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Gastric bacteria can either be ingested or ascend from the distal bowel; however, their survival is usually limited by gastric acidity and motility. A reduction in gastric acid can result in bacterial overgrowth in the stomach and proximal small bowel, and the number of organisms rises as the intragastric pH rises.

The increased risk of noncardia gastric cancer seen in patients with hypochlorhydria may be explained by an excess of nitrates and N-nitroso compounds (NOCs). These compounds are found in the diet of populations with a high gastric cancer risk, but can also be produced by the organisms that exist in the hypochlorhydria stomach. It has long been hypothesized that nitrates and NOCs act as one of the triggers in the atrophy-metaplasia-dysplasia-carcinoma path. However, although indirect data have linked the premalignant changes of metaplasia and dysplasia to NOCs, direct measurement of gastric nitrates and NOCs has not confirmed such a link.

The role of Helicobacter pylori in bacterial overgrowth is mainly as a cause of hypochlorhydria resulting from atrophic gastritis, leading to a reduction in the parietal cell mass. Acid-suppressing drugs can result in bacterial overgrowth and increased nitrates and NOCs, although there is no current evidence for an increased risk of gastric cancer in patients taking them. One explanation is that the stomach appears to be colonized by different organisms than those in patients with hypochlorhydria for other reasons. There is some evidence that bacterial overgrowth per se can cause gastric inflammation in mice; however, although in humans the degree of gastric inflammation is greater when overgrowth is more prominent this may simply reflect the greater degree of hypochlorhydria in patients with a more severe H pylori-induced inflammation.

Key Words: Bacterial overgrowth; Gastritis; Hypochlorhydria; N-nitroso compounds.
The introduction of pharmacological acid suppression, initially with histamine type 2 receptor antagonists (11) and more recently with proton pump inhibitors (PPIs) (12), induces bacterial colonization (of non- Helicobacter species), especially in patients taking a PPI. Helicobacter-infected patients taking a PPI show a greater degree of colonization than do patients who are H pylori-negative. This is discussed in detail below.

CONSEQUENCES OF GASTRIC COLONIZATION

Enhanced nitrite production
Nitrites are required for the production of NOCs and can originate from three potential sources. They can be found in many foods such as cured meats, baked foods and cereals, while buccal and gastric bacteria can also convert dietary and/or salivary nitrate to nitrite. Twenty-five per cent of absorbed nitrate is secreted in the saliva and 40% of this is reduced to nitrite in the mouth. This appears to be due to reducing bacteria found in deep clefts at the back of the tongue. Swallowed nitrites can also be reduced to nitrites in the gastric lumen by colonizing bacteria. As the pH rises, the role of gastric bacteria as nitrite producers becomes more important, contributing 90% of nitrite load in a hypochlorhydria patient (15), and nitrite levels in gastric juice are also increased in these patients (16). Studies measuring gastric nitrite indirectly suggested a link between high concentrations of nitrite in gastric juice with an increased risk of gastric metaplasia, dysplasia and carcinoma, although this has not actually been confirmed by direct measurement (17). However, the persistence of nitrites in the stomach is dependent on the intragastric pH and the presence of ascorbic acid. At an acid pH and with ascorbic acid present, nitrites are rapidly reduced to nitric oxide, which can be detected in gas from the stomachs of individuals with normal acid secretion (18). Ascorbic acid is actively secreted by healthy gastric mucosa; however, its secretion is reduced in hypochlorhydric gastric juice. Hence, nitrites will persist because both of the factors needed for their conversion to nitric oxide (ascorbic acid and gastric acid) are decreased.

Production of NOCs
NOCs are composed of nitrosamides (R\textsubscript{2}NNO\textsubscript{2}COR\textsubscript{3}) and nitrosamines (R\textsubscript{2}NNOR\textsubscript{3}). They are recognized carcinogens in animals and can induce gastric cancer in rodents. They can be formed in the gastric lumen from the nitrosation of primary, secondary and tertiary amines, amino acids, peptides, amides, imides, bile acids, guanidines and urea.

CAUSES OF BACTERIAL OVERGROWTH

Reduction in gastric acid from any cause may result in bacterial overgrowth in the stomach and the small intestine. Autoimmune gastritis resulting from the production of parietal cell antibodies in pernicious anemia is the classical natural cause. Distal gastrectomy (removing the gastrin-producing G cells of the antrum) can also result in bacterial overgrowth. The introduction of pharmacological acid suppression, initially with H\textsubscript{2} receptor antagonists (11) and more recently with proton pump inhibitors (PPIs) (12), induces bacterial colonization of the stomach (Table 1). However, chronic infection with H pylori resulting in gastric atrophy and loss of parietal cell mass is the most common cause of hypochlorhydria and/or achlorhydria worldwide.

There appears to be a difference between the organisms found in the stomachs of patients with reduced acid due to autoimmune gastritis compared with those taking acid suppressing medication. In the former, coliforms predominate, while in the latter, Gram-positive organisms are found. The reasons for this are not clear but could relate to the shorter history of hypochlorhydria in acid suppression leading to colonization by organisms swallowed from the oropharynx (13,14).
Correa's hypothesis of gastric carcinogenesis was based on epidemiological studies identifying achlorhydria and/or hypochlorhydria (19,20), diets high in nitrate or nitrite and low in vitamin C (21-26), and H pylori infection (27,28) as risk factors for cancer of the mid and distal stomach.

**H pylori colonization and bacterial overgrowth**

The role of H pylori infection in bacterial overgrowth is complex. Acid suppression allows H pylori gastritis to spread from the antrum to the corpus. Local and distal omeprazole treatment in 29 healthy volunteers. They simultaneously studied the effect of H pylori status on pH and bacterial overgrowth during omeprazole treatment in 29 healthy volunteers. They concluded that acid suppression is more marked, bacterial overgrowth is greater, postmeal nitrite levels are higher and ascorbic acid levels are lower in H pylori-positive compared with negative patients. They found predominantly oropharyngeal organisms, some of which were capable of reducing nitrite to nitrate and of synthesizing NOCs.

H pylori infection can result in atrophic gastritis with an increased risk of gastric cancer. Whether this is due to a direct effect of the organism, a result of NOCs from bacterial overgrowth or a combination of the two is not yet known. H pylori infection has, however, been shown to enhance the carcinogenicity of nitrosamines in rodent models (30). Given the combination of bacterial overgrowth and gastric inflammation present in the stomach of H pylori-positive patients taking PPIs, there is some concern about the long term risks of gastric cancer, which are discussed below.

There does not appear to be a link between NOCs and premalignant changes in the gastric mucosa. Intestinal metaplasia is a precursor for gastric cancer and is known to be associated with H pylori infection, low ascorbic acid levels and bile reflux. However, intestinal metaplasia is not associated with elevated gastric nitrite or total NOC (17) and, at present, it appears that NOCs are pure carcinogens and do not contribute to 'precancerous' mucosal changes.

**Acetaldehyde production and bacterial overgrowth**

Acetaldehyde (31) is a known carcinogen (32). Bacterial overgrowth in the hypochlorhydric stomach enhances the production of acetaldehyde from ethanol after ingestion. Acetaldehyde levels are also higher in alcohol dehydrogenase deficient individuals (common in the Far East). Alcohol does not necessarily need to be ingested because bacterial and yeast overgrowth can result in ethanol production.

Treatment with a PPI increases acetaldehyde production from ethanol in the gastric juice, probably as a result of bacterial overgrowth. Several organisms are associated with acetaldehyde production, including *Neisseria*, *Stomatococcus* and *Streptococcus* species. Therefore, acetaldehyde could be considered together with NOCs as potential gastric carcinogens.

**Effects of bacterial overgrowth on the gastric mucosa**

The reduction of nitrates to nitrites and the subsequent production of NOCs has been the principal focus of the effect of bacterial overgrowth in the stomach. Could bacterial overgrowth affect the gastric mucosa by any other mechanisms?
which showed, in mice, that bacterial overgrowth alone can result in gastric inflammation.

Sanduleanu and colleagues (41,42) have addressed this issue in two papers. They have shown that non-\textit{H pylori} flora (both luminal and mucosally associated) was significantly increased in those patients on acid suppression therapy who were infected with Helicobacter species than those who were not. In their second paper, they showed that the simultaneous presence of \textit{H pylori} and non-\textit{H pylori} bacteria was associated with a 20-fold increased risk of developing atrophic gastritis, suggesting a synergistic effect between the two infections. The weakness of their hypothesis, however, is that the greater the atrophy, the lower will be the acid secretion and, consequently, the greater the bacterial overgrowth. In other words, the increased bacterial overgrowth may reflect the higher degree of atrophy rather than vice versa. Nevertheless, the hypothesis is interesting and more research is needed in this area.

Bacterial overgrowth and bile acid metabolism

Bile reflux into the stomach is associated with an increased incidence of intestinal metaplasia (43). Some species of bacteria colonizing the stomach and small intestine during bacterial overgrowth are capable of deconjugating bile acids. Much of the attention has been focused on the role that bile plays in gastroesophageal reflux disease. The concentration of bile acids reaching the esophagus and their toxic effects are known to vary with pH depending on the degree of ionization (44). Unconjugated bile acids tend to precipitate in solutions with a pH lower than 4. Esophageal perfusion studies in animal models have shown that unconjugated bile acids can cause mucosal damage in alkaline solutions (45,46); however, no equivalent data exist for the effect of unconjugated bile acids on the gastric mucosa. Bile acids can also act as a substrate for nitrosation to produce NOCs and there is evidence of genotoxicity from these products (47).

CONCLUSION

Non-\textit{H pylori} bacterial colonization of the stomach occurs when the pH of the gastric juice rises. The number of bacteria present increases as the pH increases, and the resulting organisms can be of oropharyngeal or fecal origin. Decreased gastric acid secretion for any reason can lead to bacterial overgrowth; both H2 receptor antagonists and PPIs are known to cause it. Many organisms metabolize nitrite to nitrite and others are capable of inducing nitrosation to NOCs. They may also increase acetaldehyde production and deconjugate bile salts. It is unclear whether these metabolic activities or others as yet undefined may increase the gastric inflammatory response in the human hypochlorhydric stomach. There is good evidence that gastric bacterial overgrowth per se causes inflammation in the stomachs of mice, and some data in humans show that the inflammatory response is greater when overgrowth is prominent, but this finding may merely reflect the greater degree of hypochlorhydria in those patients with a more severe \textit{H pylori}-induced inflammation.

REFERENCES

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Bacterial overgrowth as a risk factor for gastritis


