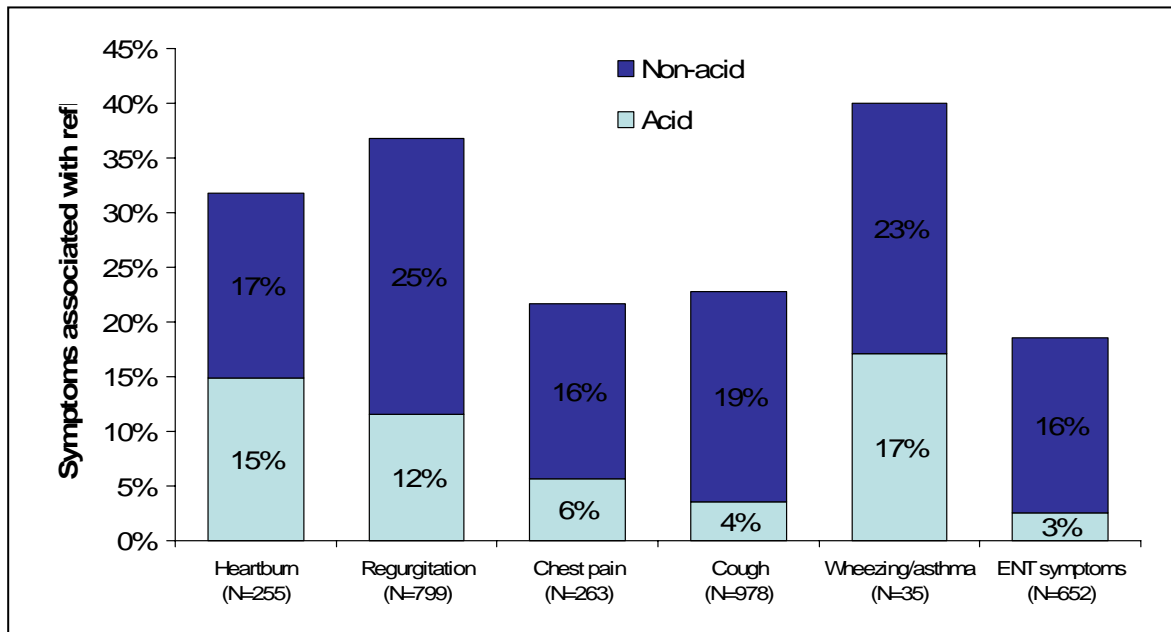
More accurately, he said, GPs should be thinking in terms of the possibility of the non-acid elements in the reflux, such as bile, pancreatic enzymes, pepsin and food.

The main problem facing GPs is the persistence of symptoms, despite the fact that a significant proportion of patients are on long term proton pump inhibitor (PPI) therapy. "Indeed, it has been estimated that as many as 30% of long-term PPI users continue to experience moderate-to-severe symptoms of reflux disease," he reported.

"Compliance with prescribed treatment may be a problem," said Professor Hungin, "but we have to accept that there is a hidden reservoir of non-responders."

There is certainly data to suggest, he continued, that among patients who do not respond to PPIs, there is a significant element of non-acid or mixed reflux – in both the presence and non-presence of oesophagitis. Thus, whereas the role of acid is firmly established in GORD, the role of non-acid reflux in patients whose symptoms persist despite adequate acid suppression is clearly an important issue.

Professor Hungin reported data from nearly 3,000 US patients, which showed that there is a high proportion of symptoms associated with the non-acid component of reflux – for example, 17% non-acid reflux vs 15% for acid reflux in patients with heartburn, 25% vs 12% for regurgitation, 16% vs 6% for chest pain, 19% vs 4% for cough, 23% vs 17% for wheezing/asthma, and 16% vs 3% for ENT symptoms.



Citing another study, he said that 172 of 200 patients (86%) continued to experience symptoms despite being maintained on twice-daily PPIs. Of those, 35% were found to be associated with non-acid reflux compared to only 8% with acid reflux. It was perhaps surprising, he commented, that in 57% of cases, symptoms were not actually associated with any reflux at all.

These findings were supported by data from a third study, in which 48% of “typical” GORD symptoms in 99 patients undergoing pH monitoring were said to be related to non-acid reflux compared to just 11% that were acid-related. Again, a significant proportion of symptoms (41%) could not be attributed to reflux.

In a further study, “typical” symptoms were reported in 9% of 72 patients with bile reflux, 12% with mixed reflux, 28% with acid reflux, and in 51% with no reflux.

“This illustrates the level of uncertainty with which GPs have to manage these patients,” he commented. “It is far more complicated than we could ever have imagined.”

In terms of the mechanisms involved in non-acid reflux, he reported that although the composition of the total refluxate – in terms of acid, bile and pepsin – is probably very important, making the link to oesophageal damage is still not straightforward.

It has been shown, he said, that both conjugated and un-conjugated bile acids cause oesophageal damage – and also that synergism between acid and bile is clinically significant in the pathogenesis of duodenal GORD.

In terms of treatment, while there are surgical options, the key to management is a medical-based approach, insisted Professor Hungin. As well as lifestyle changes, there is the potential to decrease transient lower oesophageal sphincter relaxation (e.g. with baclofen), to decrease visceral sensation (e.g. with tricyclics) and to decrease the level of reflux itself (e.g. with alginates).

He said that in this clinical setting, alginates possess a number of suitable characteristics: promoting adhesion to oesophageal mucosa, stimulating the immune system in the oesophagus, and inhibiting pepsin activity. “The tenacity of the alginates to stick around in the oesophagus is clearly very helpful in treating the non-acid elements of reflux disease,” he said.

In conclusion, Professor Hungin said that the cause of non-PPI responsive GORD remains poorly understood. Indeed, it is still not clear if it is actually related to non-acid reflux. It has been said, he continued, that refractory GORD may or may not be about acid or non-acid.....and may not be GORD at all!

“At a practical level, we are left with a large group of patients requiring further attention. Referral for investigation is an option, but is secondary care really geared up for batteries of complex tests? For many GPs, the simple answer may be empirical therapy.

“Having discovered ‘GORD’, and possibly duodenal GORD, and their complications, we may now have to cope with the limitations of acid-suppressing therapy.”

This report is sponsored by an unrestricted educational grant from Reckitt Benckiser.