Published in final edited form as:

Int J Endocr Oncol. 2017 ; 4(4): 167–185. doi:10.2217/ije-2017-0018.

Diagnosis of Zollinger–Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing

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Abstract

In recent years the diagnosis of Zollinger-Ellison syndrome (ZES) has become increasingly controversial with several new approaches and criteria proposed, differing from the classical biochemical criterion of inappropriate hypergastrinemia (i.e., hypergastrinemia in the presence of hyperchlorhydria) (Table 1). These changes have come about because of the difficulty and potential dangers of stopping proton pump inhibitors (PPIs) for gastric acid analysis; the recognition that many of the current assays used to assess gastrin concentrations are unreliable; the development of sensitive imaging modalities that detect neuroendocrine tumors (NETs) including an increasing number of the primary gastrinomas; the increased use of percutaneous or endoscopic ultrasound (EUS)-directed biopsies/cytology and the general lack of availability of acid secretory testing. In this article we will discuss the basis for these controversies, review the proposed changes in diagnostic approaches and make recommendations for supporting the diagnosis of ZES in the modern era.

Keywords

Zollinger-Ellison syndrome; gastrinoma; hypergastrinemia; proton pump inhibitor; Secretin test; MEN1; gastric acidity testing; neuroendocrine tumor diagnosis; chromogranin A; atrophic gastritis

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Financial and competing interests disclosure

This study was partially supported by intramural funds of NIDDK, NIH[DK053200-26]. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

I. Relevant Background

ZES is a clinical disorder classically characterized by the development of acid peptic disease, often severe and unremitting in nature, due to gastric acid hypersecretion induced by ectopic release of gastrin from a neuroendocrine tumor, a gastrinoma [1–3]. It is now known that 70–80% of patients the gastrinomas are duodenal in location, in contrast to older studies which primarily reported a pancreatic location [4–6]. The duodenal and pancreatic gastrinomas behave similarly clinically [2]. The autosomal dominant inherited disease, Multiple Endocrine Neoplasia-type 1 (MEN1) [7] is the cause of the ZES in 20–30% of cases, which contrasts with insulinomas and glucagonomas, in which MEN1 is present in <3% of cases [1, 8]. The pathogenesis of sporadic i.e. nonherited gastrinomas, in 70–80% of patients remains unclear [8, 9]. The exact percentage of all gastrinomas that are duodenal in location in various series of patients with ZES and is due to MEN1 is not reported and will be difficult to determine, because in MEN1 patients the duodenal gastrinomas are frequently small (<0.5cm), almost always multiple and surgery is not routinely performed in all MEN1 patients.

Similar to patients with other functional pNET (F-pNET) syndromes, all patients with ZES have two main management considerations: control of the hormone-excess state (with ZES this consists of hyperchlorhydria) [3, 10–14] and treatment directed at the pNET itself [15], because similar to other pNETs (excepting for insulinomas), 60–90% of gastrinomas, whether duodenal or pancreatic, are malignant [3, 16, 17]. The gastric acid hypersecretion in ZES can be profound with mean basal acid output increased >4 fold increased, with values up to 11-fold normal [10]. Prior to the availability of effective medical therapies, complications due to gastric acid hypersecretion were the main cause of death in both sporadic (non-MEN1) ZES patients (70–80%) and in patients with MEN1/ZES [17–20]. These lethal complications (bleeding, penetration, perforation, fistulization, etc.) could develop rapidly if the gastric acid hypersecretion was not controlled [17, 19, 21]. Initially, because gastrinoma resection was rarely curative, only total gastrectomy adequately controlled the profound acid hypersecretion [17, 20, 21]. However, with the availability of histamine H₂-antagonists in the 1980s [11, 22, 23], and later the availability of PPIs (omeprazole, lansoprazole, rabeprazole, esomeprazole, or pantoprazole) [11, 13, 24–26], medical control of acid hypersecretion, both acutely and long-term, is possible in almost every patient [11, 27, 28].

At present, with appropriate surgical management, up to 50–60% of patients with sporadic ZES are disease-free immediately postoperatively and 30–40% are disease-free long-term [4, 29–31]. In contrast, almost no patients with MEN1/ZES are rendered disease-free without aggressive resections (Whipple procedures, etc.), because of the almost uniform multiplicity of the gastrinomas in the duodenum, their small size and frequent metastases to adjacent lymph nodes [4, 29, 32–35]. This fact which combined with the excellent prognosis of MEN1/ZES in patients with small tumors (<2–2.5 cm), renders the role of routine surgery in MEN1/ZES patients controversial [4, 29, 32–35]. Currently, routine surgical exploration in MEN1/ZES patients with small pNETs (i.e. <2–2.5 cm) is not recommended in any guidelines, although it is recommended in MEN1/ZES patients with larger tumors [15, 33,

34, 36]. In patients with MEN1/ZES with small duodenal gastrinomas (<2–2.5cm) not undergoing surgery, it is recommended that they be followed closely and undergo repeat imaging at least yearly.

Results from the above studies and others [4, 29, 30, 37] have demonstrated that surgical resection in sporadic ZES patients extends overall- and disease-related survival and also decreases the subsequent development of liver metastases, which are the main determinant of long-term survival in these patients [38–40]. This has led to the proposal that all patients with sporadic ZES with resectable disease and no medical contraindication limiting surgery, should undergo exploratory laparotomy and attempted surgical resection [12, 15, 36, 41].

II. Current approach and criteria for diagnosing ZES (Table 1) (from recent guidelines/reviews) [4, 10, 12, 13, 15, 36, 42–45]

When ZES is suspected, the initial study almost always performed is a determination of a fasting serum gastrin concentration (FSG) [12, 13, 42, 45–48] (Table 1). This is a highly sensitive test for ZES (97–100%) [42] when properly performed, with a sensitivity >99% in the NIH studies [42]. In some older series 6–18% of ZES patients were reported to have at least one normal FSG value, however persistently normal values are very uncommon [42, 49, 50]. In more recent series [42] normal FSGs are uncommonly seen [42], excepting after gastrinoma resection [51], after parathyroidectomy in MEN1/ZES patients with hyperparathyroidism [52] or when the FSG is improperly performed, because the patient is not fasting or because the gastrin assay is faulty [53, 54].

Even when the gastrin assay is accurate, the problem with the FSG determination is in its specificity, because it can be elevated by three different processes. Elevations can be appropriate (i.e., physiological), in that it is the normal physiological response to hypo-/achlorhydria; inappropriate in which hypergastrinemia is associated with hyperchlorhydria, as occurs in ZES, or due to a gastrin assay error [13, 17, 45, 54–56] (Table 2). Appropriate hypergastrinemic conditions such as chronic gastritis, pernicious anemia, pan-gastritis-associated *H. pylori* infections and ingestion of potent gastric acid antisecretory drugs (especially PPI's) are by far the most common causes of fasting hypergastrinemia and thus they need to be differentiated from other inappropriate causes such as ZES. Furthermore, within the inappropriate group, ZES needs to be differentiated from other causes, particularly antral-predominant *H. pylori* infections with or without antral G cell hyperplasia and the very rarely encountered retained antrum syndrome (Table 2). An unusual position is occupied by both *H. pylori* infections and chronic renal failure, which can with cause hypergastrinemia by appropriate mechanisms(hypo-/achlorhydria) or be associated more uncommonly, with hyperchlorhydria (Table 2) [17, 57–59].

Although it is incorrectly believed by many that very high levels of FSG (>5–10 fold normal) are strongly suggestive of ZES, in fact, high levels of FSG can occur with any of the causes of appropriate hypergastrinemia, with the result that no level of hypergastrinemia alone can differentiate appropriate from inappropriate hypergastrinemia [45, 60]. For example, FSG levels of >1000–2000 pg/ml [10–20-fold elevated] are not uncommon in patients with chronic atrophic gastritis [61–64], and although PPIs usually increase FSG <3-

fold, in >20% they increase FSG >4-fold and FSG levels >5-fold increased (>5-elevated) are not rare, and even FSG >1000 pg/ml [>10-fold elevated] have been reported [65, 66, 66–70].

Therefore, to unequivocally distinguish ZES and other inappropriate causes of hypergastrinemia from appropriate/physiological causes of hypergastrinemia, an assessment of gastric pH and/or acid output (mEq/hr) is recommended in all current guidelines [4, 10, 12, 13, 15, 36, 42–45] (Table 1). Because a recent detailed analysis in more than 1000 ZES patients found that >99% had a basal gastric pH off antisecretory drugs of 2, this criterion is now included in the requirements for ZES diagnosis (Table 1). To distinguish ZES from other causes of inappropriate hypergastrinemia (*H. pylori* infection, etc., Table 2), additional studies such as determination of a basal acid output (BAO), a secretin provocative test or possible assessment for presence of a NET using somatostatin receptor scintigraphy (SRI) with either ⁶⁸Ga-DOTATATE PET/CT or ¹¹¹In-DTPA-octreotide with SPECT/CT (SRS) imaging are recommended (Table 1).

There is no genetic test that recognizes all patients with ZES. In the 20–25% of patients that have MEN1/ZES, genetic testing is recommended for family counseling, confirmation of the diagnosis of MEN1 and can discover within a family with an established mutation, family members with MEN1 who are asymptomatic. Genetic testing does not identify which members of the MEN1 family have ZES.

III. Why making a firm and timely diagnosis of ZES is important

The unequivocal determination of whether ZES is or is not present has important implications for many aspects of patient management. First, as was reviewed above, ZES is almost invariably associated with acid hypersecretion [10] that must be controlled acutely and long-term. This involves not only medication expense, but also regular follow-up, periodic dose-adjustment in some patients, and careful attention to control of acid secretion with parental drugs when oral medications cannot be taken [11, 12, 23, 27, 28, 71, 72]. Second, because gastrinomas are malignant in 60–90% of cases, treatment directed at the gastrinoma must also be considered [12, 15, 44]. This involves detailed imaging studies and if MEN1/ZES is not present and the tumor is potentially resectable, surgical exploration [12, 15, 44]. Third, if unresectable metastatic disease is present, anti-tumor treatments are often required [41] and acid hypersecretion must be controlled during all such therapies. Fourth, because of the frequent occurrence of MEN1 in patients with ZES [7, 8], all ZES patients must be screened for MEN1 syndrome initially and re-evaluated with time as hyperparathyroidism does not always precede the diagnosis of ZES [7, 73]. Fifth, the presence of MEN1/ZES introduces several special concerns including the role of family counseling as well as the need to search for other endocrinopathies; which have a major impact on the approach to the gastrinoma itself as well as to plan surgical of other functional (present 10–23%) and nonfunctional pNETs (NF-pNETs), (present 80–100%), which are frequently present as well [12, 18, 33, 35, 74, 75].

On the other hand, failure to make the diagnosis of ZES also has significant implications. The mean time to diagnosis is over 6 years [2], but even so, about 30–40% of patients are cured long term [18, 35, 74, 75]. Failure to make a timely diagnosis, however, leaves the

patient at risk for the development of metastatic disease which can make a significant impact on outcome. An important study from the NIH and La Sapienza University in Rome previously documented the fact that, despite a clear increase in pNET incidence with time [18, 35, 74, 75], referrals to these centers for ZES, and the frequency with which a firm diagnosis of ZES was made, declined with the general availability of PPIs, which exposes individuals to this very risk [18, 35, 74, 75]. Moreover, with 20–25% of ZES patients having MEN1, such a delay also contributes to delay in recognition of MEN1 syndrome which has major implications for the index patient as well as his/her extended family.

For the above reasons, the inappropriate diagnosis of the presence of ZES in a patient suspected of having the disease, who does not have the disease, has as much importance as the failure to establish the disease in a patient with ZES.

IV. What are the current controversies in the diagnosis of ZES?

The current diagnostic controversies relate to three main areas. First, some investigators have proposed that pH assessments can generally be performed without stopping potent antisecretory drugs such as PPIs [45, 60, 76] and numerous recent reports (see below) have questioned whether an assessment of gastric pH is even needed in most patients to make the diagnosis of ZES. Second, recent studies [53, 54] have documented that >50% of the currently used gastrin assays are inaccurate. Third, the roles of supplementary testing with secretin testing [12, 45, 77–79] and, in occasional patients, a full gastric analysis [10, 12, 13, 45] (Table 1), are now unclear for different reasons. Secretin was not available for several years; however, synthetic human secretin, which is fully biologically active [80] is now available (ChiRhoStim, NDC #67066-005-01, Burtonsville, MD). Some have proposed that secretin testing can replace an assessment of gastric pH, whereas others have questioned its utility for the diagnosis of ZES, because false positive results can occur with achlorhydria [78]. Gastric analysis requires technical expertise and is now done only rarely with the result that it is not generally available, as it was in the past [10, 51]. Moreover, the role of non-biochemical testing for ZES is of increasing importance because of recent advances in neuroendocrine tumor specific imaging studies with SRI using either ⁶⁸Ga-DOTATATE PET/CT or ¹¹¹In-DTPA-octreotide with SPECT/CT imaging. With improvements in imaging, the role of biopsy or cytology in diagnosing ZES, particularly in patients with advanced disease or typical presenting symptoms, is less clear.

V. Are these controversies in the diagnosis of ZES clinically relevant?

To establish how the diagnosis of ZES is changing in the light of the aforementioned controversies, we analyzed the basis for the diagnosis in the last 20 ZES cases reported in the literature over the last 4 years (2013–2017) [81–100] with sufficient information to determine how the diagnosis was reached. In 19 of these cases (95%)[81–94, 96–100], no assessment of gastric acidity was performed. Moreover, there was no standard definition of the diagnosis used and the basis of the diagnosis varied in the different cases. In general, in the different cases the specific diagnosis was suspected by first identifying fasting hypergastrinemia and then supporting evidence was obtained using imaging studies, secretin testing, and/or immunohistochemical or pathological findings. These results suggest that the

modern approach to the diagnosis of ZES that is generally being used is different from the classical approach involving assessing gastric acidity as described above.

VI. Examination of the basis for the current controversies in the diagnosis of ZES?

As was alluded to above, the current controversies regarding diagnosis can be divided into 1) issues relating to problems with determining gastric acidity, 2) issues relating to the reliability of gastrin testing, and 3) issues relating to the selection of confirmatory tests.

1. In contrast to the past [10] when gastric analysis was routinely available, gastric acid testing (assessing basal acid output) only remains available in very few centers in the US (<5) and other countries [4, 45, 60]. Moreover, assessment of stimulated acid output (previously of value to exclude achlorhydria, assess maximal acid output(MAO), determine BAO/MAO ratios) [10, 12, 13, 45]) is no longer possible because of the lack of availability of reliable gastric acid stimulants (i.e., histalog or pentagastrin). On the other hand, access to gastric pH measurements whether performed with a trans-nasal pH probe or by collecting gastric fluid at the time of upper GI endoscopy and interrogating it with pH paper or a pH electrode [45, 60], is generally available. However, this approach is underutilized and of limited validity for diagnosis using pH paper in the pH “grey zone” between pH 2.0 and 4.0. It should be noted that this pH range is commonly encountered in patients take antisecretory drugs which is a second major factor that impacts on the validity of gastric analysis. The widespread use of PPIs to treat both GERD and suspected PUD symptoms, as well as many other nonspecific symptoms of the upper GI tract, which in some series account for >50% of all PPI use [75, 101, 102], impacts significantly on the diagnosis of ZES, because the condition is usually only considered once the patient is already taking therapy. PPIs have a much longer duration of action than histamine H₂-receptor antagonists (the effects last up to one week or more after stopping therapy). Furthermore, because of their extended potency at suppressing acid secretion, PPIs cause hypergastrinemia in 80–100% of non-ZES patients, in ranges that overlap with most ZES patients [45, 48, 60, 65, 67–70, 103–105]. Therefore, to differentiate the source of the hypergastrinemia (appropriate due to drug induced acid suppression or inappropriate as in ZES), almost all guidelines, recommended PPIs be stopped for at least a week prior to gastric analysis. Many ZES patients, especially those with GERD, are reluctant to do this. Furthermore, several recent papers [4, 76, 106] have highlighted the significant potential risks associated with PPI withdrawal in ZES patients which include leading to severe acid-peptic complications if not performed under carefully controlled conditions. For these reasons, some investigators [76, 106] have proposed that the diagnosis of ZES should not be made by stopping PPIs and instead, if possible, other criteria excluding gastric acid testing, should be utilized, though none of these approaches have been studied prospectively.

2. In terms of the reliability of the gastrin assays themselves, recent studies have shown that the various gastrin assays used by many laboratories give unreliable results in 58% of cases, either underestimating or overestimating the true gastrin value [53, 54]. This is primarily due to the use of incompletely characterized antibodies in the assay kits with variable interactions with the different forms of gastrin [53, 54]. This is potentially a major problem for the diagnosis of ZES. Accurate assessment of serum gastrin is essential for the initial determination of hypergastrinemia [11, 12, 42, 45] when the disease is initially suspected, as well as for secretin testing [77], which is done later during the diagnostic algorithm, in selected cases to confirm the disease (Table 1).
3. Many factors impact on the utility of confirmatory testing (secretin stimulation, imaging modalities and biopsy confirmation) to diagnose ZES. The precise role for the use of specific imaging modalities for diagnosis of NETs, as a factor combined with other criteria such as hypergastrinemia to establish the diagnosis of ZES, specifically is yet undefined. SRI using either ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging is now becoming increasingly available and numerous studies show they have excellent sensitivity and selectivity (high specificity) for NETs [107–109]. SRS has a sensitivity of 40–60% for duodenal gastrinomas, which are relatively small usually, and 60–100% for pancreatic gastrinomas [31,107–109]. It has a reported false positive rate of 0–12% but is higher in MEN1/ZES patients because of the multiple endocrine tumors these patients develop. The sensitivity is higher with ^{68}Ga -DOTATATE PET/CT but the exact number for duodenal and pancreatic gastrinomas has not being reported in any perspective study[31].

SRI is increasingly being used, not only to localize NETs, but also potentially for NET diagnosis [110–112] in patients with ZES and other conditions without the need for tissue acquisition. In several of the recent ZES papers reviewed above, the results of SRI in hypergastrinemic patients was used to support a diagnosis of ZES, rather than confirming the diagnosis with an assessment of gastric pH, as is recommended in the existing guidelines [82, 90–92, 96, 98] (Table 1). While the presence of a tissue diagnosis of a NET in a patient with hypergastrinemia and/or typical symptoms has always been used to help confirm the diagnosis [75;83–85;89;91], this approach is increasingly being used [83, 84, 99, 113], without a preceding measurement of acid secretory capability, because of the increased availability of endoscopic ultrasound and percutaneous biopsy/cytologic techniques. However, this approach has not yet been factored into any proposed guidelines for the diagnosis of ZES and not all NETs identified this way, are invariably the cause of the hypergastrinemia.

A final factor leading to difficulty in diagnosing ZES is an unclear definition of the role of secretin testing, its availability and its limitations. Secretin testing has been well studied in ZES and several criteria proposed with high sensitivity and specificity including an increase of 200 pg/ml [114], 110 pg/ml [115] and 120 pg/ml [77]. In a study [77] involving an analysis of secretin testing results from 537 ZES patients in the literature, 462 non-ZES patients, and 293 prospectively studied ZES patients, the 120 pg/ml criterion was positive

in significantly more ZES patients than the criterion of 200 pg/ml (94% vs 85%) and had equal sensitivity to the 110 pg/ml criterion (93%). Because of its potentially greater specificity, the criterion of 120 pg/ml (sensitivity-94%, specificity-100%), rather than the 110 pg/ml criterion, was recommended [77]. Unfortunately, secretin was not available for several years leading investigators to develop alternative approaches for diagnosing ZES and these approaches may have persisted, despite secretin's reappearance in recent years. Synthetic human secretin is now licensed and approved in the US, but is still not available in Europe and therefore is not widely used in Europe. It has an important clinical use in the diagnosis of ZES in some patients, as reviewed here and below, and hopefully it will become available again in Europe and be a useful tool for ZES diagnosis there again. Another factor contributing to the limited use of secretin testing is the fact that it can give false-positive results in patients with achlorhydria [77, 116] or in patients taking potent antisecretory drugs such as PPIs [79]. Therefore, as with FSG determinations, secretin testing is best performed early on when the patient is first seen and not yet taking any PPIs or after the PPI is held to allow for the development of an acidic gastric pH (which, as described above, needs to be performed with caution, best done in a specialty unit.). At present the threshold level of gastric pH required to prevent false positive results with secretin testing is unknown. Because of these limitations and the fact that it is not positive in all ZES patients (6–13 % have false negative results [77]), some have concluded that the secretin test is generally not useful for the diagnosis of ZES [78]. Despite this concern a recent [72] ENETs consensus guideline for Standard of Care in NETs dealing with biomarkers, specifically recommends secretin testing in suspected ZES patients, after excluding fundic atrophic gastritis (primarily by biopsy and serology).

VII. Proposed solutions to the current controversies in the diagnosis of ZES?

VII.A. Proposed solution A: Don't stop PPIs abruptly and instead try to administer the PPI less frequently or hold doses and assess gastric pH [78, 106]

This approach is already used by many centers and it can be carried out successfully if done appropriately. First, as most new patients with ZES are taking PPIs when first seen because they have had acid peptic symptoms for several years (the mean delay in diagnosis is 6–8 years) [2], this approach is applicable to most newly suspected ZES patients. Before this is attempted, however, it is essential to first exclude the presence of active peptic disease by endoscopy and if ulceration is present, PPI therapy that adequately suppresses acid to allow healing of all active disease should be instituted before holding or stopping the PPI. At this initial endoscopy, gastric pH can be tested and a fasting gastrin assessed which can either support or establish the diagnosis (pH $\geq$ 2, hypergastrinemia). It is also very helpful to question the patient about whether they ever miss PPI doses and, if so, for how long, to provide a guide to how sensitive the individual patient is to PPI delay or withdrawal. A fact not generally appreciated is that ZES patients taking PPIs are frequently more sensitive to delaying or stopping the PPI than nonZES patients, because of their preexisting gastric acid hypersecretion. ZES patients without controlled acid hypersecretion often have compensatory increased pancreatic secretion [117, 118] likely due to increased plasma secretin levels [117–119], because of excessive duodenal bulb acid exposure. However, once

gastric acid secretion is controlled with PPI therapy, this compensatory response is largely reversed, resulting in an increased sensitivity to recurrent gastric acid hypersecretion with potential serious consequences if therapy is stopped acutely and not carefully monitored.

In practice this approach is not easy to carry out, even in centers dealing with ZES, because the duration of action of PPI's is very variable in different patients and therefore patients may need to be tested on multiple occasions to reach a gastric pH ≥ 2 . It is important to realize that just reaching an acidic pH is not sufficient to make the diagnosis of ZES with hypergastrinemia [10]. In the study establishing the diagnostic criterion of pH ≥ 2 , this was the minimum degree of gastric acidity that included 100% of ZES patients [10]. In older studies on non-ZES patients, acidic pH values with hypergastrinemia were not infrequently reported [120–123]. An alternative approach which is likely safer and easier to perform is to replace the PPI with a histamine H₂-receptor antagonist (H₂RA), such as ranitidine (400–600 mg every 4–6 hrs), which has a much shorter duration of action, followed by H₂RA withdrawal for at least 12, but up to 30 hours [10] before obtaining a pH and concomitant gastrin. All of this needs to be done under close supervision with the patient well informed to notify his/her caregivers if acid peptic symptoms develop because massive GI bleeding can occur quickly in ZES patients once acid control is lost. Our general approach is to provide the patient with a letter describing the process for presentation to the ER should symptoms occur in which we request rapid placement of a nasogastric tube for symptom relief rather than antisecretory therapy administration, to maintain the integrity of the evaluation.

VII.B. Proposed solution B: While taking PPIs, don't assess gastric pH and instead consider other measures that could support the diagnosis. [suggested for MEN1 patients [76] and used in many recent literature cases (see IV. above)] [81–85, 87–100]

Unfortunately, there are no serologic tests that completely exclude all causes of hypo/achlorhydria, including drug-induced acid suppression. Whereas anti-parietal and anti-intrinsic factor antibodies would be suggestive of the presence of chronic atrophic gastritis (CAG), they are not positive in all patients with CAG, and their false-positive rates have not been studied in ZES patients [124, 125]. Autoimmune markers are also not useful in other causes of physiologic hypergastrinemia, including drug-induced acid suppression.

Upper gastrointestinal endoscopy can be very helpful in suggesting the possible cause of the FSG. In CAG or pernicious anemia, atrophic gastric mucosa can be seen, whereas in ZES, prominent gastric folds are seen in >90% of ZES patients [2, 124–126]. As discussed below, prominent gastric folds are not specific for ZES, but are highly suggestive in the proper clinical context (See Table 3,4). These clinical impressions can be supported by the appropriate gastric biopsies [124, 125] (Table 3,4). Furthermore, gastric fluid pH can be assessed easily at the time of upper gastrointestinal (UGI) endoscopy using a pH electrode, pH meter on the aspirated gastric fluid or pH paper[127].

Other features suggestive of ZES such as NET specific imaging with ⁶⁸Ga-DOTATATE PET/CT or ¹¹¹In-DTPA-octreotide with SPECT/CT imaging together with other features of MEN1 or typical acid-peptic symptoms and/or a positive cytology or biopsy for a NET or gastrinoma, combined with proven fasting hypergastrinemia as discussed above, are an

attractive alternative approach that may be sufficient to support the diagnosis of ZES, but these approaches have limitations too.

Using the detection of hypergastrinemia together with positive clinical features of MEN1 (e.g., a family or personal history of typical endocrinopathies, including hypercalcemia, pituitary or pancreatic tumors) as diagnostic of ZES in a possible MEN1 patient [76], is unreliable, because unfortunately, there are many other nonZES diagnoses that fulfill these combinations too. For example, cases of primary hyperparathyroidism, often associated with atrophic gastritis [128–130] or even established MEN1 syndrome associated with antral G cell hyperplasia and/or *H. pylori* infections together with hypergastrinemia [57–59, 128, 131–133], but without ZES, have been described. In addition, coexisting PPI-induced hypergastrinemia accompanying an idiopathic endocrinopathy is not uncommon and 20–40% of MEN1/ZES patients have a negative family history [7]. In the case of a patient with known MEN1, the development of fasting hypergastrinemia while not taking PPIs, especially if associated with GERD/peptic symptoms, is highly suspicious for ZES [7, 8]. However, in a known MEN1 patient taking PPIs, the hypergastrinemia could just as well be due to the PPI, as to a possible gastrinoma, and distinguishing the two without a concomitant gastric pH assessment is virtually impossible. In this latter situation, the identification of any additional features of MEN1, except for a biopsy/cytology of a NET showing gastrin, will not help in distinguishing these two possibilities and unless the tissue specimen was obtained at endoscopy from visible mass lesions (usually multiple) in the duodenum, one cannot reliably distinguish gastrinomas from other non-functional or functional NETs that do not produce gastrin. We believe that it is important to make a correct diagnosis up front because it has life-long management consequences [7, 8, 18].

Using tumor imaging studies in combination with the hypergastrinemia to diagnose ZES, as is increasingly being done in recently reported cases [82, 84, 87, 88, 90, 94, 110, 134] with patients taking or not taking PPIs, has other limitations. In the presence of PPI therapy, one cannot exclude the presence of appropriate hypergastrinemia if a tumor is seen on cross-sectional imaging studies (CT, ultrasound, or MRI), whether the patient has MEN1 syndrome or not and the mass itself may not even be a NET. However, if SRI is used for imaging with either ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging combined instead of a cross-sectional imaging study, the likelihood of ZES is higher but this too is not always diagnostic, because overexpression of somatostatin receptors does occur in certain non-endocrine tumors (breast, prostate, lymphomas, CNS, lung, etc.) [108, 135], non-endocrine tissues, and almost all well-differentiated neuroendocrine tumors [108, 135], even if ZES is absent. There are some specific situations that strongly support a diagnosis of ZES (Table 3) without the presence of a pH measurement but it is essential to realize that PPI therapy clearly confounds the diagnosis in most other scenarios (Table 4).

Using positive cytology or a biopsy for a NET or gastrinoma in combination with the detection of fasting hypergastrinemia to diagnose ZES has been used in several recently reported ZES cases [84, 85, 89, 113], but here too, there can be several concerns depending on the clinical circumstances. Fasting hypergastrinemia in a patient not taking PPIs, but with active GERD or peptic ulcer disease or a history of diarrhea responding to PPI therapy, is

strongly supportive of ZES in the presence of a positive biopsy or cytology for a NET, and especially so if a gastrinoma is identified. However, it is important to remember that many NETs (especially pNETs), not associated with ZES, can exhibit positive gastrin immunohistochemically [136–143], so that this feature alone cannot establish the diagnosis of ZES, and, as was mentioned above, the PPI therapy itself could always be the cause of the hypergastrinemia.

VIII. Discussion and proposal of new criteria to support the diagnosis of ZES when gastric acidity can not be assessed

The current reality is that although the functional criteria based on demonstrating inappropriate hypergastrinemia (Table 1) with an elevated fasting FSG together with a concomitant gastric acid pH ≥ 2 are well established to specifically identify ZES, they are not being used in regular clinical practice. This is occurring despite almost every recent guideline or expert review of diagnosis of ZES containing these criteria [1, 4, 12, 25, 36, 144, 145]. As was reviewed in this article, the principal basis for the failure to follow these guidelines is the failure to assess gastric pH which is due to the widespread decreased use of gastric acidity assessments, in particular, fueled by the difficulties of measuring gastric acidity when patients have been taking PPIs. The previous lack of availability of secretin for secretin provocative testing (which has now been corrected), compounded the situation and the increased use of and availability of sensitive imaging modalities such as ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging which have specificity for NETs, has led some to believe that functional biochemical testing could be bypassed. Finally, the rise in use of tumor biopsy/cytology, particularly coupled with endoscopic ultrasound, has rendered biochemical testing unnecessary in the eyes of some authorities. These changes have resulted in a situation whereby 95% of the recently reported cases with ZES were diagnosed without using the classical functional criteria requiring gastric pH assessment and simultaneous FSG inappropriateness listed in Table 1. However, as we discuss in some detail below, the accuracy of this approach is not established and may lead to misdiagnoses.

The major problem confronting physicians attempting to make a diagnosis of ZES is not the sensitivity of the gastrin assay itself, which has a very high sensitivity for ZES, if appropriately determined[42]. Rather, it is a problem in specificity because there is no level of fasting hypergastrinemia alone which can distinguish ZES from hypergastrinemia due to several other causes such as appropriate hypergastrinemia (physiological) due to achlor-/hypochlorhydria. This is an essential distinction, because appropriate (physiological) causes of hypergastrinemia such as chronic atrophic gastritis with or without *H. pylori* infection, are approximately 10,000 to 100,000 times more common than ZES. ZES has an incidence of 2–5/million/year [12, 17], whereas atrophy of the gastric mucosa due to chronic gastritis occurs in general in Western populations in 3–6% of individuals [17, 146, 147]. Therefore, for the diagnostic criteria for ZES to have any specificity, it is essential that causes of appropriate (physiological) hypergastrinemia due to achlor-/hypochlorhydria be excluded.

Unfortunately, in most of the proposed ZES cases recently reported in the literature, the criteria outlined in Table 1 were rarely met. The principal criteria being used in these recent reports are the documentation of fasting hypergastrinemia together with a diagnosis of an intra-abdominal tumor either established as a possible NET using SRI with ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging or by cytology, biopsy or surgery. Although in a few cases the FSG was determined prior to the commencement of PPI therapy, in most of these patients, the FSG determinations were performed while the patients were taking PPI, so that appropriate (physiological) hypergastrinemia could not be excluded (Table 2). SRI was developed for localization/tumor staging in patients with NETs and although some studies recommend it could be useful for the initial diagnosis of NETs [110–112], it is generally not used for this as a screening test. The use of SRI with ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging as a diagnostic tool for gastrinoma and the source of the hypergastrinemia, is potentially fraught with problems, because this diagnostic approach will demonstrate positivity with any benign or malignant process overexpressing somatostatin receptor subtypes 2, 5 [107, 135, 148, 149]. This includes such diverse processes as arthritis, infections, thyroid disease, granulomatous diseases, other malignancies (breast, prostate, CNS, etc.), indolent carcinoids (stomach, rectum, lung, etc.) and indolent NF-pNETs that can occur in 1–1.5% of the population [3, 107, 135, 150]. Even though the conclusion that the fasting hypergastrinemia in a patient with suspected ZES taking PPIs and identified to have a NET by cytology/biopsy, may have a stronger association, the conclusion that ZES is established is not correct. As was mentioned above, hypergastrinemia may not be related to the NET itself, because many NETs express gastrin immunocytochemically, but do not secrete it [136–143]. The establishment of MEN1/ZES in a patient with MEN1 can be even more difficult because these patients develop NF-pNETs and NETs in other locations [8, 33], so that SRI with ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging as a diagnostic tool for proving a positive image represents a gastrinoma specifically, is generally not helpful. The problem with using cytology/biopsy with these patients is that the gastrinomas are frequently small, usually duodenal in location and not seen on EUS or other conventional imaging modalities [5, 8, 151–153]. Furthermore, pancreatic gastrinomas occur in up to 15% of MEN1/ZES patients [8] and must be distinguished from the pancreatic NF-pNETs, which are generally present as well [8, 34]. Another approach recently used in the literature to attempt to establish the diagnosis of ZES without assessing gastric acidity, is to use of the secretin test. While the secretin test, when performed prior to PPIs in patients with gastric pH ≤ 2 , has high sensitivity for detecting ZES [94% using a criterion of ≥ 120 pg/ml increase [77]] and high specificity [100%, using a criterion of ≥ 120 pg/ml increase [77]], several studies report that it can give false positive tests if performed in patients with achlorhydria [77, 116] or hypochlorhydria, such as when taking PPIs [79, 154]. Therefore, if it is used in a patient taking PPIs, the secretin test result may not be valid. Furthermore, if it is used in a patient prior to starting PPIs with hypergastrinemia, if chronic atrophic gastritis is in fact the underlying cause of the hypergastrinemia, again the secretin test will not be valid.

Therefore, as discussed in the above paragraph, none of the increasingly used criteria for the diagnosis of ZES, which are used in >95% of current papers, unequivocally establish the

diagnosis of ZES. This is especially true for patients with ZES without advanced disease, who are presenting early in their disease course, and are the group in which it is particularly important to make a diagnosis, because surgery can be curative in this group and extend survival [4, 29, 37]. This problem for the diagnosis of ZES is unique because, in contrast with insulinomas, the standard criteria for insulinoma diagnosis are widely accepted [44, 72, 145, 155]. This is occurring, even though with both insulinomas and gastrinomas, the diagnostic tests used are based on similar approaches, in demonstrating inappropriate hormone release (gastrin or insulin), in face of an abnormal biologic response (increased acid secretion or hypoglycemia). In the case of insulinomas the diagnosis is established by demonstrating the presence of hypoglycemia with inappropriate hyperinsulinemia (often combined with increased proinsulin levels), usually accomplished during a 72-hour fast [44, 72, 145, 155]. Why this approach is widely accepted and almost universally used for the diagnosis of insulinomas, whereas assessment of the acid secretory status for diagnosing ZES is not being accepted, is not entirely clear. It is likely partially related to several of the points made in earlier paragraphs, such as lack of widespread availability of assessment of gastric acidity and concerns about the potential dangers of withdrawing PPIs.

There are, in general, two approaches that can be taken towards resolving the marked dichotomy between the widely recognized and recommended criteria for the diagnosis of ZES outlined in Table 1 and the widespread failure to use them in practice. One is to continue emphasizing the current guidelines and to point out the problems with the popular approach of not using these guidelines. However, one could argue that for the last twenty years this approach has been tried and the result is that it is a failure at present, in that 95% of new cases are not using this approach, or paying any attention to the many papers published over this time containing these guidelines.

A second approach would be to attempt to develop new guidelines that support by varying degrees, the diagnosis of ZES. This could be done by trying to combining several of the approaches currently being used, to propose some criteria without gastric pH assessment, that if fulfilled, would have varying degrees of strength, in supporting the diagnosis of ZES, but still not unequivocally establish the diagnosis, as the established criteria in Table 1 do. We have attempted to do this in Table 3 and Table 4, although this results in a rather lengthy algorithm of possibilities with varying degrees of precision which are not known or established. If it is not possible at all to assess gastric acidity, which is the recommended approach whenever possible, then in a patient suspected of having sporadic ZES (non MEN1) and **not taking PPIs**, the combination of symptoms and signs of PUD (preferably active) combined with positive SRI, cytology or biopsy for a NET (preferably showing gastrinoma) or a positive secretin test, strongly supports a diagnosis of ZES (Table 3). Similarly, a history of diarrhea, which has responded to PPI or histamine H₂ receptor antagonist therapy, could be substituted for the active PUD requirement [2, 17, 47, 156, 157]. Diarrhea is now uncommon with routine peptic disease with antacids rarely being used, however, when carefully sought for in ZES patients, it is present in 60–75% [2, 158] and characteristically responds readily to adequate acid suppression [2, 13, 17, 156, 157]. These criteria are only strongly suggestive of ZES, because for each criterion, some uncommon/rare disorder(s), that is not ZES, could be listed that can cause the combination

of signs and symptoms. For example, active peptic disease could be due to other nonZES causes, particularly NSAID/aspirin use, the positive SRI could be due to an unrelated disorder or a false positive, diarrhea could rarely occur with atrophic gastritis due to bacterial overgrowth, and is rarely reported with PPIs[159–161], whereas the positive SRI could be due to the development of type 1 gastric carcinoid tumors which commonly occur in atrophic gastritis.

In a patient **not taking PPI's** and suspected of having ZES with known MEN1 or strongly suspected of having MEN1 (i.e., a positive family history; hyperparathyroidism or pituitary disease present) having, in addition, either the presence of active peptic ulcer disease (or a recent history of it) or improvement in diarrhea with PPI or histamine H₂ receptor antagonist therapy or having a positive cytology or biopsy for NET (preferably a proven gastrinoma), with the finding of fasting hypergastrinemia, would also be strongly supportive of the diagnosis of ZES (Table 3). However, it is important to remember that SRI in MEN1 patients can be positive from many of the different NETs these patients develop [8, 18, 33, 162], so that it does not have the specificity that it has in possible sporadic ZES cases and therefore is not as useful for the possible diagnosis of ZES specifically (as opposed to NETs in general). Therefore, in a hypergastrinemic patient suspected of having ZES with known MEN1 or strongly suspected of having MEN1 with only a positive SRI or other imaging positive for NET, the diagnosis of ZES is only weakly supported.(Table 3). Similarly, in a patient without MEN1 with fasting hypergastrinemia without PUD or diarrhea, a positive SRI or imaging for possible tumor is also only weakly supportive for the diagnosis of ZES. However, if a gastric biopsy shows absence of atrophic gastritis with negative serum autoimmune markers for atrophic gastritis is obtained also, then this would provide moderate support for making a tentative diagnosis of ZES (Table 3).

While we would strongly recommend, at least, an attempt to support the diagnosis of ZES be made using the above criteria in all patients prior to their being treated with PPIs, we realize in many cases this will not be done. Therefore, we have attempted to propose some criteria that could be useful in this situation (Table 4). In all of the above scenarios **if the patient also is taking PPI therapy**, the overriding concern of superimposed appropriate hypergastrinemia lowers the confidence of a secure diagnosis significantly, such that we propose a step-wise reduction in confidence for each of the aforementioned situations mentioned in Table 3 (see Table 4).

Two scenarios can be proposed to moderately support the diagnosis of ZES (ZES is likely) in a patient **taking PPI therapy**, who has active PUD, a history compatible with recent PUD or a history of improvement in diarrhea with PPIs (Table 4.A). One scenario would include such a patient with or without MEN1 with a positive biopsy or cytology for a neuroendocrine tumor (NET) (stronger support if a gastrinoma is found) (Table 4.A.1). A second scenario is such a patient without MEN1 but with a positive somatostatin receptor scintigraphy imaging (SRI) with either ⁶⁸Ga-DOTATATE PET/CT or ¹¹¹In-DTPA-octreotide with SPECT/CT imaging (Table 4.A.2). This later scenario would be downgraded to weakly supportive (a tentative diagnosis) of the diagnosis of ZES in patients with MEN1 (Table 4.B. 2). This occurs because these patients very frequently have other nongastrinoma NETs including NF-pNETs, carcinoids (gastric, lung, thymus), pituitary and adrenal NETs, which

may all be positive on somatostatin receptor scintigraphy imaging (SRI) with either ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging, and thus a positive SRI result provides minimal support for the diagnosis of ZES [33, 163–165].

Weak support (a tentative diagnosis) would be proposed in a **patient taking PPIs** and suspected of ZES due to fasting hypergastrinemia without any history of PUD or diarrhea without MEN1, but in addition has a negative gastric antral/body biopsy for atrophic gastritis combined with a negative result for parietal cell antibodies/intrinsic factor antibodies, and a positive somatostatin receptor scintigraphy imaging (SRI) with either ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging (sporadic disease only) or positive cytology biopsy for NET (gastrinoma), (Table 4.B.2). Weak support is proposed because atrophic gastritis detection is dependent on biopsy number and location and thus can be missed, and parietal cell antibodies (70–80%) and intrinsic factor antibodies (20–40%) are not positive in all patients with atrophic gastritis, thus atrophic gastritis can be missed with this approach [124, 125, 166–169].

Only minimal support (supporting only a possible diagnosis) for the diagnosis of ZES can be proposed for a patient **without MEN1 taking PPIs** and suspected of ZES due to fasting hypergastrinemia without active PUD, a history compatible with recent PUD or a history of improvement in diarrhea with PPIs, but with a positive SRI (Table 4.C.1). This proposal is weakened by the fact that the exclusion of atrophic gastritis, or PPI-induced hypergastrinemia or other causes of appropriate/physiological hypergastrinemia, rests on the patient's history which can be inaccurate, if PUD is not present, which will be the case in most patients.

Similarly, only minimal support (supporting only a possible diagnosis) for the diagnosis of ZES can be proposed for a patient **with MEN1 or strongly suspected of having MEN1, taking PPIs** and suspected of ZES due to fasting hypergastrinemia without active PUD, a history compatible with recent PUD or a history of improvement in diarrhea with PPIs, but with prominent gastric folds (Table 4.C.2). Prominent folds are present in 92% of ZES patients so their presence does support the diagnosis of ZES[2]. However, there are numerous other causes of prominent gastric folds, including Menetrier's disease, neoplasms (carcinoma, lymphoma, neurofibroma, lipomas), *H. pylori* infections, other infectious causes, varices, chronic gastritis and gastric polyps [170–172].

This latter scenario would be strongly supportive of ZES in the absence of PPI therapy, but the potential role of appropriate hypergastrinemia confounding the diagnosis makes us lower the level of support under therapy. The same limitations hold true for other scenarios in patients taking PPIs (Table 4), such as patients with fasting hypergastrinemia who have active PUD, a history compatible with recent PUD or a history of improvement in diarrhea with PPIs combined with a positive secretin test or even a high index of suspicion for MEN1 syndrome, because the secretin test can be inappropriately positive in the presence of achlorhydria (Table 4) and MEN1 patients are at risk for other NETs as well as gastrinomas (Table 4).

IX. Conclusion

This paper briefly reviews the current status for diagnosing ZES. While well-established guidelines that are both sensitive and specific exist, they are rarely used in modern clinical practice (5% of current cases reported). This is primarily due to the lack of use of assessments of gastric acidity, that in turn is largely due to the difficulty in stopping PPIs. Each of these aspects is discussed in detail, and based on currently used approaches to the diagnosis of ZES that are being used, possible new criteria that do not involve assessing gastric acidity and that would support a diagnosis of ZES in various situations are proposed, that could be generally used. These criteria would make a tentative diagnosis of ZES and provide more certainty than the approaches generally used in practice now. The preferred approach, whenever possible, to diagnose ZES in any patient remains using the established criteria of documenting gastric acidity and inappropriate hypergastrinemia, and we still maintain that this is best established in specialized centers well-versed in the diagnosis and management of ZES.

References

1. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: Advances. *Best Pract Res Clin Gastroenterol.* 2012; 26:737–753. [PubMed: 23582916]
2. Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome: clinical presentation in 261 patients. *Medicine (Baltimore).* 2000; 79(6):379–411. [PubMed: 11144036]
3. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: Pancreatic endocrine tumors. *Gastroenterology.* 2008; 135:1469–1492. [PubMed: 18703061]
- ★4. Ito T, Igarashi H, Jensen RT. Zollinger-Ellison syndrome: Recent advances and controversies. *Current Opinion in Gastroenterology.* 2013; 29:650–661. Paper reviewing the controversies in the management /treatment of ZES. [PubMed: 24100728]
5. Thom AK, Norton JA, Axiotis CA, Jensen RT. Location, incidence and malignant potential of duodenal gastrinomas. *Surgery.* 1991; 110:1086–1093. [PubMed: 1745977]
6. Pipeleers-Marichal M, Somers G, Willems G, et al. Gastrinomas in the duodenum of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. *N Engl J Med.* 1990; 322:723–727. [PubMed: 1968616]
7. 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 patients from the literature. *Medicine (Baltimore).* 2004; 83(1):43–83. [PubMed: 14747767]
8. Jensen RT, Berna MJ, Bingham MD, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management and controversies. *Cancer.* 2008; 113(7 suppl):1807–1843. [PubMed: 18798544]
- ★ ★9. Jensen, RT. Zollinger-Ellison syndrome. In: Podolsky, DK, Camilleri, M, Fitz, JG, KAN, Shanahan, F., Wang, TC., editors. *Yamada's Textbook of Gastroenterology.* West Sussex, UK: John Wiley and Sons, Ltd., 16 A.D; p. 1078-1102. Recent chapter reviewing all aspects of ZES
10. Roy PK, Venzon DJ, Feigenbaum KM, et al. Gastric secretion in Zollinger-Ellison syndrome: correlation with clinical expression, tumor extent and role in diagnosis - A prospective NIH study of 235 patients and review of the literature in 984 cases. *Medicine (Baltimore).* 2001; 80(3):189–222. [PubMed: 11388095]
11. Ito T, Igarashi H, Uehara H, Jensen RT. Pharmacotherapy of Zollinger-Ellison syndrome. *Expert Opin Pharmacotherapy.* 2013; 14(3):307–321.
12. Jensen RT, Niederle B, Mitry E, et al. Gastrinoma (duodenal and pancreatic). *Neuroendocrinology.* 2006; 84(3):173–182. [PubMed: 17312377]

13. Osefo N, Ito T, Jensen RT. Gastric Acid hypersecretory States: recent insights and advances. *Curr Gastroenterol Rep*. 2009; 11(6):433–441. [PubMed: 19903418]
14. Jensen, RT., Norton, JA., Oberg, K. Neuroendocrine Tumors. In: Feldman, M.Friedman, L.S., Brandt, L.J., editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Diseases*. Philadelphia: Elsevier Saunders; 2016. p. 501-541.
15. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology*. 2016; 103(2):153–171. [PubMed: 26742109]
16. Anlauf M, Garbrecht N, Henopp T, et al. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. *World J*. 2006; 12(34): 5440–5446.
17. Jensen, RT., Gardner, JD. Gastrinoma. In: Go, VLW.DiMagno, EP.Gardner, JD.Lebenthal, E.Reber, HA., Scheele, GA., editors. *The Pancreas: Biology, Pathobiology and Disease*. New York: Raven Press Publishing Co; 1993. p. 931-978.
18. Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of Death and Prognostic Factors in Multiple Endocrine Neoplasia Type 1: A Prospective Study: Comparison of 106 MEN1/Zollinger-Ellison Syndrome Patients With 1613 Literature MEN1 Patients With or Without Pancreatic Endocrine Tumors. *Medicine (Baltimore)*. 2013; 92(3):135–181. [PubMed: 23645327]
19. Mignon M, Cadiot G. Natural history of gastrinoma: lessons from the past. *Ital J Gastroenterol Hepatol*. 1999; 31(Suppl 2):S98–S103. [PubMed: 10604111]
20. Ellison EH, Wilson SD. The Zollinger-Ellison syndrome: Re-appraisal and evaluation of 260 registered cases. *Ann Surg*. 1964; 160:512–530. [PubMed: 14206854]
21. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann Surg*. 1955; 142:709–728. [PubMed: 13259432]
22. Collen MJ, Howard JM, McArthur KE, et al. Comparison of ranitidine and cimetidine in the treatment of gastric hypersecretion. *Ann Intern Med*. 1984; 100:52–58. [PubMed: 6318628]
23. 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. [PubMed: 8362529]
24. Nieto JM, Pisegna JR. The role of proton pump inhibitors in the treatment of Zollinger-Ellison syndrome. *Expert Opin Pharmacother*. 2006; 7(2):169–175. [PubMed: 16433582]
25. Phan J, Benhammou JN, Pisegna JR. Gastric Hypersecretory States: Investigation and Management. *Curr Treat Options Gastroenterol*. 2015; 13(4):386–397. [PubMed: 26342486]
26. Metz DC, Sostek MB, Ruzniewski P, et al. Effects of esomeprazole on Acid output in patients with zollinger-ellison syndrome or idiopathic gastric Acid hypersecretion. *Am J Gastroenterol*. 2007; 102(12):2648–2654. [PubMed: 17764495]
27. 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(1):39–48. [PubMed: 15645403]
28. Metz DC, Strader DB, Orbuch M, et al. Use of omeprazole in Zollinger-Ellison: A prospective nine-year study of efficacy and safety. *Aliment Pharmacol Ther*. 1993; 7:597–610. [PubMed: 8161665]
29. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med*. 1999; 341(9):635–644. [PubMed: 10460814]
30. Norton JA, Fraker DL, Alexander HR, Jensen RT. Value of surgery in patients with negative imaging and sporadic zollinger-ellison syndrome. *Ann Surg*. 2012; 256(3):509–517. [PubMed: 22868363]
31. Atema JJ, Amri R, Busch OR, et al. Surgical treatment of gastrinomas: a single-centre experience. *HPB (Oxford)*. 2012; 14(12):833–838. [PubMed: 23134185]
32. Norton JA, Alexander HR, Fraker DL, et al. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. *Ann Surg*. 2001; 234(4):495–506. [PubMed: 11573043]

33. Ito T, Jensen RT. Imaging in multiple endocrine neoplasia type 1: recent studies show enhanced sensitivities but increased controversies. *Int J Endocr Oncol.* 2016; 3(1):53–66. [PubMed: 26834963]
34. Norton JA, Krampitz G, Jensen RT. Multiple Endocrine Neoplasia: Genetics and Clinical Management. *Surg Oncol Clin N Am.* 2015; 24(4):795–832. [PubMed: 26363542]
35. Bartsch DK, Albers MB. Controversies in surgery for multiple endocrine neoplasia type-1-associated Zollinger-Ellison syndrome. *Int J Endo Oncol.* 2015; 2(4):263–271.
36. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS Treatment Guidelines: Well-Differentiated Neuroendocrine Tumors of the Stomach and Pancreas. *Pancreas.* 2010; 39(6):735–752. [PubMed: 20664472]
37. Norton JA, Fraker DL, Alexander HR, et al. Surgery increases survival in patients with gastrinoma. *Ann Surg.* 2006; 244(3):410–419. [PubMed: 16926567]
38. Singh MH, Fraker DL, Metz DC. Importance of surveillance for multiple endocrine neoplasia-1 and surgery in patients with sporadic Zollinger-Ellison syndrome. *Clin Gastroenterol Hepatol.* 2012; 10(11):1262–1269. [PubMed: 22902777]
39. Fraker DL, Norton JA, Alexander HR, Venzon DJ, Jensen RT. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. *Ann Surg.* 1994; 220:320–330. [PubMed: 7916560]
40. Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors and survival in patients with longstanding Zollinger-Ellison syndrome. *J Clin Oncol.* 1999; 17:615–630. [PubMed: 10080607]
41. Ito T, Igarashi H, Jensen RT. Therapy of metastatic pancreatic neuroendocrine tumors (pNETs): recent insights and advances. *J Gastroenterol.* 2012; 47(9):941–960. [PubMed: 22886480]
42. 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. [PubMed: 17108778]
43. Grimaldi F, Fazio N, Attanasio R, et al. Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. *J Endocrinol Invest.* 2014; 37(9):875–909. [PubMed: 25038902]
44. Jensen RT, Cadiot G, Brandi ML, et al. ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Functional Pancreatic Endocrine Tumor Syndromes. *Neuroendocrinology.* 2012; 95(2):98–119. [PubMed: 22261919]
- ★45. Metz DC. Diagnosis of the Zollinger-Ellison syndrome. *Clin Gastroenterol Hepatol.* 2012; 10(2): 126–130. Paper reviewing the controversies in the diagnosis of ZES. [PubMed: 21806955]
46. 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(10):1055–1068. [PubMed: 19226290]
47. Cadiot G, Jais P, Mignon M. Diagnosis of Zollinger-Ellison syndrome. From symptoms to biological evidence. *Ital J Gastroenterol Hepatol.* 1999; 31:S147–S152. [PubMed: 10604120]
48. Banasch M, Schmitz F. Diagnosis and treatment of gastrinoma in the era of proton pump inhibitors. *Wien Klin Wochenschr.* 2007; 119(19–20):573–578. [PubMed: 17985090]
49. 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. [PubMed: 2598759]
50. Jais P, Mignon M. Normal serum gastrin concentration in gastrinoma [letter]. *Lancet.* 1995; 346:1421–1422.
51. Fishbeyn VA, Norton JA, Benya RV, et al. Assessment and prediction of long-term cure in patients with Zollinger-Ellison syndrome: the best approach. *Ann Intern Med.* 1993; 119:199–206. [PubMed: 8323088]
52. Norton JA, Venzon DJ, Berna MJ, et al. Prospective study of surgery for primary hyperparathyroidism (HPT) in Multiple Endocrine Neoplasia type 1 (MEN1), and Zollinger-Ellison syndrome (ZES): longterm outcome of a more virulent form of HPT. *Ann Surgery.* 2008; 247(3):501–510.

53. Rehfeld JF, Bardram L, Hilsted L, Poitras P, Goetze JP. Pitfalls in diagnostic gastrin measurements. *Clin Chem.* 2012; 58(5):831–836. [PubMed: 22419747]
- ★54. Rehfeld JF, Gingras MH, Bardram L, et al. The Zollinger-Ellison Syndrome and Mismeasurement of Gastrin. *Gastroenterology.* 2011; 140(5):1444–1453. Paper reporting unreliability of many gastrin commercial assays. [PubMed: 21315717]
55. Schubert ML, Peura DA. Control of gastric acid secretion in health and disease. *Gastroenterology.* 2008; 134(7):1842–1860. [PubMed: 18474247]
56. Papay KD, Falck VG, Poulsen SS, et al. Juvenile polyposis of the stomach--a novel cause of hypergastrinemia. *Nat Rev Gastroenterol Hepatol.* 2010; 7(10):583–588. [PubMed: 20808292]
57. Metz DC, Weber HC, Orbuch M, et al. *Helicobacter pylori* infection: a reversible cause of hypergastrinemia and hyperchlorhydria which can mimic Zollinger-Ellison syndrome. *Dig Dis Sci.* 1995; 40:153–159. [PubMed: 7821103]
58. Annibale B, Rindi G, D'Ambra G, et al. Antral gastrin cell hyperfunction and *helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1996; 10:607–615. [PubMed: 8853766]
59. Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas: a prospective study. *Ann Intern Med.* 1996; 125:26–34. [PubMed: 8644985]
- ★60. Ito T, Cadiot G, Jensen RT. Diagnosis of Zollinger-Ellison syndrome: Increasingly difficult. *World J Gastroenterol.* 2012; 18(39):5495–5503. Paper reviewing the controversies in diagnosis of ZES. [PubMed: 23112541]
61. 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. [PubMed: 3715400]
62. Vannella L, Sbrozzi-Vanni A, Lahner E, et al. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. *Aliment Pharmacol Ther.* 2011; 33(12):1361–1369. [PubMed: 21492197]
63. Delle Fave G, Marignani M, Moretti A, et al. Hypergastrinemia and enterochromaffin-like cell hyperplasia. *Yale J Biol Med.* 1998; 71:291–301. [PubMed: 10461360]
64. 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(3):198–202. [PubMed: 9085454]
65. Raines D, Chester M, Diebold AE, et al. A prospective evaluation of the effect of chronic proton pump inhibitor use on plasma biomarker levels in humans. *Pancreas.* 2012; 41(4):508–511. [PubMed: 22460728]
66. Sanduleanu S, DeBruine A, Stridsberg M, et al. Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid-suppressive therapy. *Eur J Clin Invest.* 2001; 31(9):802–811. [PubMed: 11589723]
67. Dhillon WS, Jayasena CN, Lewis CJ, et al. 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(Pt 2):153–155. [PubMed: 16536918]
68. Lamberts R, Creutzfeldt W, Stockmann F, et al. Long term omeprazole treatment in man: effects on gastric endocrine cell populations. *Digestion.* 1988; 39:126–135. [PubMed: 3410169]
69. Pregun I, Herszenyi L, Juhasz M, et al. Effect of proton-pump inhibitor therapy on serum chromogranin a level. *Digestion.* 2011; 84(1):22–28. [PubMed: 21304238]
70. Jansen JB, Klinkenberg-Knol EC, Meuwissen SG, et al. 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. [PubMed: 2199288]
71. Metz DC, Forsmark C, Lew EA, et al. Replacement of oral proton pump inhibitors with intravenous pantoprazole to effectively control gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Am J Gastroenterol.* 2001; 96(12):3274–3280. [PubMed: 11774936]
72. Oberg K, Couvelard A, Delle Fave G, et al. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Biochemical Markers. *Neuroendocrinology.* 2017

73. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type 1. *Am J Med.* 1994; 97:436–444. [PubMed: 7977432]
74. Lopez CL, Falconi M, Waldmann J, et al. Partial pancreaticoduodenectomy can provide cure for duodenal gastrinoma associated with multiple endocrine neoplasia type 1. *Ann Surg.* 2013; 257(2): 308–314. [PubMed: 22580937]
- ★75. Jensen RT, Norton JA. Treatment of Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1: Some Clarity But Continued Controversy. *Pancreas.* 2017; 46(5):589–594. Paper reporting difficulty/controversies in treating gastrinomas in MEN1/ZES patients. [PubMed: 28426491]
- ★76. Singh Ospina N, Donegan D, Rodriguez-Gutierrez R, Al-Hilli Z, Young WF Jr. Assessing for Multiple Endocrine Neoplasia Type 1 in Patients Evaluated for Zollinger-Ellison Syndrome- Clues to a Safer Diagnostic Process. *Am J Med.* 2017; 130(5):603–605. Paper proposing ZES be diagnosed by different methods. [PubMed: 28011308]
77. Berna MJ, Hoffmann KM, Long SH, et al. 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(6):331–364. [PubMed: 17108779]
- ★78. Poitras P, Gingras MH, Rehfeld JF. Secretin stimulation test for gastrin release in zollinger-ellison syndrome: to do or not to do? *Pancreas.* 2013; 42(6):903–904. Paper reviewing the utility of secretin test for ZES diagnosis. [PubMed: 23851427]
- ★79. Shah P, Singh MH, Yang YX, Metz DC. Hypochlorhydria and achlorhydria are associated with false-positive secretin stimulation testing for zollinger-ellison syndrome. *Pancreas.* 2013; 42(6): 932–936. Paper reporting false positive secretin tests in patients with hypo-/achlorhdria. [PubMed: 23851430]
80. Metz DC, Buchanan M, Purich E, Fein S. A randomized controlled crossover study comparing synthetic porcine and human secretins with biologically derived porcine secretin to diagnose Zollinger-Ellison Syndrome. *Aliment Pharmacol Ther.* 2001; 15(5):669–676. [PubMed: 11328261]
81. Matsubayashi H, Kawata N, Kakushima N, et al. A case of type 1 multiple endocrine neoplasia with esophageal stricture successfully treated with endoscopic balloon dilation and local steroid injection combined with surgical resection of gastrinomas. *BMC Gastroenterol.* 2017; 17(1):37. [PubMed: 28270118]
82. Lenhart A, Hassan M, Meighani A, Sadiq O, Siddiqui Y. A Perplexing Case of Abdominal Pain That Led to the Diagnosis of Zollinger-Ellison Syndrome. *Case Rep Gastrointest Med.* 2017; 2017:7636952. [PubMed: 28321346]
83. Amar A, Madhani K, Virk H, Butt Z. Zollinger-Ellison Syndrome: A Rare Case of Chronic Diarrhea. *Gastroenterology Res.* 2016; 9(6):103–104. [PubMed: 28058079]
84. Lee HW, Chung JW, Kim YJ, et al. Synchronous Peripancreatic Lymph Node Gastrinoma and Gastric Neuroendocrine Tumor Type 2. *Clin Endosc.* 2016; 49(5):483–487. [PubMed: 27209642]
85. Twerdahl EH, Costantino CL, Ferrone CR, Hodin RA. Primary Hepatic Gastrinoma. *J Gastrointest Surg.* 2016; 20(3):662–663. [PubMed: 26556475]
86. Goyal R, Debi U, Dey P, Prasad KK, Thapa BR. Zollinger-Ellison syndrome: an unusual case of chronic diarrhoea in a child. *Malays J Pathol.* 2016; 38(3):321–325. [PubMed: 28028304]
87. Sparkman BK, Earl TM. Sporadic, Primary Lymph Node Gastrinoma. *Am Surg.* 2016; 82(7):155–157. [PubMed: 27457843]
88. Alshikho MJ, Noureldine SI, Talas JM, et al. Zollinger-Ellison Syndrome Associated with von Recklinghausen Disease: Case Report and Literature Review. *Am J Case Rep.* 2016; 17:398–405. [PubMed: 27292293]
89. Zhang WD, Liu DR, Wang P, et al. Clinical treatment of gastrinoma: A case report and review of the literature. *Oncol Lett.* 2016; 11(5):3433–3437. [PubMed: 27123130]

90. Ogawa S, Wada M, Fukushima M, et al. Case of primary hepatic gastrinoma: Diagnostic usefulness of the selective arterial calcium injection test. *Hepatol Res.* 2015; 45(7):823–826. [PubMed: 25145887]
91. Harper S, Carroll RW, Frilling A, Wickremesekera SK, Bann S. Primary lymph node gastrinoma: 2 cases and a review of the literature. *J Gastrointest Surg.* 2015; 19(4):651–655. [PubMed: 25623161]
92. Teng A, Haas C, Lee DY, et al. Primary lymph node gastrinoma. A diagnosis of exclusion. A case for duodenotomy in the setting of a negative imaging for primary tumor: A case report and review of the literature. *Int J Surg Case Rep.* 2014; 5(11):849–852. [PubMed: 25462049]
93. Stroker E, Leone L, Vandeput Y, Borbath I, Lefebvre C. Severe symptomatic hypomagnesaemia induced by the chronic use of proton pump inhibitors: a case report of a patient with Zollinger-Ellison syndrome. *Acta Clin Belg.* 2014; 69(1):62–65. [PubMed: 24635401]
94. Lee NE, Lee YJ, Yun SH, et al. A case of Zollinger-Ellison syndrome in multiple endocrine neoplasia type 1 with urolithiasis as the initial presentation. *Korean J Gastroenterol.* 2013; 61(6): 333–337. [PubMed: 23877214]
95. Okada K, Sudo T, Miyamoto K, et al. The Selective Arterial Calcium Injection Test is a Valid Diagnostic Method for Invisible Gastrinoma with Duodenal Ulcer Stenosis: A Case Report. *Hiroshima J Med Sci.* 2016; 65(1):13–17. [PubMed: 27348901]
96. Atalar K, Warren OJ, Jacyna M, Jiao LR. Laparoscopic resection for primary lymph node gastrinoma. *Pancreas.* 2013; 42(4):723–725. [PubMed: 23591435]
97. Campana D, Fusaroli P, Cacciari G. Multiple gastrinomas of the duodenum in a patient with sporadic Zollinger-Ellison syndrome. *Endocrine.* 2013; 44(3):815–816. [PubMed: 23613167]
98. Citak EC, Taskinlar H, Arpacı RB, et al. Primary lymph node gastrinoma: a rare cause of abdominal pain in childhood. *J Pediatr Hematol Oncol.* 2013; 35(5):394–398. [PubMed: 23743959]
99. Jayaram P, Shindel A, Buxbaum J. Duodenal Gastrinoma Discovered on Evaluation for Incidental Gastric Carcinoid. *Clin Gastroenterol Hepatol.* 2017
100. Murase N, Uchida H, Tainaka T, et al. Laparoscopic-assisted pancreaticoduodenectomy in a child with gastrinoma. *Pediatr Int.* 2015; 57(6):1196–1198. [PubMed: 26711921]
101. Pinto-Sanchez MI, Yuan Y, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. *Cochrane Database Syst Rev.* 2017; 3:CD011194. [PubMed: 28271513]
102. Ahrens D, Behrens G, Himmel W, Kochen MM, Chenot JF. Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. *Int J Clin Pract.* 2012; 66(8):767–773. [PubMed: 22805269]
103. Corleto VD, Annibale B, Gibril F, et al. 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. [PubMed: 11563994]
104. Arnold R. Diagnosis and differential diagnosis of hypergastrinemia. *Wien Klin Wochenschr.* 2007; 119(19–20):564–569. [PubMed: 17985088]
105. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas PJ. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. *Aliment Pharmacol Ther.* 2015; 42(6):649–663. [PubMed: 26177572]
- ★106. Poitras P, Gingras MH, Rehfeld JF. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. *Clin Gastroenterol Hepatol.* 2012; 10(2):199–202. Paper reporting dangers of stopping PPIs in ZES. [PubMed: 21871248]
107. Gibril F, Reynolds JC, Chen CC, et al. Specificity of somatostatin receptor scintigraphy: a prospective study and the effects of false positive localizations on management in patients with gastrinomas. *J Nucl Med.* 1999; 40:539–553. [PubMed: 10210211]
- ★108. Ito T, Jensen RT. Molecular imaging in neuroendocrine tumors: recent advances, controversies, unresolved issues, and roles in management. *Curr Opin Endocrinol Diabetes Obes.* 2017; 24(1): 15–24. Paper reviewing the importance and potential pitfalls in use of molecular imaging of NETs including gastrinomas. [PubMed: 27875420]

109. Fendler WP, Barrio M, Spick C, et al. 68Ga-DOTATATE PET/CT interobserver agreement for neuroendocrine tumor assessments: results from a prospective study on 50 patients. *J Nucl Med*. 2016
110. Matsumura S, Okuyama Y, Doi R, et al. (68)Ga-DOTATOC-PET/CT for effective diagnosis and treatment of pancreatic tail gastrinoma with multiple liver metastases: a case report. *Nihon Shokakibyo Gakkai Zasshi*. 2016; 113(1):86–93. [PubMed: 26743558]
111. Kjaer A, Knigge U. Use of radioactive substances in diagnosis and treatment of neuroendocrine tumors. *Scand J Gastroenterol*. 2015; 50(6):740–747. [PubMed: 25959100]
112. Ambrosini V, Fanti S. 68Ga-DOTA-peptides in the diagnosis of NET. *PET Clin*. 2014; 9(1):37–42. [PubMed: 25029932]
113. Campana D, Brocchi E, Tomassetti P. Multiple gastric endocrine tumours and gastrinomas of the duodenum in a patient with ZES MEN 1. *Dig Liver Dis*. 2008; 40(6):476. [PubMed: 18282753]
114. McGuigan JE, Wolfe MM. Secretin injection test in the diagnosis of gastrinoma. *Gastroenterology*. 1980; 79:1324–1331. [PubMed: 7439637]
115. Deveney CW, Deveney KS, Jaffe BM, Jones RS, Way LW. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison syndrome). *Ann Intern Med*. 1977; 87:680–686. [PubMed: 931203]
116. 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. [PubMed: 3582916]
117. Dyck WP. Pancreatic hypersecretion in the Zollinger-Ellison syndrome. Case report. *Gastroenterology*. 1971; 60(1):90–95. [PubMed: 5544096]
118. Dreiling DA, Greenstein A. Pancreatic function in patients with Zollinger-Ellison syndrome. Observations concerning acid-bicarbonate secretion ratios. *Am J Gastroenterol*. 1972; 58(1):66–72. [PubMed: 4558375]
119. Schaffalitzky de Muckadell OB, Fahrenkrug J. Radioimmunoassay of secretin in plasma. *Scand J Clin Lab Invest*. 1977; 37(2):155–162. [PubMed: 616043]
120. Gedde-Dahl D. Radioimmunoassay of gastrin. Fasting serum levels in humans with normal and high gastric acid secretion. *Scand J Gastroenterol*. 1974; 9(1):41–47. [PubMed: 4476922]
121. Wesdorp RI, Fischer JE. Plasma-gastrin and acid secretion in patients with peptic ulceration. *Lancet*. 1974; 2(7885):857–860. [PubMed: 4137887]
122. Steen J, Herning M, Christiansen PM, Rehfeld JF. Relationship between basal serum gastrin concentrations and gastric acid secretion in peptic ulcer disease. *Scand J Gastroenterol*. 1980; 15(8):949–952. [PubMed: 7233069]
123. Trudeau WL, McGuigan JE. Relations between serum gastrin levels and rates of gastric hydrochloric acid secretion. *N Engl J Med*. 1971; 284(8):408–412. [PubMed: 5540478]
124. Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. *Clin Exp Gastroenterol*. 2017; 10:19–27. [PubMed: 28223833]
125. Dixon MF, Genta RM, Yardley JHCP. Classification and grading of gastritis. The upgraded Sydney System. International workshop on the histopathology of gastritis, Houston 1994. *Am J Surg Pathol*. 1996; 20(10):1161–1181. [PubMed: 8827022]
126. Dai YC, Tang ZP, Zhang YL. How to assess the severity of atrophic gastritis. *World J Gastroenterol*. 2011; 17(13):1690–1693. [PubMed: 21483628]
127. 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(12):1467–1473. [PubMed: 17101299]
128. Corleto VD, Goebel SU, Panzuto F, et al. Co-existence of hyperparathyroidism, hypergastrinemia, and multiple gastric carcinoids is not always due to incomplete expression of the MEN-1 syndrome. *Dig Liver Dis*. 2003; 35(8):585–589. [PubMed: 14567464]
129. Corleto VD, Minisola S, Moretti A, et al. Prevalence and causes of hypergastrinemia in primary hyperparathyroidism: a prospective study. *J Clin Endocrinol Metab*. 1999; 84(12):4554–4558. [PubMed: 10599718]

130. Massironi S, Cavalcoli F, Rossi RE, et al. Chronic autoimmune atrophic gastritis associated with primary hyperparathyroidism: a transversal prospective study. *Eur J Endocrinol.* 2013; 168(5): 755–761. [PubMed: 23447517]
131. Lamers CB, Rotter JI, Jansen JB. Gastrin cell function in familial multiple endocrine neoplasia type I. *Gut.* 1988; 29:1358–1363. [PubMed: 2904393]
132. Skogseid B, Oberg K, Benson L, et al. A standardized meal stimulation test of the endocrine pancreas for early detection of pancreatic endocrine tumors in multiple endocrine neoplasia type I syndrome: five years experience. *J Clin Endocrinol Metab.* 1987; 64(6):1233–1240. [PubMed: 2883195]
133. Weber HC, Venzon DJ, Jensen RT, Metz DC. Studies on the interrelation between Zollinger-Ellison syndrome, *Helicobacter pylori* and proton pump inhibitor therapy. *Gastroenterology.* 1997; 112:84–91. [PubMed: 8978346]
134. Naswa N, Sharma P, Soundararajan R, et al. Diagnostic performance of somatostatin receptor PET/CT using (68)Ga-DOTANOC in gastrinoma patients with negative or equivocal CT findings. *Abdom Imaging.* 2013; 38(3):552–560. [PubMed: 22743840]
135. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. 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. [PubMed: 8404961]
136. Sato M, Kiil F, Nishitani A, et al. Large and asymptomatic pancreatic islet cell tumor in a patient with multiple endocrine neoplasia type I. *Endocrine.* 2000; 13(3):263–266. [PubMed: 11216636]
137. Hayashi M, Floyd JC Jr, 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(4):681–694. [PubMed: 14970]
138. Liu TH, Tseng HC, Zhu Y, et al. Insulinoma. An immunocytochemical and morphologic analysis of 95 cases. *Cancer.* 1985; 56(6):1420–1429. [PubMed: 2992737]
139. Yamaguchi K, Enjoji M. Endocrine neoplasms of the pancreas: a clinicopathologic study of 24 cases and immunohistochemical remarks. *Surg Today.* 1992; 22(4):305–312. [PubMed: 1392340]
140. Gurevich L, Kazantseva I, Isakov VA, et al. The analysis of immunophenotype of gastrin-producing tumors of the pancreas and gastrointestinal tract. *Cancer.* 2003; 98(9):1967–1976. [PubMed: 14584081]
141. Heitz PU, Kasper M, Polak JM, Kloppel G. Pancreatic endocrine tumors. Immunohistochemical analysis of 125 tumors. *Hum Pathol.* 1982; 13:263–271. [PubMed: 7076209]
142. 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. [PubMed: 6127037]
143. Tomita T. Immunocytochemical staining for islet amyloid polypeptide in pancreatic endocrine tumors. *Islets.* 2011; 3(6):344–351. [PubMed: 21983096]
144. Epelboym I, Mazeh H. Zollinger-Ellison syndrome: classical considerations and current controversies. *Oncologist.* 2014; 19(1):44–50. [PubMed: 24319020]
145. Granberg D. Biochemical Testing in Patients with Neuroendocrine Tumors. *Front Horm Res.* 2015; 44:24–39. [PubMed: 26303702]
146. Redeen S, Petersson F, Kechagias S, Mardh E, Borch K. Natural history of chronic gastritis in a population-based cohort. *Scand J Gastroenterol.* 2010; 45(5):540–549. [PubMed: 20180646]
147. Yao JC, Eisner MP, Leary C, et al. Population-based study of islet cell carcinoma. *Ann Surg Oncol.* 2007; 14(12):3492–3500. [PubMed: 17896148]
148. Kaemmerer D, Peter L, Lupp A, et al. Molecular imaging with (68)Ga-SSTR PET/CT and correlation to immunohistochemistry of somatostatin receptors in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2011; 38(9):1659–1668. [PubMed: 21626438]
149. Sclafani F, Carnaghi C, Di Tommaso L, et al. Detection of somatostatin receptor subtypes 2 and 5 by somatostatin receptor scintigraphy and immunohistochemistry: clinical implications in the diagnostic and therapeutic management of gastroenteropancreatic neuroendocrine tumors. *Tumori.* 2011; 97(5):620–628. [PubMed: 22158494]

150. Sollini M, Erba PA, Fraternali A, et al. PET and PET/CT with 68gallium-labeled somatostatin analogues in Non GEP-NETs Tumors. *ScientificWorldJournal*. 2014; 2014:194123. [PubMed: 24693229]
151. Norton JA, Alexander HR, Fraker DL, Venzon DJ, 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 (ZES)? *Ann Surg*. 2004; 239(5):617–626. [PubMed: 15082965]
152. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann Surg*. 2004; 240(5):757–773. [PubMed: 15492556]
153. Ruszniewski P, Amouyal P, Amouyal G, et al. Localization of gastrinomas by endoscopic ultrasonography in patients with Zollinger-Ellison syndrome. *Surgery*. 1995; 117:629–635. [PubMed: 7778027]
154. Goldman JA, Blanton WP, Hay DW, Wolfe MM. Case Report: False-Positive Secretin Stimulation Test for Gastrinoma Associated with the Use of Proton Pump Inhibitor Therapy. *Clin Gastroenterol Hepatol*. 2009; 7(5):600–602. [PubMed: 19245850]
155. Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol*. 2005; 19(5):783–798. [PubMed: 16253900]
156. Jensen RT. Overview of chronic diarrhea caused by functional neuroendocrine neoplasms. *Semin Gastrointest Dis*. 1999; 10(4):156–172. [PubMed: 10548409]
157. Zimmer V, Schilling MK, Buecker A, Lammert F, Raedle J. Chronic diarrhea responding to proton pump inhibitors: a clinical sign of Zollinger-Ellison syndrome. *Am J Med*. 2009; 122(11):e9–e10.
158. Mignon M, Ruszniewski P, Haffar S, et al. Current approach to the management of tumoral process in patients with gastrinoma. *World J Surg*. 1986; 10:703–710. [PubMed: 2875567]
159. Law EH, Badowski M, Hung YT, et al. Association Between Proton Pump Inhibitors and Microscopic Colitis. *Ann Pharmacother*. 2017; 51(3):253–263. [PubMed: 27733667]
160. Masclee GM, Coloma PM, Kuipers EJ, Sturkenboom MC. Increased risk of microscopic colitis with use of proton pump inhibitors and non-steroidal anti-inflammatory drugs. *Am J Gastroenterol*. 2015; 110(5):749–759. [PubMed: 25916221]
161. Vaezi MF, Yang YX, Howden CW. Complications of Proton Pump Inhibitor Therapy. *Gastroenterology*. 2017
162. Sadowski SM, Millo C, Cottle-Delisle C, et al. Results of (68)Gallium-DOTATATE PET/CT Scanning in Patients with Multiple Endocrine Neoplasia Type 1. *J Am Coll Surg*. 2015; 221(2): 509–517. [PubMed: 26206648]
163. Gibril F, Chen Y-J, Schrupp DS, et al. Prospective study of thymic carcinoids in patients with Multiple Endocrine Neoplasia Type 1. *J Clin Endocrinol Metab*. 2003; 88(3):1066–1081. [PubMed: 12629087]
164. Gibril F, Reynolds JC, Roy PK, et al. Ability of somatostatin receptor scintigraphy to identify patients with localized gastric carcinoids: A prospective study. *J Nucl Med*. 2000; 41(10):1646–1656. [PubMed: 11037994]
165. Lastoria S, Marciello F, Faggiano A, et al. Role of Ga-DOTATATE PET/CT in patients with multiple endocrine neoplasia type 1 (MEN1). *Endocrine*. 2016; 52(3):488–494. [PubMed: 26242621]
166. Rusak E, Chobot A, Krzywicka A, Wenzlau J. Anti-parietal cell antibodies - diagnostic significance. *Adv Med Sci*. 2016; 61(2):175–179. [PubMed: 26918709]
167. Dinis-Ribeiro M, Kuipers EJ. Identification of gastric atrophic changes: from histopathology to endoscopy. *Endoscopy*. 2015; 47(6):533–537. [PubMed: 25970548]
168. Dursun M, Yilmaz S, Yukselen V, et al. Evaluation of optimal gastric mucosal biopsy site and number for identification of *Helicobacter pylori*, gastric atrophy and intestinal metaplasia. *Hepatogastroenterology*. 2004; 51(60):1732–1735. [PubMed: 15532815]
169. Lahner E, Norman GL, Severi C, et al. Reassessment of intrinsic factor and parietal cell autoantibodies in atrophic gastritis with respect to cobalamin deficiency. *Am J Gastroenterol*. 2009; 104(8):2071–2079. [PubMed: 19491828]

170. Chen TK, Wu CH, Lee CL, Lai YC, Yang SS. Endoscopic ultrasonography in the differential diagnosis of giant gastric folds. *J Formos Med Assoc.* 1999; 98(4):261–264. [PubMed: 10389370]
171. Cooper BT. Menetrier's disease. *Dig Dis.* 1987; 5(1):33–40. [PubMed: 3297433]
172. Lambrecht NW. Menetrier's disease of the stomach: a clinical challenge. *Curr Gastroenterol Rep.* 2011; 13(6):513–517. [PubMed: 21931998]
173. Gibril F, Lindeman RJ, Abou-Saif A, et al. Retained gastric antrum syndrome. A forgotten, treatable cause of refractory peptic ulcer disease. *Dig Dis Sci.* 2001; 46(3):610–617. [PubMed: 11318541]
174. Frucht H, Howard JM, Slaff JI, et al. Secretin and calcium provocative tests in the Zollinger-Ellison syndrome: A prospective study. *Ann Intern Med.* 1989; 111:713–722. [PubMed: 2572194]

Future perspective

Zollinger-Ellison syndrome (ZES) is an uncommon disease, in which, despite more than 4000 articles, numerous practice guidelines and widely agreed on criteria for diagnosis, the delay in diagnosis (4–7 years in older studies) persists and likely is becoming even longer. In contrast to insulinoma, where the diagnostic criteria of demonstrating during a fast, the presence of hypoglycemia with elevated plasma insulin values are well accepted (i.e., inappropriate fasting hyperinsulinemia), controversy exists with ZES. The established diagnostic criteria for ZES require the demonstration of inappropriate hypergastrinemia (i.e. fasting hypergastrinemia in the presence of an acidic gastric pH 2), but they were only used in 5% of recently reported ZES cases. This failure to use established criteria is primarily due to limited access to gastric acid testing and the widespread use of PPIs. In addition to treating (and potentially masking) the symptoms of ZES by reducing gastric acid production, PPIs also cause hypergastrinemia. Therefore, to definitively establish inappropriate hypergastrinemia in a patient on PPIs, PPIs need to be withheld to assess gastric acidity. This cumbersome process is not without risk in a true ZES patient. Two approaches can be proposed to deal with this problem. First, to continue to require these established criteria and to try and increase their utilization through physician education. However, this has largely been attempted for many years with guidelines from ENETS and NANETS, and numerous other reviews and position papers on this subject, and generally has had no effect. An alternative approach would be to propose, for discussion, new criteria, which would support to varying degrees, the diagnosis of ZES, without requiring gastric acid testing, which might be more acceptable to practicing clinicians. These new criteria may help to standardize diagnostic testing for ZES in the community and permit referral to a unit with ZES expertise as necessary. However, it is important to remember that the newly proposed criteria do have exceptions and that they only support the diagnosis. We therefore recommend that consideration be given to establishing a firm diagnosis using the older established criteria prior to any significant management decisions (e.g., elective surgery for cure).

Practice points

- Zollinger-Ellison syndrome (ZES) is due to a neuroendocrine tumor (NET) ectopically secreting gastrin resulting in hyperchlorhydria causing severe peptic disease and/or diarrhea.
- The correct diagnosis of ZES is an essential step for its proper management.
- Classically, all guidelines emphasize that both fasting hypergastrinemia and hyperchlorhydria (gastric acid pH ≥ 2) need to be demonstrated to support the diagnosis of ZES.
- No level of hypergastrinemia alone is sufficient to make the diagnosis of ZES.
- Proton pump inhibitors (PPIs) are now widely used for many conditions and are making the diagnosis of ZES more difficult because they can cause hypergastrinemia in normals and non-ZES patients and also delay the diagnosis of ZES by masking symptoms.
- Although current guidelines stress that in most patients the diagnosis of ZES requires holding PPIs, this was not done in 95% of recently reported ZES cases.
- Withdrawal of PPIs to assess gastric acidity in potential ZES patients can be difficult and associated with severe peptic complications if not appropriately performed.
- Access to gastric analysis is limited and routine assessments of gastric pH are not commonly performed.
- While the recommended criteria for diagnosing ZES have been validated, they are not being used.
- This paper, for the first time proposes for discussion new criteria stratified by the presence or absence of PPI therapy and without the need for assessing gastric acidity that could be considered to support the diagnosis of ZES, and which could be more easily used and accepted by most clinicians, even if they are imperfect.

Table 1**Currently recommended approach and criteria for the biochemical diagnosis of ZES**

- I. When ZES is suspected, the initial test recommended is a **fasting serum gastrin (FSG)** determination in the absence of antisecretory therapy (Sensitivity- 98–100% in ZES patients various series [42]).
[Today the FSG determination is frequently performed when ZES is first suspected and in many cases patients are taking antisecretory therapy. If the FSG is not elevated, it should be repeated, and if it remains normal, ZES is essentially excluded (>97%) except for uncommon exceptions ⁽¹⁾. However, even if the FSG is elevated, ZES cannot be diagnosed without confirmation of concomitant inappropriate secretion of gastric acid and exclusion of other rare conditions (e.g., retained antrum syndrome)].
- II. An elevated FSG can only be accurately interpreted together with a measure of gastric secretory capacity (usually a **gastric pH**) to confirm the presence of inappropriate hypergastrinemia. This generally requires delaying or stopping gastric antisecretory therapy, which is a potentially dangerous maneuver particularly if the patient is taking PPI's and not performed under appropriate conditions.
- III. If the **FSG is increased >10-fold** [generally >1000 pg/ml, with normal <100 pg/ml] and **the gastric pH is 2**, then ZES is present [retained gastric antrum syndrome [173] can usually be excluded by history] (The combination of FSG>10 fold increased and gastric pH 2 is present in 32% of ZES patients [42, 174].
- IV. If the **FSG is increased, <10-fold** [generally <1000 pg/ml with normal <100 pg/ml] and **the gastric pH is 2, additional testing is recommended** (either a **secretin test or a basal acid output (BAO)**). [Some have used sensitive imaging modalities (such as ⁶⁸Ga-DOTATATE PET/CT positivity as an alternative approach instead] ⁽²⁾
- V. A **secretin test(performed off PPIs)** demonstrating an increase in serum gastrin of >120 pg/ml has a sensitivity of 94% and specificity of 100% for ZES [77] ⁽³⁾. A **BAO>15 mEq/hr** (no previous gastric surgery; >5 mEq/hr after previous gastric acid reducing surgery) with the FSG/pH changes listed in IV above, establishes the diagnosis of ZES [10, 17, 42].

⁽¹⁾ZES patients post incomplete gastrinoma resection [51], MEN1/ZES patients post effective parathyroidectomy (usually 3.5–4 gland resection) for hyperparathyroidism [52], and uncommonly other ZES patients (0–2%) [42] can have a normal FSG.

⁽²⁾The role of imaging for diagnosis of ZES has not been systematically studied and is not clearly defined at present.

⁽³⁾Achlorhydria is a well-recognized cause of false-positive secretin testing [79, 116]

Table 2

Causes of hypergastrinemia

I. Appropriate (Physiological) hypergastrinemia with achlorhydria/hypochlorhydria	
1.	Chronic atrophic gastritis (CAG)/pernicious anemia (common)
2.	Treatment with potent gastric acid antiseecretory agents [especially PPIs] (common)
3.	Chronic renal failure (uncommon)
4.	Pangastritis <i>H. pylori</i> infection (common)
5.	Post acid-reducing surgery/vagotomy (uncommon)
II. Inappropriate Hypergastrinemia with hyperchlorhydria	
1.	Antral predominant <i>H. pylori</i> infection (common)
2.	Gastric outlet obstruction
3.	Antral G cell hyperfunction/hyperplasia (uncommon)
4.	Chronic renal failure (uncommon)
5.	Short bowel syndrome (rare)
6.	. Retained gastric antrum syndrome (rare)
7.	Juvenile polyposis of the stomach(rare)
8.	ZES (uncommon)
III. Assay Error	

Table 3

Possible new criteria for diagnosing ZES in patients with **Fasting Hypergastrinemia in the absence of PPI therapy**

- A. Strongly supportive of ZES diagnosis**
1. Active peptic ulcer disease (PUD) or a history compatible with recent PUD or improvement in diarrhea with PPIs combined with:
 - a. a positive somatostatin receptor scintigraphy imaging (SRI) with either ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging.
 - b. a positive biopsy or cytology for a neuroendocrine tumor (NET) (stronger support if a gastrinoma is found)
 - c. a positive secretin test
 - d. known or strongly suspected MEN1 syndrome (i.e., a positive family history, hyperparathyroidism or pituitary disease)
 2. A patient with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism or pituitary disease) with a positive gastrinoma by cytology/biopsy
- B. Moderately supportive of ZES diagnosis (consider this a tentative diagnosis)**
1. Positive somatostatin receptor scintigraphy imaging (SRI) with either ^{68}Ga -DOTATATE PET/CT or ^{111}In -DTPA-octreotide with SPECT/CT imaging (sporadic disease only) or positive cytology or biopsy for a NET, ideally a gastrinoma, (sporadic disease or MEN1 syndrome present) with a biopsy-proven absence of atrophic gastritis and negative autoimmune markers. ^(1,2)
- C. Weakly supportive of ZES diagnosis (insufficient alone for even a tentative diagnosis)**
1. A patient with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism or pituitary disease) with positive imaging or an SRI ⁽¹⁾
 2. MEN1 syndrome absent but positive SRI or imaging for possible tumor ⁽³⁾.

⁽¹⁾ Under such conditions a NET is confirmed but since MEN1 patients develop multiple NETs in various locations NET(s) identified on SRI may not be a gastrinoma(s) [8, 8, 18, 18, 33, 33, 162, 162].

⁽²⁾ Five biopsies (2-antrum, 2-corpus, 1-incisura angularis) of the stomach are recommended to diagnose atrophic gastritis [124, 125].

⁽³⁾ SRI can be positive in nongastrinoma NETs, numerous other tumors and both physiological and pharmacologic processes [see text], so alone is not specific for gastrinoma [107, 108, 135].

Table 4

Possible new criteria supporting the diagnosis of ZES in patients with **Fasting Hypergastrinemia taking PPIs** ⁽¹⁾

- A. Moderately supportive of ZES diagnosis (ZES is likely)**
 1. In a patient with or without MEN1 with active peptic ulcer disease (PUD) or a history compatible with recent PUD or improvement in diarrhea with PPIs combined with a positive biopsy or cytology for a neuroendocrine tumor (NET) (stronger support if a gastrinoma is found).
 2. In a patient without MEN1 with active peptic ulcer disease (PUD) or a history compatible with recent PUD or improvement in diarrhea with PPIs combined with a positive somatostatin receptor scintigraphy imaging (SRI) with either ⁶⁸Ga-DOTATATE PET/CT or ¹¹¹In-DTPA-octreotide with SPECT/CT imaging. ⁽²⁾
- B. Weakly supportive of ZES diagnosis (consider this a tentative diagnosis)**
 1. In a patient without active PUD or history of diarrhea responding to PPIs without MEN1 with a biopsy-proven absence of atrophic gastritis and negative autoimmune markers with a positive SRI ^(3,4)
 2. In a patient without active PUD or history of diarrhea responding to PPIs with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism or pituitary disease) with a biopsy-proven absence of atrophic gastritis. ⁽³⁾ and negative autoimmune markers. ⁽⁴⁾
- C. Minimally supportive of ZES diagnosis (consider this a possible diagnosis only)**
 1. In a patient without active PUD or history of diarrhea responding to PPIs without MEN1 with a positive SRI
 2. A patient with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism or pituitary disease) without active PUD or history of diarrhea responding to PPIs with prominent gastric folds ⁽⁵⁾.

⁽¹⁾ The potential for a false-positive secretin test in patients with hypo-/achlorhdria limits the usefulness of the secretin test in patients taking PPIs unless the gastric pH ≥ 2 .

⁽²⁾ Under these conditions a NET is likely but since MEN1 patients develop multiple NETs in various locations NET(s) a positive SRI or biopsy may not be a gastrinoma(s) [8, 18, 33, 162]

⁽³⁾ Five biopsies (2-antrum, 2-corpus, 1-incisura angularis) of the stomach are recommended to diagnose atrophic gastritis [124, 125].

⁽⁴⁾ Biopsy and autoimmune markers can both be negative in confirmed autoimmune gastropathy [124, 125].

⁽⁵⁾ Prominent gastric folds are present in 92% of ZES patients when initially seen, however they are not specific for ZES [2]