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Gastric acid hypersecretory states: recent insights and advances

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Abstract

Gastric acid hypersecretory states are a group of disorders characterized by basal hypersecretion of gastric acid and historically include a number of disorders associated with hypergastrinemia, hyperhistaminemia and of unknown etiology. Although gastric acid secretion is infrequently measured, it is important to recognize the role of gastric hypersecretion in the symptomatology of these disorders because they share a number of features of symptom pathogenesis and in treatment. In this article recent important articles reporting insights into their diagnosis, pathogenesis and treatment are reviewed. Particular attention is paid to Zollinger-Ellison syndrome, because it has the most extreme acid hypersecretion of this group of disorders and because of the large number of recent articles dealing with various aspects of the diagnosis, molecular pathogenesis or treatment of the gastrinoma itself or the acid hypersecretion. Two new hypersecretory disorders including rebound acid hypersecretion after the use of PPIs and acid hypersecretion with cysteamine treatment in children with cytosis are also reviewed.

I. Introduction

Gastric acid secretion is largely control by cholinergic, histaminergic and peptidinergetic (especially gastrin) pathways[1•]. Disorders in a number of these pathways can lead to gastric acid hypersecretion (Table 1) including ones, which primarily mediate the hypersecretion by causing hypergastrinemia, causing hyperhistaminemia or by an unknown etiology. While these disorders may have different etiologies, they frequently share similar clinical features [i.e., peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD)] due to the effects of the acid hypersecretion on the esophagus, stomach and the duodenum. In some cases where the hypersecretion is severe, the PUD/GERD may be refractory and severe enough to lead to complications such as PUD penetration, perforation, and bleeding or esophageal strictures. The most severe disease is seen in patients with Zollinger-Ellison syndrome (ZES), where gastric acid hypersecretion is frequently >5 times the upper limit of normal [2•]. In addition to PUD/GERD the acid hypersecretion can result in diarrhea and malabsorption of nutrients, particularly vitamin B₁₂ and iron[3,4].

Currently the gastric acid hypersecretion mediated by these different disorders can all be treated by gastric antsecretory agents. Of these the most effective and generally used are proton pump

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inhibitors (PPIs) because of their long duration of action allowing once a day dosing. Histamine H₂ receptor antagonists are also effective but because of their lower potency and shorter durations of action, more frequent dosing is required and in some cases such as ZES, higher doses are needed in some patients than used in routine peptic ulcer disease[5].

At present gastric acid secretory rates are only measured in a few centers and therefore these disorders are frequently not suspected or diagnosed by measuring the gastric secretion. Nevertheless, it is important to recognize these disorders, because a number have specific other aspects of their treatment, rather than just chronic treatment with gastric antisecretory agents, that are needed or if undertaken may lead to cure of the disorder (i.e., *H. pylori*). Of these disorders the most severe gastric acid hypersecretion is seen in patients with ZES [2•], therefore it is essential this disorder be diagnosed, the acid hypersecretion appropriately treated both short-term and long-term, and that treatment also be directed against the gastrinoma, itself [6•].

In this paper, advances in the diagnosis and treatment of the disorders listed in Table 1 will be briefly reviewed. This review will concentrate on recent studies, primarily within the last 3–4 years, and will not attempt to cover all areas if there is not a recent specific study. There are a number of recent reviews dealing with these general aspects including reviews on ZES [7], mastocytosis[8] and *H. pylori* and acid secretion[1]. There have been no recent articles on acid secretion and renal failure, antral G short bowel syndrome, basophilic granulocytic leukemia, head injuries, stress related acid hypersecretion, or hypertrophy hypersecretory gastropathy, and a reader interested in these disorders is referred to older literature dealing with these areas [9].

Of these gastric acid hypersecretory disorders (Table 1), the disorder which has been the most dealt with in studies over the last few years, is various aspects of ZES. The areas covered by these studies will be dealt with first.

II. Advances in aspects of Zollinger-Ellison syndrome (ZES)

II.A. General

ZES is a clinical syndrome characterized primarily by refractory peptic ulcer disease[4] which is due to ectopic release of gastrin by a neuroendocrine tumor (gastrinoma)[10] resulting in gastric acid hypersecretion[2•]. All patients with gastrinomas have two major treatment problems: treatment must be directed at controlling the acid hypersecretion and because 60–90% of gastrinomas are malignant, treatment must be directed against the gastrinoma itself [5]. In addition 20–25% of gastrinomas occur in patients with Multiple Endocrine Neoplasia type 1 (MEN1) which is an autosomal dominant disorder associated with hyperplasia/tumors of the parathyroid, pituitary, adrenal, and a number of other organs which besides requiring specific treatments, they can effect the approach to the ZES as well as the need for genetic counseling [11,12•]. MEN1/ZES will be dealt with in more detail below in Section II.D.

II.B. Clinical, Diagnosis and Differential Diagnosis of ZES

Patients with ZES continue to present primarily with pain (83%), however in contrast to older reports, an increasing proportion have diarrhea (71%)[4]. In contrast to older studies, most patients at present do not have ulcers in unusual locations with the majority having routine appearing duodenal ulcers[4]. The diagnosis should be suspected in any patient with PUD/GERD who is *H. pylori* negative, refractory to treatment, has a virulent ulcer/GERD course, has ulcers in unusual locations or has recurrent ulcers; with PUD/GERD with a family/personal history of endocrinopathies such as hyperparathyroidism which would suggest MEN1/ZES or in a patient with PUD/GERD with hypergastrinemia or prominent gastric folds on endoscopy

which occur in up to 92% of all ZES patients[4,11,13]. There continues to be a long delay in diagnosis with a mean of 5.8 years in the NIH series of 261 patients[4].

Recent studies provide evidence that the delay in diagnosis of ZES is not decreasing, but in fact, will likely increase with the widespread use of PPIs to treat idiopathic GERD/PUD[4, 14]. This is occurring with PPIs, because of their long duration of action and potency, they can themselves cause hypergastrinemia [14,15], as well as mask the diagnosis of ZES[10,14,16•, 17,18]. They do this by controlling symptoms in most patients with ZES with conventional doses used to treat idiopathic PUD/GERD[5,19], which is in contrast to histamine H₂-receptor antagonists, which frequently do not control symptoms of ZES with conventional doses, leading the physician to suspect ZES[3,14]. In 60% of ZES patients the fasting gastrin levels are less than 10-fold elevated[10] and these levels can overlap with those caused by PPIs which can increase fasting gastrin levels in 80–100% of non-ZES patients and in some series, they increase fasting gastrin levels >5-fold in up to 20% of the nonZES patients[13–15,17,18,20•, 21].

As reviewed in the previous paragraph, the fasting serum gastrin levels of patients without ZES, while taking PPIs, can overlap with those commonly seen in ZES patients, and therefore ZES can not be reliably diagnosed in any patient from a given fasting serum gastrin value, while being treated with PPIs[10,13,15,20•]. It is therefore recommended that the fasting gastrin level as well as a secretin provocative test (see next paragraph) be performed after stopping PPIs[10,16•,17]. Because PPIs have such a long duration of action it is recommended that they be stopped for one week if possible after insuring no active peptic disease is present [10,16•,17]. During this time off the PPI suspected patients should be treated with high doses of histamine H₂-receptor antagonists, which can be stopped 48 hours prior to testing. It should also be realized that there are a proportion of patients, who can usually be suspected by history, who have difficulty when PPIs are stopped for only a short period of time. This difficulty can occur even when the patient is covered by histamine H₂-receptor antagonists, and these patients should only have their PPIs stopped in diagnostic units that are familiar with this disease diagnosis and management [10].

Fasting hypergastrinemia occurs in 97–99% of ZES patients, and because measurement of serum gastrin is widely available and simple, it is the initial study usually performed in patients in which ZES is suspected[10,17]. It is important to realize that increasingly various commercial gastrin-assay kits are being used by various laboratories to measure gastrin and in some cases their results may not agree with the gastrin-radioimmunoassay results which have been almost universally used until the present. No given fasting gastrin level, no matter how high alone, is diagnostic of ZES, because similar high levels may occur with diseases that cause physiological hypergastrinemia due to achlorhydria/ hyochlorhydria [atrophic gastritis, pernicious anemia] [10]. Therefore, it is essential to measure the gastric pH at the time of the fasting gastrin level determination to insure the presence of acid[2•,13,16•,17]. A recent study involving 235 ZES patients from the NIH and a review of 984 in the literature concluded that a gastric pH level <2 was present in >99% of ZES patients[2•]. In patients with a fasting gastrin level >10-fold elevated (40%) and a gastric pH <2, the diagnosis of ZES can be made after exclude the possibility of retained gastric antrum by history[2•,10]. In patients with fasting gastrin levels <10-fold elevated and gastric pH <2, an assessment of basal acid output and a secretin provocative test are recommended[2•,10,16•]. This is required because the other diseases listed in Table 1 that are associated with hypergastrinemia can cause these findings [13]. A basal acid output (BAO) of >15 mEq/hr in patients without previous gastric surgery and a positive secretin test establishes the diagnosis in this group of patients[10,16•]. A BAO of >15 mEq/hr will be found in 80–90% of such ZES patients[2•]. Acid secretion is now only measured in a few centers and historically measured using a nasogastric tube. Recently an

endoscopic method has been described[22] which facilitates the measurement and may result in more widespread availability of this methodology.

Synthetic secretin has now become available in the US replacing GIH secretin and can be used for the secretin test. A recent analysis of 293 NIH ZES patients and 537 patients from the literature has established a criterion of ≥ 120 pg/mL as the one with the highest sensitivity (94%) and a specificity of 100%, and should replace the old criteria of ≥ 200 pg/mL[16•]. Gastrinomas are known to possess secretin receptors[3,23] and a recent study demonstrates that all gastrinomas from 54 patients possessed secretin receptor mRNA and the amount present in the gastrinoma correlated with the magnitude of the secretin –stimulated gastrin increase seen in the patients during the secretin test[23]. It is important that the secretin test should be performed while the patient is not taking PPIs, because recently a false positive secretin test has been reported in such a patient for the first time[24•]. Secretin is difficult to obtain in some countries and recently a glucagon stimulation test for ZES has been described and proposed as an alternative when secretin is not available[25].

Patients with MEN1/ZES can present special problems in diagnosis and this will be discussed below in Section II.D.

II.C. Pathology, tumor biology and molecular biology of gastrinomas

In early studies >85% of gastrinomas were reported in the pancreas, however, in recent studies, both in sporadic ZES (no-MEN1) and in MEN1/ZES patients, 70–90% of gastrinomas are found in the duodenum[3,12•]. Rarely gastrinomas are reported in the ovary, gastric antrum, liver, biliary epithelium, hilum of spleen, mesentery, and lymph nodes[3,26,27]. The existence of primary lymph node gastrinomas remains controversial, although long-term cures after resection of gastrinomas only in lymph nodes are reported[26]. Recently two extra-abdominal sites are reported to also give rise to gastrinomas: the ventricle of the heart and non-small lung cancers[6••].

Most gastrinomas (60–90%) are reported as malignant with metastases usually to adjacent lymph nodes, later to the liver and very late in the course of the disease to bone and distant sites[3]. Lymph node metastases occur in 40–75% of duodenal gastrinomas, 50% for pancreatic tumors and at presentation approximately one-third of patients have a primary only, 1/3 a primary with lymph node metastases only and 1/3 have liver metastases[28,29]. Approximately 25% of sporadic and 15% of MEN1 tumors show aggressive growth with a 10-yr survival of 30%, whereas the others show indolent growth with a 10-yr survival of 96%[28,30,31]. In almost all studies the presence of liver metastases or the their development are the most important prognostic factors, whereas the presence of lymph node metastases has a minimal prognostic value[28,30]. In various studies other prognostic factors include the extent and rate of growth of liver metastases, presence of ectopic Cushing's syndrome, presence of bone metastases, various histological features, high tumor marker levels, various flow-cytometric or molecular features and high proliferative indices[6••,30].

The cell of origin of gastrinomas remains unclear, however, recent studies of pancreatic endocrine tumors (PETs)/gastrinomas in patients with MEN1/ZES have provided some insights. One study of MEN1 patients concluded the PETs arise from acinar/ductal tissues, not from islets[32], whereas another study concluded they arise from islets[33]. Duodenal gastrinomas in MEN1/ZES patients are proposed to arise from G cell-originating proliferative lesions in a similar manner to the described sequence for development of gastric ECLomas in hypergastrinemic states[34]. Similar lesions were not found in patients with sporadic duodenal gastrinomas[34].

In general compared to common adenocarcinomas, there is limited knowledge of their molecular pathogenesis of any PETs, including gastrinomas[35•]. Alterations in common oncogenes or tumor suppressor genes are uncommon in these tumors. Some insights have come from studies of inherited disorders that develop PETs including MEN1, von Hippel Lindau disease (VHL), tuberous sclerosis and von Recklinghausen's disease (neurofibromatosis) [12•]. These will be discussed in more detail in a later section (Section II.D). MEN1 is due to mutations in the *MEN1* gene on chromosome 11q13, which encodes for a 610 amino acid protein, menin, a nuclear protein, which binds to numerous transcription factors[12•]. Sporadic PETs show a loss of heterozygosity at 11q13 in 20–90% and 27–39% have an *MEN1* gene mutation[12•]. Recent studies also suggest in PETs, alterations in the DPC/SMAD4 gene; p16/MTS1 gene; amplification of HER2/neu proto-oncogene; increased IGF-1R expression; loss of tumor suppressor genes on chromosome 3p and X; and genome-wide-alleleotyping and comparative-genomic-hybridization show chromosomal gains (especially 7q,17p,17q, 20q) and losses (especially 1p, 3, 3p, 6p, 22q) are frequently present in gastrointestinal neuroendocrine tumors (NETs)(PETs and carcinoids)[35•]. However, the frequency of chromosomal losses/gain in different sites varies between PETs and carcinoids, providing evidence they have a different pathogenesis[6•]. Gene expression profiling using microarrays [6•,35•] have identified in PETs numerous additional altered genes, however there is not clear concordance from all studies and none have been established as clearly important for pathogenesis[6•].

II.D. Inherited disorders associated with ZES (MEN1, von Recklinghausen's disease [neurofibromatosis 1(NF-1)], tuberous sclerosis)

PETs occur in 80–100% of patients with the autosomal dominant disorder, MEN1, but in many patients they are nonfunctional, asymptomatic, and microscopic[12•]. Functional PETs occur in 20–80% in various series with gastrinomas occurring in a mean of 54%, insulinomas in 18% and other PETs<3%[11,12•]. MEN1 patients, who have a defect in the *MEN1* gene on 11q13, characteristically develop tumors or hyperplasia of multiple endocrine and non-endocrine tissues[12•]. This results in parathyroid hyperplasia with hyperparathyroidism (95–100%); anterior pituitary tumors (54–65%); adrenal adenomas (27–60%); carcinoids [gastric (7–35%),lung (0–6%),thymic (0–8%)]; thyroid adenomas (0–10%), skin lesions [angiofibromas (>88%), collagenomas (72%), lipomas (34%)]; CNS tumors (0–8%) and smooth muscle tumors (1–7%)[12•,36].

MEN1/ZES patients need to be recognized because they present a number of distinct problems in diagnosis and management[11,12•]. The other endocrinopathies including functioning pituitary adenomas and hyperparathyroidism (HPT) require specific treatment and in the case of HPT its presence may affect the activity of the gastrinoma[11,12•]. The correction of the hyperparathyroidism in an MEN1/ZES patient by an effective 3.5-4-gland parathyroidectomy may result in a decrease in fasting gastrin levels to normal, decrease in acid secretory rate, and a change in the secretin test from positive to negative all of which can mask the ZES[37•]. The gastrinomas are found in the duodenum in 75–100% of patients with MEN1/ZES, are multiple and in >50% associated with lymph node metastases, but rarely liver metastases[12•]. Because of this, they are rarely curable by simple enucleation/resection and their management is controversial[12•,38]. Recent prospective studies[36,39] show that patients with MEN1/ZES need to be carefully assessed for gastric carcinoids and advanced esophageal disease, which is much more frequent than in sporadic ZES. All patients with MEN1/ZES were found to have gastric ECL cell hyperplasia with advanced ECL cell changes occurring in 53% and carcinoids in 23%, which is a rate at least 70-fold greater than occurs in sporadic ZES[36]. In MEN1/ZES patients[39] esophageal stricture was 3-fold higher; the premalignant lesion, Barrett's esophagus 5-fold higher; dysplasia 8-fold higher than in patients with sporadic ZES, and one patient died of esophageal cancer. Analysis of possible contributing variables suggested failure

to recognize and adequately treat the gastric acid hypersecretion likely contributed to these increased incidences[39].

PETs occur in 0–10% of patients with NF-1 which are primarily duodenal somatostatinomas, uncommonly in patients with tuberous sclerosis and in each disease; patients with ZES have been rarely reported[12•].

II.E. Tumor localization

Determination of tumor extent and location are essential to all aspects of the management of patients with ZES, as with other PETs[6••]. Somatostatin receptor scintigraphy (SRS) with SPECT imaging is the most sensitive methodology for whole body imaging that is generally available for detecting both the primary tumor and metastases (liver, bone)[40]. A conventional imaging study (CT,MRI) is usually also performed with contrast to allow better localization to a given region[40]. For small gastrinomas (<1cm) such as those in the duodenum, conventional imaging studies [ultrasound,CT,MRI] detect <20% and SRS <50% [6••]. Overall SRS detects 50–70% of primaries, >90% of patients with liver metastases and is the most sensitive modality for detecting distant metastases (bone, etc)[6••]. It is important to realize that SRS can cause false positive responses (up to 12%) which can include: for technical reasons (gallbladder uptake,etc), due to diseases of the thyroid, breast, granuloma-producing, as well as inflammatory processes[41,42], and recently described is the presence of pancreatic polypeptide hyperplasia[43], Crohn's disease and pulmonary fibrosis. Prospective studies show the use of SRS will change the management in 12–53% of patients with GI neuroendocrine tumors[41]. Endoscopic ultrasound (EUS) remains valuable for imaging most pancreatic PETs including gastrinomas, but visualizes <50% of duodenal gastrinomas[38,44]. Positron-emission-tomographic scanning is receiving increased attention for detection of PETs such as gastrinomas[45]. Recent studies show ¹¹C-5-hydroxytryptophan or ⁶⁸Ga-labeled-somatostatin analogues have greater sensitivity than SRS or conventional imaging studies and therefore will likely become increasingly important in the future for PET localization [45,46•].

II.F. Treatment of gastric acid hypersecretion in ZES

In ZES gastric acid hypersecretion is frequently >5 times normal[2••] and must be controlled acutely and long-term or peptic-disease complications will eventually develop [PUD penetration, bleeding, perforation or esophageal stricture][1,3]. Medical treatment controls acid hypersecretion in almost every patient and total gastrectomy is now rarely needed except under unusual circumstances[47]. The original PPIs (omeprazole,lansoprazole) [5,18] were very successful in controlling acid secretion in ZES, and recent studies[5] show the more recent PPIs, rabeprazole[5,48], pantoprazole[5,49], esomeprazole[5,50] are also successful, both acutely and long-term.

Long-term PPI use has proven remarkably safe without any serious or doserelated side-effects and except for some patients who develop vitamin B₁₂ deficiency likely secondary to achlorhydria-induced malabsorption[18,51,52]. In particular no evidence of an increased incidence of gastric carcinoids due to the PPI usage in ZES has been seen or of other cancers which has been seen in experimental and/or animal studies[18]. An increased incidence of bone fractures and osteoporosis is reported in some studies[53] of patients with idiopathic PUD taking PPIs, but is not reported in ZES patients. Histamine H₂-receptor antagonists are also effective, although high doses and frequent dosing is required by many patients[3].

Some patients require parenteral antisecretory drug treatment and both histamine H₂ receptor antagonists, intravenous(IV) omeprazole or pantoprazole have been shown to be effective in ZES[3,5]. At present intravenous pantoprazole, lansoprazole, or esomeprazole are available

[5,6••] and are the drugs of choice for parenteral treatment of acid secretion in ZES. This has occurred because intravenous omeprazole was never approved for IV use and with histamine H₂-receptor antagonists, constant IV administration is required, whereas studies with the IV PPI, pantoprazole, show intermittent dosing can be used[5].

II.F. Surgical treatment of the gastrinoma

All agree that the ideal treatment of ZES is successful resection of the gastrinoma[38,54,55]. The importance of possible surgical resection has become even more important since a recent study demonstrated, for the first time that surgery can increase survival in patients with gastrinomas[56]. Cure remains possible in approximately one-half of the patients because at presentation 20–30% have nonresectable liver metastases, 20–25% have MEN1/ZES which is not curable without aggressive surgery (Whipple resection), and others have multiple lymph node metastases, which may not be found, at surgery[56]. A high cure rate is only possible if routine duodenotomy is performed at the time of surgery, because without it, small duodenal tumors, which are increasingly found, will be missed[29]. Furthermore, routine removal of lymph nodes in the pancreatic head area is essential, because a proportion of gastrinomas are found only in lymph nodes, whose resection, can result in long-term cure[26,38]. At present 50–60% of ZES patients without MEN1 will be cured immediately postoperative and 25–30% at 5-years[26,29,38]. The role of surgery in patients with MEN1/ZES remains controversial, because they are rarely cured without aggressive resections, because the gastrinomas are invariably multiple, frequently small (<0.5cm) and >50% are associated with lymph node metastases[12•,29]. Whipple resections which can be curative, are not recommended routinely, because of their morbidity and the excellent long-term survival of patients treated more conservatively[12•]. A number of studies show in MEN1/ZES patients, PETs <2 cm are not associated with increased mortality, so it has been recommended that only MEN1/ZES patients with tumor >2 cm on imaging have routine surgical exploration[12•].

II.G. Treatment of advanced disease (metastatic gastrinoma)

With the ability to control the acid hypersecretion long-term medically, the natural history of the gastrinoma is becoming an increasing determinant of long-term survival[28,30]. Ten year-survival rates are 96–100% for patients without metastatic disease, 96–100% with lymph node metastases and 26–30% with liver metastases[28,30]. Natural history studies demonstrate in approximately 25% (15% in MEN1/ZES) of patients the gastrinomas pursue an aggressive growth pattern[28,30,31]. Important prognostic factors include the presence and extent of liver metastases; development of ectopic Cushing's syndrome, bone or liver metastases; presence of high tumor markers; female gender; large primary tumor; presence of pancreatic gastrinoma and various flow cytometric and molecular features[28,30,31]. Similarly, in patients with MEN1/ZES the growth of the PETs is becoming an increasing important determinant of long-term survival, as the hyperparathyroidism and hormone-excess states such as ZES, are better-controlled[12•].

Numerous agents are used in patients with malignant gastrinomas and other PETs including biotherapy [somatostatin analogues, α -interferon), peptide receptor radionuclide therapy (PRRT), liver-directed therapy (embolization with/without chemotherapy), surgical debulking, chemotherapy [(classical-streptozotocin±5-fluorouracil±doxorubicin) or with newer agents], liver transplantation and/or newer novel therapies including angiogenesis inhibitors, tyrosine kinase inhibitors or growth factor receptor inhibitors[57]. The results with many of the older treatments [classical chemotherapy, embolization, liver transplantation, debulking] have been reviewed and will not be dealt with in detail here, with only a few general points made, whereas results from some of the newer approaches will be briefly reviewed.

In malignant gastrinomas, similar to other malignant PETs, somatostatin-analogues (octreotide, lanreotide) either alone or combined with α -interferon are frequently used in patients with increasing tumor burdens, especially those without extensive disease and with slow-growing tumors[6•]. This approach is controversial and not proven to extend survival, however, because of relatively low toxicity it is commonly used[57].

No recent studies have specifically examined the use of new anti-tumor treatments in only ZES patients, however, a number of recent studies have included them in studies of patients with different types of advanced, malignant PETs[58•,60,61]. Recently the cytotoxic effects of PRRT were reported using ^{177}Lu labeled somatostatin analogues (which emit β -particles and γ -rays)[58•], which bind to somatostatin receptors that are frequently over-expressed by most PETs (receptor subtypes 2,5) and are internalized by the PET[6•,40]. A complete tumor response occurred in 2%, partial response in 32% and stabilization in 34%[58•]. Approximately 30% of the patients developed acute side-effects (nausea, vomiting, pain) which were usually mild, WHO grade 3 or 4 anemia, leucopenia, or thrombocytopenia occurred in <1% of the administrations and 2 patients(1.5%) had serious side-effects (renal failure, hepatorenal syndrome)[58•]. No control study has demonstrated increased survival with PRRT and this therapy is not approved for use in any country, however, these promising results are undergoing further evaluation in a number of centers[6•,58•]. Other new therapies showing potential promise, in most studies in small number of patients with advanced PETS, include studies with tyrosine kinase inhibitors (sunitinib, sorafenib), growth factor receptor inhibitors (bevacizumab) and mTOR inhibitors [everolimus(RAD 001), temsirolimus],[59•,60,61].

III. Advances in other, nonZES gastric acid hypersecretory states(Table 1)

III.A. General: other hypersecretory states

Over the last 5-years there have been few new studies in these non-ZES disorders. Below a few general comments from older studies will be made and any new study results incorporated. Two newer disorders which were not generally covered in older studies dealing with acid hypersecretion[9•] are rebound hypersecretion and gastric hypersecretion with cysteamine treatment of patients with cystinosis, which will be covered in the following sections.

III.B. Systemic mastocytosis and acid hypersecretion

Systemic mastocytosis (SM), which results in the abnormal accumulation of mast cells in various tissues, results in hyperhistaminemia[62]. Gastrointestinal symptoms develop in 51% (range-16–85%) of patients with SM and peptic ulcer disease in 23% (range 5–44%)[8]. The mean basal acid secretory rate in 27 patients in the literature was 18.2 mEq/hr (range-0–39) [8] and in one prospective study, 38% of SM patients had acid hypersecretion[8]. Effective treatment of the acid hypersecretion in these patients may not only relieve peptic symptoms, but also prevent PUD complications such as bleeding which can occur in these patients[8].

III.C. Idiopathic acid hypersecretion

Acid hypersecretion occurs in 25–33% of patients with routine PUD and it is now known that in many of these patients it was due to the presence of *H. pylori* infection[9•]. It is therefore important to exclude *H. pylori* infection as a cause of the acid hypersecretion, because if present, effective treatment may completely reverse the high secretory rate in some patients (see next section). Patients with acid hypersecretion without *H. pylori* infection or without other causes have been described both in the past[9•] and recently[63•,64]. Idiopathic acid hypersecretion has been well-controlled by histamine H_2 -receptor antagonists although high, frequent doses may be required[9•] as well as by various PPIs (omeprazole, lansoprazole, esomeprazole, rebeprazole, pantoprazole)[9•,48–50].

III.D. Acid hypersecretion with *H. pylori* infection

H. pylori infection can result in increased, decreased or no overall change in the level of gastric acid secretion[1]. In some patients the infection is antral-predominant with sparing of the oxyntic mucosa resulting in increased gastrin release and acid hypersecretion[9•]. This increased acid secretion can result in the occurrence of PUD and in some patients increased GERD symptoms[18]. Eradication of the *H. pylori* infection in this group of patients can result in correction of the hypergastrinemia, a decrease in the basal acid secretory rate, healing of the peptic ulcer and amelioration of the GERD symptoms[18]. Some studies have shown higher acid secretion in *H. pylori* positive patients with Barrett's esophagus and supported the proposal that the level of acid secretion could be an important factor in the development of Barrett's esophagus.

III.E. Rebound acid hypersecretion

Increased gastric acid secretion is well described after stopping the long-term use of histamine H₂-receptor antagonists[18,65], however its occurrence after the prolonged use of PPIs is controversial[18,66•]. Some studies provide evidence it occurs in 60–90% of patients after long-term PPI usage[18,65]. Evidence has been provided that the mechanism of the rebound hypersecretion post use of PPIs was, at least in part, mediated by the hypergastrinemia that occurred as result of the marked inhibition of the acid secretion by the PPI[18,65]. The PPI-induced hypergastrinemia stimulates an increase in parietal cell mass leading to an increased maximal acid output, an increased ECL cell mass and ECL activity[18,65]. In contrast to these studies, a recent systematic review[66•] of all reports of rebound hypersecretion after PPI use concluded that there is no strong evidence for a clinically relevant increased acid output after PPI therapy is stopped. The resolution of whether rebound hypersecretion occurs in humans after chronic PPI treatment is important because it has potentially important clinical implications. This is especially true for patients with mild-moderate GERD treated long term with PPIs, where an attempt to stop the PPI is often considered. In this situation rebound hypersecretion after attempting to stop the PPI, could result in a worsening of the occurrence or severity of GERD symptoms and therefore resulting in prolongation of the PPIs use[18].

III.F. Acid hypersecretion after cysteamine treatment in patients with cystinosis

Cystinosis is an autosomal recessive disorder which results in the accumulation of intra-lysosomal cystine[67•]. Daily cysteamine treatment can lower intracellular cystine levels and reduce the rate of progression of renal failure and damage to other organs otherwise caused by cystine accumulation[67•]. Cysteamine treatment may be associated with GI symptoms and chronic treatment in laboratory animals is known to be ulcerogenic[67•].

Children with cystinosis treated with cysteamine develop hypergastrinemia and increased gastric acid production within 60 minutes of receiving oral cysteamine[67•]. Treatment with PPIs (esomeprazole, omeprazole) results in reduced cysteamine-induced gastric acid hypersecretion and improvement in gastrointestinal symptoms[67•].

IV. Conclusions

Although currently gastric acid secretion is infrequently measured, it remains important to recognize diseases associated with gastric acid hypersecretion as they share a common pathogenesis of symptoms and treatment approaches. In this article recent important articles reporting insights into their diagnosis, pathogenesis and treatment are reviewed. Particular attention is paid to Zollinger-Ellison syndrome, because it has the most extreme acid hypersecretion of this group of disorders, has been the best studied and because of the numerous advances in different areas of its diagnosis and treatment. Particular attention is also paid to two

new acid hypersecretory disorders: rebound acid hypersecretion after the use of PPIs and acid hypersecretion with cysteamine treatment in children with cytosis.

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Table 1

Etiological classification of gastric acid hypersecretory states

A. Associated With Hypergastrinemia
1. Zollinger-Ellison syndrome
2. Antral G cell hyperplasia/hyperfunction
3. Helicobacter pylori infection
4. Gastric outlet obstruction
5. Short-bowel syndrome
6. Retained gastric antrum syndrome
7. Chronic renal failure (rare)
8. Cysteamine treatment in children with cystinosis
B. Associated With Hyperhistaminemia
1. Systemic mastocytosis
2. Basophilic granulocytic leukemia
C. Unknown Etiology
1. Idiopathic hypersecretion
2. Associated with non-gastrin secreting tumor (non-ZES tumor)
3. Rebound hypersecretion
4. Possible association with gastric hypersecretory states
a. Hypertrophic, hypersecretory gastropathy
b. Associated with stress
c. Associated with head lesions
d. Cystic fibrosis