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FIELD OF VISION

Diagnosis of Zollinger-Ellison syndrome: Increasingly difficult

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Abstract

In the present paper the increasing difficulty of diagnosis of Zollinger-Ellison syndrome (ZES) due to issues raised in two recent papers is discussed. These issues involve the difficulty and need to withdraw patients suspected of ZES from treatment with Proton Pump Inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole) and the unreliability of many gastrin radioimmunoassays. The clinical context of each of these important issues is reviewed and the conclusions in these articles commented from the perspective of clinical management.

Key words: Zollinger-Ellison syndrome; Gastrinoma; Hypergastrinemia; Secretin test; Serum gastrin; Gastrin; Neuroendocrine tumor

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INVITED COMMENTARY ON HOT ARTICLES

Two recent papers by Poitras *et al*[1] and Rehfeld *et al*[2] call attention to two areas that are making it more difficult to diagnosis Zollinger-Ellison syndrome (ZES). In this short review after listing the papers and their abstracts, the importance of these two issues will be briefly commented on.

Background: General

ZES is a clinical syndrome due to the ectopic secretion of gastrin by a neuroendocrine tumor (gastrinoma), located primarily in the duodenum (60%-80%) or pancreas (10%-40%), resulting in gastric acid hypersecretion, which if left untreated results in refractory peptic ulcer disease, severe gastroesophageal reflux disease, diarrhea and finally death, primarily due to the complications of the refractory peptic ulcer disease[3-6]. The diagnosis of ZES, like the diagnosis of other ectopic hormonal pancreatic endocrine syndromes, historically requires the demonstration of inappropriate release of the hor-

mone and evidence of hormonal hypersecretion[3,6-8]. In the case of ZES this requires the demonstration of inappropriate gastrin release by demonstrating fasting hypergastrinemia in the presence of gastric acid hypersecretion[3,6-10]. This is clinically most frequently accomplished by demonstrating the inappropriate presence of fasting hypergastrinemia when gastric fluid is acidic with a pH $\leqslant$ 2 is present or gastric hypersecretion is present [> 15 mEq/h basal acid output (no previous gastric acid reducing surgery), > 5 mEq/h (if gastric acid reducing surgery)][7,8,11-14]. The combination of fasting hypergastrinemia and elevated gastric acid secretion are required for ZES diagnosis because numerous unrelated conditions can cause one or the other of these alone[5,6,8,10,14]. The most frequent cause of fasting hypergastrinemia is physiological hypergastrinemia (also called appropriate hypergastrinemia) due to the presence of hypo/achlorhydric, which in normal individuals results in a reciprocal increase in gastrin release from the G cells of the gastric antrum causing hypergastrinemia[7,8,10,14,15]. This is most frequently due to chronic atrophic gastritis, commonly due to the presence of a *Helicobacter pylori* (*H. pylori*) infection that spares the antrum or due to pernicious anemia[7,8,10,14,15]. A second very frequent cause is the use of potent gastric acid anti-suppressant drugs such as proton-pump inhibitors (PPIs) (omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole), which is discussed in the next paragraph. Other less common causes of hypochlorhydric/achlorhydria include chronic renal failure and vagotomy, which can be distinguished by appropriate other laboratory/clinical investigations[5,8,10,13]. Similarly, the presence of gastric acid hypersecretion without hypergastrinemia can be seen in patients with idiopathic gastric acid hypersecretion and a few other uncommon conditions (mastocytosis, basophilic granulocytic leukemia)[8,16,17].

While the diagnosis of ZES sounds simple enough, in recent years it is becoming increasingly more difficult, due to a number of developments, and now, as pointed out in the above two papers, it is even further complicated. Let's first consider the issues that were complicating the diagnosis of ZES prior to these two papers. First, acid secretion is now rarely measured and therefore generally not available, so alternatives to the classical basal acid output assessment were proposed. These include, in addition to the presence of fasting hypergastrinemia, an endoscopic measurement of gastric acid output[18], the use of either pH paper or a pH meter to establish the presence of an acidic pH in gastric fluid, assessment for the presence of other features of ZES such as the presence of a tumor on imaging or pathologic studies and the development of gastric fluid pH criteria , that when coupled with the presence of hypergastrinemia, support the diagnosis of ZES[1,11,14]. Second, the widespread use of PPIs is markedly complicating the ability to diagnosis ZES, because their use interferes with both needed assessments to establish the diagnosis of ZES: the measurement of fasting gastrin levels and the assessment of acid secretion[5,10,12,14,19]. This occurs because PPIs have a very long duration of action, with their gastric acid suppressive action lasting up to one week[13,20,21] which not only contributes to their marked effectiveness, but also makes it difficult to withdraw patients from these drugs to assess gastric secretion[1,5,14]. Furthermore, their potent antisecretory activity can lead to fasting hypergastrinemia due to the PPIs and thus mislead one into suspecting ZES[14,19,22]. The result of the PPIs is that they both mask the diagnosis of ZES, leading to delays in diagnosis, because they effectively control all presenting clinical symptoms, but also they can lead to a false diagnosis[3,5,14,19,23]. False diagnoses occur because long-term use of PPIs can cause fasting hypergastrinemia in 80%-100% of patients without ZES[24-27] with fasting gastrin values > 4 fold increased in 20%-25% of patients[24-27] and in some cases the gastrin levels are > 10-fold elevated into ranges that are frequently thought to reflect ZES[25,26].

Commentary paper

In Poitras *et al*[1] two patients are reported in whom ZES was suspected (later proven) after presenting with severe symptoms of gastroesophageal disease, subsequently treated with PPIs with symptom improvement and when the PPIs were withdrawn, both patients developed severe complications of peptic disease (patient No. 1, esophageal stricture requiring repeated dilatations; patient No. 2, intestinal perforation). It was proposed that PPI therapy should always be maintained and diagnostic evaluations be performed while taking PPIs[1]. This is a novel recommendation and would have a marked effect on the diagnostic approach to patients suspected of having ZES. This recommended approach differs from the approach recommended in recent consensus guidelines and by most authorities in recent reviews, wherein, it is recommended that acid antisecretory drugs have to be stopped at some point to establish the diagnosis of ZES. Specifically, both the North American Neuroendocrine Tumor Network guidelines[9] and the European Neuroendocrine Tumor Network's guidelines[3,12], as well as a recent reviews of the diagnosis of ZES by a number of authorities[7,10,14,22,28], all recommend that PPIs need to be generally stopped to establish the diagnosis of ZES.

Is there any additional evidence to support this novel recommended diagnostic approach for ZES in paper 1[1]? Others have reported severe esophageal strictures in patients with ZES, since the time that antisecretory drugs were available, whose acid hypersecretion was not controlled[29-31] and in one large study[32], 8% (10/122) patients with ZES required repeated esophageal dilations, because of previous poor control of the acid hypersecretion. We don't find additional cases in the literature to patient No. 1 described in this report[1], however, we have seen one patient with ZES who developed a severe long, esophageal stricture requiring a stent, because antisecretory medications were withdrawn at an outside hos-

pital for diagnosis (unreported case). Similarly intestinal perforations have been reported in a number of patients with ZES since antisecretory drugs became available. Intestinal perforations were reported in 7% of patients with ZES in one large series (11/160 cases)[33] and in a number of other case reports[34,35], with the perforations occurring prior to the diagnosis in most cases. However, we have seen three cases of ZES patients who developed intestinal perforations when taken off of antisecretory drugs for diagnostic reasons[33,34] (unpublished 2 cases). One case occurred after a patient with suspected ZES reduced the PPI dose they were taking on their own because they developed constipation while taking the PPI and then presented with a duodenal perforation after 5 d of stopping the PPI in preparation for a secretin test[34]. Two other cases occurred prior to the use of PPIs early in our experience and we have seen no additional cases at National Institutes of Health (NIH) in the last 20 years in acid studies of more than 300 patients with ZES, the majority of who were taking PPIs prior to diagnosis. These latter results demonstrate that acid secretory studies can be safely carried out if proper precautions are taken, even if patients are taking PPIs, although it requires a center well versed in performing these studies, and a proven approach, one of which is discussed below, However, the query raised by Poitras *et al*[1] still remains, as to whether it is necessary to withdraw antisecretory medications in most patients with ZES to establish the diagnosis.

Unfortunately, the evidence suggests, as concluded in the accompanying editorial[14] to paper No. 1[1], that to clearly establish the diagnosis of ZES, some appropriate assessment of gastric acid acidity/secretion is required after withdraw of PPIs in almost every patient. What is the evidence? First, it is both fortunate and unfortunate that PPIs are so effective in patients with ZES as well as patients with idiopathic peptic disease. It is fortunate because PPIs are very effective at controlling gastric acid secretion in these patients[5,7,36,37]. However, it is unfortunate for diagnostic purposes, because their effectiveness results in that fact that with PPIs, the usual doses used in idiopathic peptic disease are often effective also in ZES and result in hypo/achlorhydria in both ZES patients and in patients without ZES. In contrast with Histamine H_2-receptor antagonists, frequently 10-fold greater doses than used in treating patients with idiopathic peptic disease are required in ZES patients, with more frequent dosing to control the hypersecretion, however these high doses in ZES and the usual doses in patients without ZES, rarely result in hypo/achlorhydria[5,7,36,37]. Therefore, in most patients taking PPIs where ZES is suspected, the gastric pH will not be < 2 (the range required for diagnosis of ZES)[7,11], and therefore physiological and pathological hypergastrinemia can not be distinguished on the drug. Second, there is no feature of the clinical course that unequivocally allows one to establish the presence of ZES, with most patients currently presenting with idiopathic peptic ulcer disease or gastroesophageal reflux disease which is indistinguishable from that seen in non-ZES patients[7,14,35,38]. Third, when ZES is suspected, a fasting gastrin level is almost invariably the first diagnostic study performed[7-10,12,14,39]. Unfortunately, there is no absolute level of fasting hypergastrinemia alone that can distinguish a patient with ZES from a patient without ZES[6,39]. This will be covered in more detail below in the discussion of Rehfeld *et al*[2], however a few additional points will be made here. In the most common cause of fasting hypergastrinemia, chronic atrophic gastritis, fasting gastrin levels > 70 fold elevated have been reported and levels > 1000 or > 2000 ng/L are not uncommon[40-43], which is a similar finding in patients with pernicious anemia[44]. These values overlap with 80%-100% of patients with ZES in various series[39]. Similarly, in patients taking PPIs without ZES, which is the also one of the most common causes of hypergastrinemia, the PPIs can lead to various degrees of hypergastrinemia in different patients. Although, as pointed out in a number of studies, PPIs frequently lead to < 3 fold increase in fasting gastrin and in some studies do not increase the value out of a normal range[22,45,46], this finding can not be relied on in an individual patient. This conclusion is firmly supported by various studies which report 80%-100% of the patients without ZES in their studies treated with PPIs develop hypergastrinemia, 20%-25% > 4 fold elevated, and values > 1000 pg/mL are not uncommon[24-27,47]. These levels of PPI induced increases in fasting gastrin overlap with that seen in more than 60% of patients with ZES[6,39,48,49]. Fourth, alone, no absolute level of any other tumor marker such as a serum chromogranin A (CgA) level, can establish the diagnosis of ZES. CgA levels are elevated in 90%-100% of patients with ZES, which can be contributed to by both the gastrinoma and the gastrin induced enterochromaffin-like (ECL) cell hyperplasia which is almost always present[50-55]. However, the main problem is that PPIs or high doses of other antisecretory drugs, can increase CgA levels in patients without ZES, within a few days of use, which is thought secondary to the PPI-induced hypergastrinemia causing gastric ECL proliferative effects[27,56,57]. The PPI induced increases in CgA can are usually < 4 fold, but can be up to 40-fold, which overlaps with values seen in > 90% of patients with ZES, as well as seen in numerous, non-ZES conditions[24,27,53,54,57-59]. Fifth, the recommended establishment of a diagnosis of ZES in a hypergastrinemic patient by other methods, as proposed in paper No. 1[1], such as by attempting to establish the presence of a neuroendocrine tumor (primarily by imaging studies) or by establishing the presence of a gastrinoma, is unlikely to be successful in many patients and may lead, in fact, to false diagnoses. It is likely to be unsuccessful in many patients because < 30% of patients with ZES at presentation at the current time, have liver metastases that possibly could be biopsied and the diagnosis of a gastrinoma established by immunohistochemistry[13,60,61]. Even this does not secure the di-

agnosis, because other pancreatic neuroendocrine tumors [non-ZES primitive neuroectodermal tumors (pNETs)] can stain occasionally positively for gastrin but not be associated with ZES or the portion of the neuroendocrine tumor biopsied may not show gastrin staining[62-69]. Furthermore, localization of a primary gastrinoma, even with the use of increasingly sensitive methods such as somatostatin receptor imaging or endoscopic ultrasound studies, misses most small duodenal tumors, which are present in 60%-80% of patients with ZES[70-75]. Furthermore, cross-sectional imaging studies (computed tomographic scanning, magnetic resonance imaging, trans-abdominal ultrasound) will be negative in > 60% of all patients with duodenal tumors and thus not be able to assist in suggesting the presence of a pNET in the majority of suspected cases, especially those patients being examined early in their course[71,72,76,77]. Lastly, sensitive methods such as somatostatin receptor scintigraphy can lead to false positive localization results and in one prospective study[78,79], 12% of all possible pancreatic endocrine tumor localizations were false positive. These include the presence of an accessory spleen, gallbladder retention, an abscess, various inflammatory processes, inadequate bowel cleansing, thyroid disease, various granulomatous lung diseases, and other neuroendocrine tumors/proliferations such as gastric ECL proliferation or other gastrointestinal-neuroendocrine tumors like gastric carcinoids tumors[78-81]. Therefore, one cannot conclude that localization on a somatostatin receptor scintigraphy study in a patient with hypergastrinemia necessarily equates to localization of a gastrinoma and establishment of the diagnosis of ZES. Fifth, besides the assessment of fasting gastrin levels and gastric fluid pH, various gastrin provocative tests (primarily after secretin, occasionally after glucagon)[14,48,49,82,83] are widely used in the diagnosis of ZES. The secretin test in particular has been well studied and in one recent detailed analysis of 537 patients with ZES in the literature as well as 293 NIH patients with ZES prospectively studied, the secretin test was shown to have a sensitivity of 94% with a specificity of 100% using a criterion of ⩾ 120 ng/L increase post secretin[49]. Couldn't the secretin provocative test be used while the patient is taking PPIs to circumvent the need to stop the PPI? Unfortunately, the answer is no, because a recent study[84] reports a false positive secretin test in a patient without ZES taking PPIs. Furthermore, another study demonstrated if patients are achlorhydric, false secretin positive tests can occur[85].

Commentary on paper

In the study by Rehfeld *et al*[2], Seven of 12 tested commercial kits inaccurately measure plasma concentrations of gastrin; these assays used antibodies with inappropriate specificity that were insufficiently validated. Misdiagnosis of gastrinoma based on lack of specificity of assays for gastrin results in ineffective or inappropriate therapy for patients with ZES.

Background: An accurate assessment of fasting serum gastrin levels (FSG) is central to the diagnosis of ZES and the diagnosis cannot be made without it. This is especially true, because this is the initial study that leads to the suspicion of ZES, in most cases[2,7,9,12,83]. An assessment of FSG is generally used as the initial study not only because of its convenience and widespread availability, but also because it is elevated in almost all patients with ZES, except for a few specific situations. In a review of 2229 cases of ZES from the literature[39], FSG levels were elevated in 97% of patients and in 309 patients with ZES seen at the NIH it was elevated in 99.3% of patients[39]. These results and others[6,86,87] demonstrate that normal FSG levels are uncommon overall in patients with ZES however, in a few small subgroups with active disease, normal values are not uncommon. This includes patients with active ZES who had had unsuccessful curative resection of a gastrinoma previously, who have ZES with multiple endocrine neoplasia type 1 (MEN1) post successful parathyroidectomy for hyperparathyroidism, in patients being treated with somatostatin analogues or occasionally in patients after various anti-tumor treatments (chemotherapy, chemo-embolization, *etc*.)[86-96]. Although many physicians think FSG levels are massively elevated in ZES and easy to distinguish from other disorders, unfortunately, as pointed out above, this is not the case. Chronic atrophic gastritis, other hypo/achlorhydric conditions, chronic renal failure and the use of PPIs can cause FSG levels that overlap with those seen in most patients with ZES. Furthermore, in 60%-65% of ZES patients when initially diagnosed, the FSG levels are < 10-fold elevated and these levels overlap with a number of other conditions, some of which are much more frequent than ZES, which can also be associated with gastric acid hypersecretion, such as seen in ZES[5,13,39,48,97]. This FSG level (i.e., > or < 10 × increased) is pointed out because the existing criteria used for the diagnosis of ZES in most guidelines and reviews is divided on the basis of the elevation of FSG[3,12,14,38,39]. If the FSG is > 10-fold elevated (usually > 1000 ng/L) and the gastric fluid pH < 2, a diagnosis of ZES is established after ruling out a possible retained antrum syndrome by history[12,14,38,39,98]. On the other had if the FSG is < 10-fold increased and the gastric fold pH < 2, other conditions need to be excluded including *H. pylori* infection, antral G cell syndromes, gastric outlet obstruction and renal failure[3,7,9,38,39]. In these cases a gastric analysis with determination of basal acid output, and a secretin provocative test is recommend, or if secretin is not available, a glucagon provocative test has been recommended[7,12,49,82,87]. These latter provocative tests involve the assessment of serum gastrin before and after a secretin or glucagon injection, so an accurate assessment of serum gastrin is essential to their correct interpretation.

Specific comments: Rehfeld *et al*[2] report that in many cases that the gastrin laboratory assays being used to assess FSG levels are not giving accurate results. Only 5 of the 12 commercial assays examined accurately assessed

FSG levels with the others giving FSG values either too high or too low and thus their results could lead to an over- or under-diagnosis of ZES, based on the FSG levels reported[2]. While gastrin provocative test results (secretin, glucagon) were not assessed, a similar result would be expected with these and thus the result would not be dependable in most cases. This report raises a number of problems for physicians trying to diagnose and treat patients with ZES. First, it demonstrates that FSG levels should not be compared from different laboratories using different assays unless some validation is performed. Second and more important, this report raises a real dilemma for the practicing clinician, because it raises the question of whether he can rely on FSG values reported to him by the laboratory he uses. There is no simple solution to this dilemma. The lists of laboratories assessed in this paper[2] can be consulted to see if the one used for the blood samples sent by for the clinician's patients(s) are on this list. Because the diagnosis of ZES has such significance for any patient and alternative approach as discussed in a section below is to refer the patient to center with known expertise, or to contact them and find out which laboratory in their area they recommend to assess FSG, and confirm the results using this laboratory.

Recommended approach to diagnosis of ZES (based on points raised in papers 1, 2)

First, it is essential to realize that patients with untreated gastric acid hypersecretion with ZES can develop complications rapidly and that this needs to be adequately treated before trying to establish a diagnosis, especially by stopping PPIs. There is no urgency in establishing the diagnosis. Therefore if the patient has active peptic ulcer disease or symptoms and the diagnosis of ZES is suspected, a FSG should be drawn and the acid hypersecretion adequately controlled [our initial starting dose is equivalent to omeprazole 60 *qd*[99,100], or if complicated disease (presence of MEN1, Billroth 2 surgery, or severe gastroesophageal reflux symptoms), we start with the equivalent of omeprazole 40 *bid*][37,101-103] and the patient should undergo an upper gastrointestinal endoscopy. We start with a higher PPI dose to make sure the acid hypersecretion is initially well controlled and then later it can be reduced in many patients[37,101]. During this endoscopy, gastric pH can be measured and also the size of gastric mucosal folds noted because 92% of ZES patients have prominent gastric folds[35]. Most patients can be satisfactorily treated by this PPI dose initially, however some require higher doses and therefore it is best to assess the control of acid hypersecretion on PPI[37,99,104], however, only a few specialty centers have this capability, and thus most use control of symptoms to monitor effectiveness of treatment. If the patient has symptoms of gastroesophageal peptic disease or active disease on endoscopy they should be treated for 8-12 wk until symptom free and then the upper gastrointestinal endoscopy repeated to make sure any peptic disease is resolved before attempting to establish the diagnosis by stopping PPIs. During this time the reliability of the FSG assay used needs to be explored both by reviewing the laboratories in paper No. 2[2] and contacting some group well versed in your area with the diagnosis of ZES that uses gastrin assays regularly. If the FSG is elevated it, of course this could be due to the PPI the patient was taking when the blood sample was drawn, which is the situation in most cases, so that the diagnosis remains unclear at this point, particularly if the gastric pH was > 2. At this point many authorities recommend that consideration be given to referring the patient to a group in your area well versed in the diagnosis of ZES[7,9,12,14]. If not possible, then after the repeat endoscopy shows healing of mucosal disease and the patient is asymptomatic, one can consider PPI withdrawal for diagnosis. Our approach is similar to outlined recently[14] and briefly, is to carefully consult with the patient about the need to keep in close contact, then to substitute an H_2 receptor antagonist (usually ranitidine 450-600 every 4 to 6 h) for the PPI for 3-5 d and then stop the ranitidine for 24 h allowing liberal use of antacids. Then on the day of the test we measure FSG × 2, and measure gastric pH and acid output. We usually perform a secretin test at the same time if our index of suspicion is high[49]. This circumvents the need to take the patient off of PPIs again at a later time if the secretin test is deemed necessary. If a gastric/esophageal pH probe is available the assessment of gastric pH and FSG at early times can be done with an attempt to document a pH < 2 with an elevated FSG.

One could ask at this point why go through all of this and why is it so important to establish the diagnosis of ZES correctly in most patients. The primary reason is that the diagnosis of ZES requires special treatment and the treatment must be continued life-long if the patient is not cured[7,9,105]. If the patient is not cured, life-long PPI treatment will be required, the doses may be different than that usually used in patients with idiopathic peptic disease, periodic assessment for the presence of MEN1 will be needed because 20%-30% of ZES patients have this and its diagnosis may not be initially evident and treatment directed at the gastrinoma, which are malignant in 60%-90% of cases, must be considered[13,35,38,106,107]. The latter include periodic assessment of tumor location/extent with imaging studies, consideration of surgical resection which is recommended in ZES patients in whom MEN1 is not present, life expectancy is good and no serious surgical contra-indications are present[7,71,108-110]. Therefore a diagnosis of ZES markedly effects clinical management and thus needs to be well established.

REFERENCES

1 **Poitras P**, Gingras MH, Rehfeld JF. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. *Clin Gastroenterol Hepatol* 2012; **10**:

199-202
2 **Rehfeld JF**, Gingras MH, Bardram L, Hilsted L, Goetze JP, Poitras P. The Zollinger-Ellison syndrome and mismeasurement of gastrin. *Gastroenterology* 2011; **140**: 1444-1453
3 **Jensen RT**, Niederle B, Mitry E, Ramage JK, Steinmuller T, Lewington V, Scarpa A, Sundin A, Perren A, Gross D, O'Connor JM, Pauwels S, Kloppel G. Gastrinoma (duodenal and pancreatic). *Neuroendocrinology* 2006; **84**: 173-182
4 **Ellison EC**, Johnson JA. The Zollinger-Ellison syndrome: a comprehensive review of historical, scientific, and clinical considerations. *Curr Probl Surg* 2009; **46**: 13-106
5 **Gibril F**, Jensen RT. Zollinger-Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion. *Curr Gastroenterol Rep* 2004; **6**: 454-463
6 **Mignon M**, Jais P, Cadiot G. Clinical features and advances in biological diagnostic criteria for Zollinger-Ellison syndrome. In: Mignon M, Jensen RT, editors. Endocrine Tumors of the Pancreas: Recent Advances in Research and Management. Series: Frontiers of Gastrointestinal Research. Basel, Switzerland: S. Karger, 1995: 223-239
7 **Metz DC**, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 2008; **135**: 1469-1492
8 **Osefo N**, Ito T, Jensen RT. Gastric acid hypersecretory states: recent insights and advances. *Curr Gastroenterol Rep* 2009; **11**: 433-441
9 **Kulke MH**, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, Marx SJ, Pasieka JL, Pommier RF, Yao JC, Jensen RT. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 2010; **39**: 735-752
10 **Murugesan SV**, Varro A, Pritchard DM. Review article: Strategies to determine whether hypergastrinaemia is due to Zollinger-Ellison syndrome rather than a more common benign cause. *Aliment Pharmacol Ther* 2009; **29**: 1055-1068
11 **Roy PK**, Venzon DJ, Feigenbaum KM, Koviack PD, Bashir S, Ojeaburu JV, Gibril F, Jensen RT. Gastric secretion in Zollinger-Ellison syndrome. Correlation with clinical expression, tumor extent and role in diagnosis--a prospective NIH study of 235 patients and a review of 984 cases in the literature. *Medicine* (Baltimore) 2001; **80**: 189-222
12 **Jensen RT**, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012; **95**: 98-119
13 **Jensen RT**. Zollinger-Ellison syndrome. In: Doherty GM, Skogseid B, editors. Surgical Endocrinology: Clinical Syndromes. Philadelphia: Lippincott Williams and Wilkins, 2001: 291-344
14 **Metz DC**. Diagnosis of the Zollinger–Ellison syndrome. *Clin Gastroenterol Hepatol* 2012; **10**: 126-130
15 **Schubert ML**, Peura DA. Control of gastric acid secretion in health and disease. *Gastroenterology* 2008; **134**: 1842-1860
16 **Cherner JA**, Jensen RT, Dubois A, O'Dorisio TM, Gardner JD, Metcalfe DD. Gastrointestinal dysfunction in systemic mastocytosis. A prospective study. *Gastroenterology* 1988; **95**: 657-667
17 **Jensen RT**. Gastrointestinal abnormalities and involvement in systemic mastocytosis. *Hematol Oncol Clin North Am* 2000; **14**: 579-623
18 **Oh DS**, Wang HS, Ohning GV, Pisegna JR. Validation of a new endoscopic technique to assess acid output in Zollinger-Ellison syndrome. *Clin Gastroenterol Hepatol* 2006; **4**: 1467-1473
19 **Corleto VD**, Annibale B, Gibril F, Angeletti S, Serrano J, Venzon DJ, Delle Fave G, Jensen RT. Does the widespread use of proton pump inhibitors mask, complicate and/or delay the diagnosis of Zollinger-Ellison syndrome? *Aliment Pharmacol Ther* 2001; **15**: 1555-1561
20 **McArthur KE**, Collen MJ, Maton PN, Cherner JA, Howard JM, Ciarleglio CA, Cornelius MJ, Jensen RT, Gardner JD. Omeprazole: effective, convenient therapy for Zollinger-Ellison syndrome. *Gastroenterology* 1985; **88**: 939-944
21 **Lind T**, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole--a gastric proton pump inhibitor--on pentagastrin stimulated acid secretion in man. *Gut* 1983; **24**: 270-276
22 **Banasch M**, Schmitz F. Diagnosis and treatment of gastrinoma in the era of proton pump inhibitors. *Wien Klin Wochenschr* 2007; **119**: 573-578
23 **Wong H**, Yau T, Chan P, Ng IO, Chan G, Hui P, Law WL, Lo CM, Hedley AJ, Epstein RJ. PPI-delayed diagnosis of gastrinoma: oncologic victim of pharmacologic success. *Pathol Oncol Res* 2010; **16**: 87-91
24 **Sanduleanu S**, De Bruïne A, Stridsberg M, Jonkers D, Biemond I, Hameeteman W, Lundqvist G, Stockbrügger RW. Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid-suppressive therapy. *Eur J Clin Invest* 2001; **31**: 802-811
25 **Lamberts R**, Creutzfeldt W, Stöckmann F, Jacubaschke U, Maas S, Brunner G. Long-term omeprazole treatment in man: effects on gastric endocrine cell populations. *Digestion* 1988; **39**: 126-135
26 **Jansen JB**, Klinkenberg-Knol EC, Meuwissen SG, De Bruijne JW, Festen HP, Snel P, Lückers AE, Biemond I, Lamers CB. Effect of long-term treatment with omeprazole on serum gastrin and serum group A and C pepsinogens in patients with reflux esophagitis. *Gastroenterology* 1990; **99**: 621-628
27 **Raines D**, Chester M, Diebold AE, Mamikunian P, Anthony CT, Mamikunian G, Woltering EA. A prospective evaluation of the effect of chronic proton pump inhibitor use on plasma biomarker levels in humans. *Pancreas* 2012; **41**: 508-511
28 **Arnold R**. Diagnosis and differential diagnosis of hypergastrinemia. *Wien Klin Wochenschr* 2007; **119**: 564-569
29 **Cadiot G**, Hélie C, Vallot T, Marmuse JP, Cosnes J, Riché A, Mignon M. Stenosing esophagitis in Zollinger-Ellison syndrome. *Gastroenterol Clin Biol* 1994; **18**: 1018-1020
30 **Hoffmann KM**, Gibril F, Entsuah LK, Serrano J, Jensen RT. Patients with multiple endocrine neoplasia type 1 with gastrinomas have an increased risk of severe esophageal disease including stricture and the premalignant condition, Barrett's esophagus. *J Clin Endocrinol Metab* 2006; **91**: 204-212
31 **Bondeson AG**, Bondeson L, Thompson NW. Stricture and perforation of the esophagus: overlooked threats in the Zollinger-Ellison syndrome. *World J Surg* 1990; **14**: 361-363; discussion 363-364
32 **Miller LS**, Doppman J, Maton PN, Gardner JD, Jensen RT. Zollinger-Ellison syndrome. Advances in diagnosis and treatment. *Handbk Exp Pharmacol* 1991; **99**: 349-400
33 **Waxman I**, Gardner JD, Jensen RT, Maton PN. Peptic ulcer perforation as the presentation of Zollinger-Ellison syndrome. *Dig Dis Sci* 1991; **36**: 19-24
34 **Scaglia E**, Brixi-Benmansour H, Lubrano D, Devulder F, Thiéfin G, Cadiot G. [Duodenal perforation during a secretin test]. *Gastroenterol Clin Biol* 2008; **32**: 375-377
35 **Roy PK**, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL, Gibril F, Jensen RT. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. *Medicine* (Baltimore) 2000; **79**: 379-411
36 **Hirschowitz BI**, Simmons J, Mohnen J. Clinical outcome using lansoprazole in acid hypersecretors with and without Zollinger-Ellison syndrome: a 13-year prospective study. *Clin Gastroenterol Hepatol* 2005; **3**: 39-48
37 **Metz DC**, Strader DB, Orbuch M, Koviack PD, Feigenbaum

KM, Jensen RT. Use of omeprazole in Zollinger-Ellison syndrome: a prospective nine-year study of efficacy and safety. *Aliment Pharmacol Ther* 1993; **7**: 597-610
38 **Gibril F**, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. *Medicine* (Baltimore) 2004; **83**: 43-83
39 **Berna MJ**, Hoffmann KM, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. *Medicine* (Baltimore) 2006; **85**: 295-330
40 **Borch K**, Renvall H, Liedberg G, Andersen BN. Relations between circulating gastrin and endocrine cell proliferation in the atrophic gastric fundic mucosa. *Scand J Gastroenterol* 1986; **21**: 357-363
41 **Vannella L**, Sbrozzi-Vanni A, Lahner E, Bordi C, Pilozzi E, Corleto VD, Osborn JF, Delle Fave G, Annibale B. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. *Aliment Pharmacol Ther* 2011; **33**: 1361-1369
42 **Delle Fave G**, Marignani M, Moretti A, D'Ambra G, Martino G, Annibale B. Hypergastrinemia and enterochromaffin-like cell hyperplasia. *Yale J Biol Med* 1998; **71**: 291-301
43 **Borch K**, Stridsberg M, Burman P, Rehfeld JF. Basal chromogranin A and gastrin concentrations in circulation correlate to endocrine cell proliferation in type-A gastritis. *Scand J Gastroenterol* 1997; **32**: 198-202
44 **Brandsborg M**, Elsborg L, Andersen D, Brandsborg O, Bastrup-Madsen P. Gastrin concentrations in serum and gastric mucosa in patients with pernicious anaemia. *Scand J Gastroenterol* 1977; **12**: 537-541
45 **Agréus L**, Storskrubb T, Aro P, Ronkainen J, Talley NJ, Sipponen P. Clinical use of proton-pump inhibitors but not H2-blockers or antacid/alginates raises the serum levels of amidated gastrin-17, pepsinogen I and pepsinogen II in a random adult population. *Scand J Gastroenterol* 2009; **44**: 564-570
46 **Dekkers CP**, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Double-blind comparison [correction of Double-blind, placebo-controlled comparison] of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. The European Rabeprazole Study Group. *Aliment Pharmacol Ther* 1999; **13**: 49-57
47 **Dhillo WS**, Jayasena CN, Lewis CJ, Martin NM, Tang KC, Meeran K, Todd JF. Plasma gastrin measurement cannot be used to diagnose a gastrinoma in patients on either proton pump inhibitors or histamine type-2 receptor antagonists. *Ann Clin Biochem* 2006; **43**: 153-155
48 **Frucht H**, Howard JM, Slaff JI, Wank SA, McCarthy DM, Maton PN, Vinayek R, Gardner JD, Jensen RT. Secretin and calcium provocative tests in the Zollinger-Ellison syndrome. A prospective study. *Ann Intern Med* 1989; **111**: 713-722
49 **Berna MJ**, Hoffmann KM, Long SH, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine* (Baltimore) 2006; **85**: 331-364
50 **Maton PN**, Lack EE, Collen MJ, Cornelius MJ, David E, Gardner JD, Jensen RT. The effect of Zollinger-Ellison syndrome and omeprazole therapy on gastric oxyntic endocrine cells. *Gastroenterology* 1990; **99**: 943-950
51 **Berna MJ**, Annibale B, Marignani M, Luong TV, Corleto V, Pace A, Ito T, Liewehr D, Venzon DJ, Delle Fave G, Bordi C, Jensen RT. A prospective study of gastric carcinoids and enterochromaffin-like cell changes in multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: identification of risk factors. *J Clin Endocrinol Metab* 2008; **93**: 1582-1591
52 **Peghini PL**, Annibale B, Azzoni C, Milione M, Corleto VD, Gibril F, Venzon DJ, Delle Fave G, Bordi C, Jensen RT. Effect of chronic hypergastrinemia on human enterochromaffin-like cells: insights from patients with sporadic gastrinomas. *Gastroenterology* 2002; **123**: 68-85
53 **Goebel SU,** Serrano J, Yu F, Gibril F, Venzon DJ, Jensen RT. Prospective study of the value of serum chromogranin A or serum gastrin levels in the assessment of the presence, extent, or growth of gastrinomas. *Cancer* 1999; **85**: 1470-1483
54 **Abou-Saif A,** Gibril F, Ojeaburu JV, Bashir S, Entsuah LK, Asgharian B, Jensen RT. Prospective study of the ability of serial measurements of serum chromogranin A and gastrin to detect changes in tumor burden in patients with gastrinomas. *Cancer* 2003; **98**: 249-261
55 **Syversen U**, Mignon M, Bonfils S, Kristensen A, Waldum HL. Chromogranin A and pancreastatin-like immunoreactivity in serum of gastrinoma patients. *Acta Oncol* 1993; **32**: 161-165
56 **Ito T**, Igarashi H, Jensen RT. Serum pancreastatin: the long sought universal, sensitive, specific tumor marker for neuroendocrine tumors? *Pancreas* 2012; **41**: 505-507
57 **Pregun I**, Herszényi L, Juhász M, Miheller P, Hritz I, Patócs A, Rácz K, Tulassay Z. Effect of proton-pump inhibitor therapy on serum chromogranin a level. *Digestion* 2011; **84**: 22-28
58 **Modlin IM**, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV, Kidd M. Chromogranin A--biological function and clinical utility in neuro endocrine tumor disease. *Ann Surg Oncol* 2010; **17**: 2427-2443
59 **Bashir S**, Gibril F, Ojeaburu JV, Asgharian B, Entsuah LK, Ferraro G, Crafa P, Bordi C, Jensen RT. Prospective study of the ability of histamine, serotonin or serum chromogranin A levels to identify gastric carcinoids in patients with gastrinomas. *Aliment Pharmacol Ther* 2002; **16**: 1367-1382
60 **Weber HC**, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, Gibril F, Metz DC, Fraker DL, Norton JA. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology* 1995; **108**: 1637-1649
61 **Yu F**, Venzon DJ, Serrano J, Goebel SU, Doppman JL, Gibril F, Jensen RT. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. *J Clin Oncol* 1999; **17**: 615-630
62 **Sato M**, Kihara M, Nishitani A, Murao K, Kobayashi S, Miyauchi A, Takahara J. Large and asymptomatic pancreatic islet cell tumor in a patient with multiple endocrine neoplasia type 1. *Endocrine* 2000; **13**: 263-266
63 **Hayashi M**, Floyd JC, Pek S, Fajans SS. Insulin, proinsulin, glucagon and gastrin in pancreatic tumors and in plasma of patients with organic hyperinsulinism. *J Clin Endocrinol Metab* 1977; **44**: 681-694
64 **Liu TH**, Tseng HC, Zhu Y, Zhong SX, Chen J, Cui QC. Insulinoma. An immunocytochemical and morphologic analysis of 95 cases. *Cancer* 1985; **56**: 1420-1429
65 **Yamaguchi K**, Enjoji M. Endocrine neoplasms of the pancreas: a clinicopathologic study of 24 cases and immunohistochemical remarks. *Surg Today* 1992; **22**: 305-312
66 **Gurevich L**, Kazantseva I, Isakov VA, Korsakova N, Egorov A, Kubishkin V, Bulgakov G. The analysis of immunophenotype of gastrin-producing tumors of the pancreas and gastrointestinal tract. *Cancer* 2003; **98**: 1967-1976
67 **Heitz PU,** Kasper M, Polak JM, Kloppel G. Pancreatic endocrine tumors. *Hum Pathol* 1982; **13**: 263-271
68 **Mukai K**, Grotting JC, Greider MH, Rosai J. Retrospective study of 77 pancreatic endocrine tumors using the immunoperoxidase method. *Am J Surg Pathol* 1982; **6**: 387-399

69 **Tomita T**. Immunocytochemical staining for islet amyloid polypeptide in pancreatic endocrine tumors. *Islets* 2011; **3**: 344-351

70 **Alexander HR**, Fraker DL, Norton JA, Bartlett DL, Tio L, Benjamin SB, Doppman JL, Goebel SU, Serrano J, Gibril F, Jensen RT. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. *Ann Surg* 1998; **228**: 228-238

71 **Norton JA**, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann Surg* 2004; **240**: 757-773

72 **Thom AK**, Norton JA, Axiotis CA, Jensen RT. Location, incidence, and malignant potential of duodenal gastrinomas. *Surgery* 1991; **110**: 1086-1091; discussion 1091-1093

73 **Gibril F**, Jensen RT. Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. *Dig Liver Dis* 2004; **36** Suppl 1: S106-S120

74 **Cadiot G**, Lebtahi R, Sarda L, Bonnaud G, Marmuse JP, Vissuzaine C, Ruszniewski P, Le Guludec D, Mignon M. Preoperative detection of duodenal gastrinomas and peripancreatic lymph nodes by somatostatin receptor scintigraphy. Groupe D'etude Du Syndrome De Zollinger-Ellison. *Gastroenterology* 1996; **111**: 845-854

75 **Ruszniewski P**, Amouyal P, Amouyal G, Grangé JD, Mignon M, Bouché O, Bernades P. Localization of gastrinomas by endoscopic ultrasonography in patients with Zollinger-Ellison syndrome. *Surgery* 1995; **117**: 629-635

76 **Norton JA**, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? *Ann Surg* 2004; **239**: 617-625; discussion 626

77 **Krudy AG**, Doppman JL, Jensen RT, Norton JA, Collen MJ, Shawker TH, Gardner JD, McArthur K, Gorden P. Localization of islet cell tumors by dynamic CT: comparison with plain CT, arteriography, sonography, and venous sampling. *AJR Am J Roentgenol* 1984; **143**: 585-589

78 **Berna MJ**, Jensen RT. Uses of radiolabeled somatostatin receptor analogues in diagnosis of gastrointestinal neuroendocrine tumors. In: Modlin IM, Oberg K. A Century of Advances in Neuroendocrine Tumor Biology and Treatment. Hanover: Felsenstein CCCP, 2007: 328-339

79 **Termanini B**, Gibril F, Reynolds JC, Doppman JL, Chen CC, Stewart CA, Sutliff VE, Jensen RT. Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. *Gastroenterology* 1997; **112**: 335-347

80 **Krenning EP**, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, van Hagen M, Postema PT, de Jong M, Reubi JC. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 1993; **20**: 716-731

81 **Lebtahi R**, Cadiot G, Marmuse JP, Vissuzaine C, Petegnief Y, Courillon-Mallet A, Cattan D, Mignon M, Le Guludec D. False-positive somatostatin receptor scintigraphy due to an accessory spleen. *J Nucl Med* 1997; **38**: 1979-1981

82 **Shibata C**, Funayama Y, Fukushima K, Ueno T, Kohyama A, Satoh K, Shimosegawa T, Yamagiwa T, Sasaki I. The glucagon provocative test for the diagnosis and treatment of Zollinger-Ellison syndrome. *J Gastrointest Surg* 2008; **12**: 344-349

83 **Jensen RT**, Gardner JD, Raufman JP, Pandol SJ, Doppman JL, Collen MJ. Zollinger-Ellison syndrome: current concepts and management. *Ann Intern Med* 1983; **98**: 59-75

84 **Goldman JA**, Blanton WP, Hay DW, Wolfe MM. False-positive secretin stimulation test for gastrinoma associated with the use of proton pump inhibitor therapy. *Clin Gastroenterol Hepatol* 2009; **7**: 600-602

85 **Feldman M**, Schiller LR, Walsh JH, Fordtran JS, Richardson CT. Positive intravenous secretin test in patients with achlorhydria-related hypergastrinemia. *Gastroenterology* 1987; **93**: 59-62

86 **Yanda RJ**, Ostroff JW, Ashbaugh CD, Guis MS, Goldberg HI. Zollinger-Ellison syndrome in a patient with normal screening gastrin level. *Dig Dis Sci* 1989; **34**: 1929-1932

87 **Jensen RT**, Gardner JD. Gastrinoma. In: Go VLW, DiMagno EP, Gardner JD. The Pancreas: Biology, Pathobiology and Disease. 2nd ed. New York: Raven Press Publishing Co., 1993: 931-978

88 **Fishbeyn VA**, Norton JA, Benya RV, Pisegna JR, Venzon DJ, Metz DC, Jensen RT. Assessment and prediction of long-term cure in patients with the Zollinger-Ellison syndrome: the best approach. *Ann Intern Med* 1993; **119**: 199-206

89 **Wolfe MM**, Jain DK, Edgerton JR. Zollinger-Ellison syndrome associated with persistently normal fasting serum gastrin concentrations. *Ann Intern Med* 1985; **103**: 215-217

90 **Jensen RT**. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. *J Intern Med* 1998; **243**: 477-488

91 **Norton JA**, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK, Marx SJ, Gibril F, Jensen RT. Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia-type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. *Ann Surg* 2008; **247**: 501-510

92 **Norton JA**, Cornelius MJ, Doppman JL, Maton PN, Gardner JD, Jensen RT. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome, and multiple endocrine neoplasia type I: a prospective study. *Surgery* 1987; **102**: 958-966

93 **Ruszniewski P**, Laucournet H, Elouaer-Blanc L, Mignon M, Bonfils S. Long-acting somatostatin (SMS 201-995) in the management of Zollinger-Ellison syndrome: evidence for sustained efficacy. *Pancreas* 1988; **3**: 145-152

94 **Cryer PE**, Hill GJ II. Pancreatic islet cell carcinoma with hypercalcemia and hypergastrinemia: response to streptozotocin. *Cancer* 1976; **38**: 2217-2221

95 **Sato T**, Konishi K, Kimura H, Maeda K, Yabushita K, Tsuji M, Demachi H, Miwa A. Strategy for pancreatic endocrine tumors. *Hepatogastroenterology* 2000; **47**: 537-539

96 **von Schrenck T**, Howard JM, Doppman JL, Norton JA, Maton PN, Smith FP, Vinayek R, Frucht H, Wank SA, Gardner JD. Prospective study of chemotherapy in patients with metastatic gastrinoma. *Gastroenterology* 1988; **94**: 1326-1334

97 **Jensen RT**. Consequences of long-term proton pump blockade: insights from studies of patients with gastrinomas. *Basic Clin Pharmacol Toxicol* 2006; **98**: 4-19

98 **Gibril F**, Lindeman RJ, Abou-Saif A, Shojamanesh H, Roy PK, Peghini PL, Reynolds JC, Lubensky IA, Jensen RT. Retained gastric antrum syndrome: a forgotten, treatable cause of refractory peptic ulcer disease. *Dig Dis Sci* 2001; **46**: 610-617

99 **Termanini B**, Gibril F, Stewart CA, Weber HC, Jensen RT. A prospective study of the effectiveness of low dose omeprazole as initial therapy in Zollinger-Ellison syndrome. *Aliment Pharmacol Ther* 1996; **10**: 61-71

100 **Metz DC**, Jensen RT. Advances in gastric antisecretory therapy in Zollinger-Ellison syndrome. In: Mignon M, Jensen RT, editors. Endocrine Tumors of the Pancreas: Recent advances in research and management. Series: Frontiers of Gastrointestinal Research. Basel, Switzerland: S. Karger, 1995: 240-257

101 **Metz DC**, Pisegna JR, Fishbeyn VA, Benya RV, Feigenbaum KM, Koviack PD, Jensen RT. Currently used doses of omeprazole in Zollinger-Ellison syndrome are too high. *Gastroenterology* 1992; **103**: 1498-1508

102 **Maton PN**, Frucht H, Vinayek R, Wank SA, Gardner JD, Jensen RT. Medical management of patients with Zollinger-

Ellison syndrome who have had previous gastric surgery: a prospective study. *Gastroenterology* 1988; **94**: 294-299
103 **Miller LS**, Vinayek R, Frucht H, Gardner JD, Jensen RT, Maton PN. Reflux esophagitis in patients with Zollinger-Ellison syndrome. *Gastroenterology* 1990; **98**: 341-346
104 **Metz DC**, Pisegna JR, Fishbeyn VA, Benya RV, Jensen RT. Control of gastric acid hypersecretion in the management of patients with Zollinger-Ellison syndrome. *World J Surg* 1993; **17**: 468-480
105 **Wolfe MM**, Jensen RT. Zollinger-Ellison syndrome. Current concepts in diagnosis and management. *N Engl J Med* 1987; **317**: 1200-1209
106 **Benya RV**, Metz DC, Venzon DJ, Fishbeyn VA, Strader DB, Orbuch M, Jensen RT. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type I. *Am J Med* 1994; **97**: 436-444
107 **Jensen RT**, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 2008; **113**: 1807-1843
108 **Norton JA**, Fraker DL, Alexander HR, Venzon DJ, Doppman JL, Serrano J, Goebel SU, Peghini PL, Roy PK, Gibril F, Jensen RT. Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med* 1999; **341**: 635-644
109 **Norton JA**, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ, Jensen RT. Surgery increases survival in patients with gastrinoma. *Ann Surg* 2006; **244**: 410-419
110 **Gibril F**, Jensen RT. Advances in evaluation and management of gastrinoma in patients with Zollinger-Ellison syndrome. *Curr Gastroenterol Rep* 2005; **7**: 114-121

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