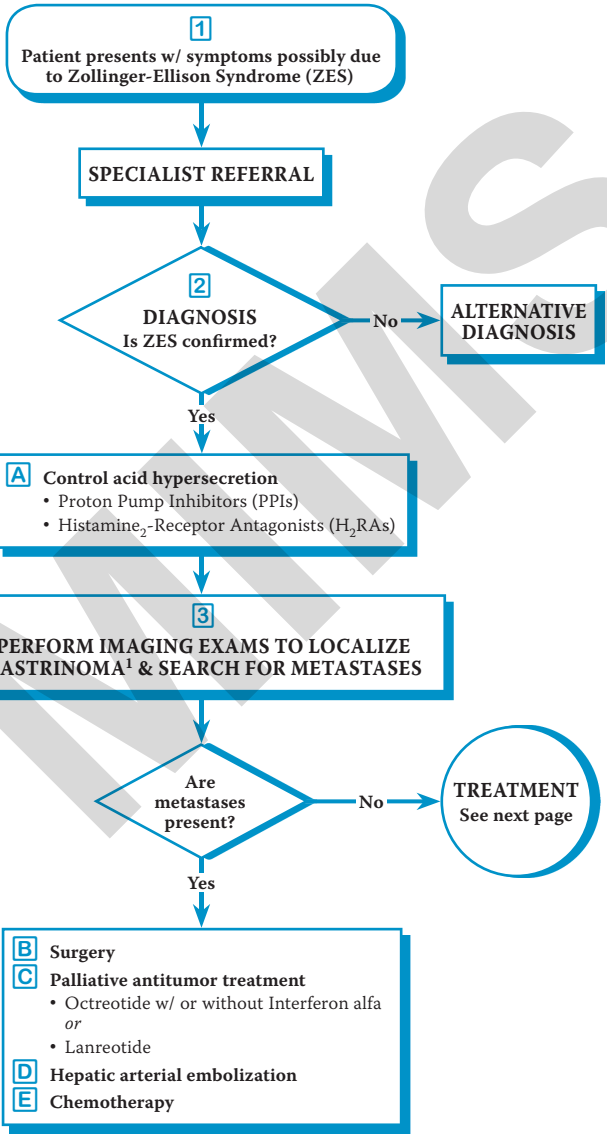
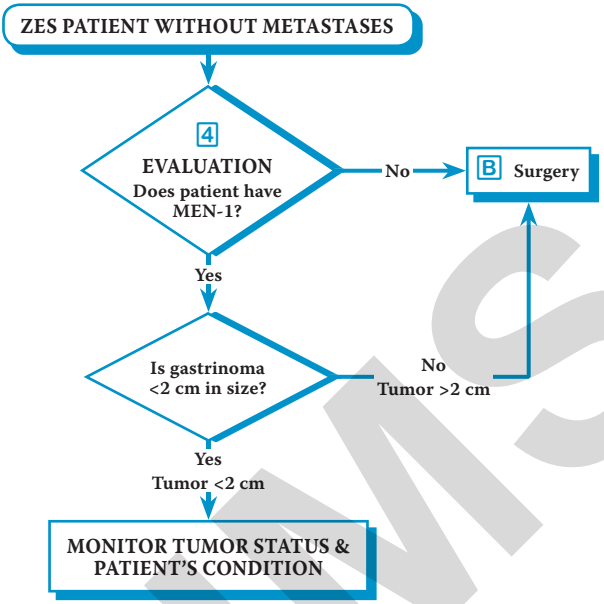
Zollinger-Ellison Syndrome (1 of 10)



[1]Please refer to Neuroendocrine Tumors Disease Management Chart for more information.



1 ZOLLINGER-ELLISON SYNDROME (ZES)

- Disease entity which refers to the triad of severe peptic ulcer disease (PUD), gastric acid hypersecretion & non-beta cell gastrin-secreting tumor primarily of the pancreas & duodenum (gastrinoma)
- Approximately two-thirds of patients have sporadic ZES while the rest is part of multiple endocrine neoplasia type 1 (MEN-1)
  - Gastrinomas that occur in relation w/ MEN-1 are associated w/ a lower chance of metastases compared to gastrinomas in sporadic ZES

Epidemiology

- Estimated incidence of ZES is 0.1-3 patients per million population
- Most patients are diagnosed between the ages of 20 & 65, but as old as 90 & as young as 7 have been identified
  - Mean age of onset is 41 years, w/ a slight male predominance
  - Mean delay in the diagnosis is 5-6 years; the widespread use of PPIs contributes significantly to the delay in diagnosis

Signs & Symptoms

ZES should be considered in the differential diagnoses of patients who present w/ abdominal pain, malabsorption & chronic watery diarrhea

Abdominal Pain

- Most common symptom, typically felt in the epigastric area & may mimic PUD
- Pancreatitis, which may cause abdominal pain & malabsorption, may occur concomitantly w/ ZES

Diarrhea

- Occurs secondary to malabsorption that results from large amounts of gastric acid that go into the small intestine, causing inactivation of pancreatic digestive enzymes & damage to the gut mucosa
- Malabsorption leading to diarrhea (& sometimes steatorrhea) may also be caused by precipitation of bile salts
- Diarrhea is seen less frequently in patients w/ MEN-1-associated ZES than in those w/ sporadic ZES
- May occur together w/ abdominal pain in about half of patients w/ ZES

Heartburn

- May mimic gastroesophageal reflux disease (GERD)

GI Bleeding

- Often develops as a consequence of peptic ulceration

Other Symptoms

- Nausea & vomiting (N/V), weight loss

2 DIAGNOSIS

- A high index of clinical awareness is necessary to correctly diagnose ZES

Physical Exam

The clinical presentation of ZES may be obscure & the physical exam may be normal

- Pallor secondary to GI bleeding
- Epigastric tenderness
- Dental erosions which are usually associated w/ symptoms of gastroesophageal reflux
- Hepatomegaly in patients w/ liver metastases

Other Clinical Features Suspicious of ZES

- Multiple duodenal &/or jejunal ulcers; postbulbar duodenal ulcer
- PUD that is poorly responsive to medical therapy
- PUD associated w/ chronic diarrhea
- PUD not associated w/ *Helicobacter pylori* or nonsteroidal anti-inflammatory drugs (NSAIDs) use
- Family history of PUD & hypercalcemia
- In patients in whom MEN-1-associated ZES is considered, symptoms &/or a family history of associated disorders ie hypercalcemia, nephrolithiasis, pituitary disorders & hyperparathyroidism should be elicited

Lab Exams

Fasting Serum Gastrin

- Best single screening test
- Gastric analysis performed concomitantly w/ serum fasting gastrin measurement increases the accuracy of the diagnosis of ZES
  - Gastric pH analysis is used to exclude hypergastrinemia resulting from achlorhydria, which may be secondary to chronic atrophic gastritis or severe *H pylori*-associated chronic gastritis
- A markedly increased serum gastrin level (>1000 pg/mL or 475 pmol/L) is specific for ZES, but is not sensitive
  - Many patients w/ gastrinoma have gastrin levels <1000 pg/ml, but normal levels of serum gastrin are very rare in untreated ZES patients
- However, about 2/3 of patients w/ ZES have serum gastrin concentrations <10 times the upper limit of normal, generally between 150 & 1000 pg/mL (or between 75 & 475 pmol/L)
  - Higher levels are more likely w/ pancreatic (compared w/ duodenal) tumors, larger tumor size, & w/ metastatic disease
- Patients should be instructed to discontinue medications that may inhibit gastric acid secretion & produce false-positive gastrin results (eg proton pump inhibitors or PPIs) at least 1 week prior to serum gastrin testing
- Serial determinations over several days should be done, because fasting gastrin levels may fluctuate from day to day
- Physicians should be aware of other medical conditions that may give rise to increased serum gastrin levels
  - Hyperlipidemia
  - Renal failure
  - Primary hyperparathyroidism
  - Vagotomy without gastric resection
  - Massive small bowel resection
  - Gastric outlet obstruction

Secretin Stimulation Test

- Should be performed in all patients suspected to have ZES whose fasting serum gastrin level is nondiagnostic
- Baseline gastrin levels are obtained twice prior to administering secretin test
- Secretin is administered via the IV route after an overnight fast, after which serum gastrin levels are measured after 2, 5, 10, 15 & 20 minutes
- ZES patients exhibit a rapid rise in gastrin levels; peak serum gastrin usually seen by 10 minutes
- A positive secretin test is most commonly defined by an elevation of serum gastrin of ≥200 pg/mL (95 pmol/L) above the baseline
  - A large study done on ZES patients & literature-based cases recommends a cutoff of >120 pg/mL which was associated w/ the highest sensitivity & specificity
- Proton pump-inhibiting medications should be discontinued 1 week before the test & patients placed on an H_2 receptor antagonist, which should be discontinued 24 hours prior to testing
- Contraindicated in patients w/ acute pancreatitis

Gastric Acid Secretory Tests

- Although may provide an ancillary role, this test is now uncommonly performed & measured
- ZES patients have an increased basal acid output (BAO): >10.6 meq/hr in men, >5.6 mEq/hr in women
- A gastric pH <2 together w/ a basal gastric secretory volume >140 mL/hr in patients without prior gastric acid-reducing interventions is highly suggestive of ZES
- Maximal acid output monitoring is infrequently performed
- Elevated serum gastrin level w/ achlorhydria makes ZES extremely unlikely

2 DIAGNOSIS (CONT'D)

Lab Exams (Cont'd)

Serum Chromogranin A (Serum CGA)

- A general marker for well-differentiated neuroendocrine tumors but does not differentiate between the various tumor subtypes
- Increased in most patients w/ gastrinomas, w/ the level of elevation correlating w/ tumor volume
- Less sensitive & specific than measurement of serum gastrin, but it may be used as a confirmatory test in difficult cases

Calcium Infusion Study

- Less sensitive & specific compared to the secretin stimulation test & more burdensome to perform
- Usually reserved for patients w/ gastric acid hypersecretion in whom there is a strong clinical suspicion of gastrinoma despite a negative secretin test

3 IMAGING EXAMS FOR LOCALIZATION OF GASTRINOMA

- Once gastric acid hypersecretion has been controlled, imaging exams should be done to locate the tumor (gastrinoma)
- Imaging exams to localize the gastrinoma & to determine the presence of metastases are important in planning the proper management strategy for ZES
- Most gastrinomas are located in the "gastrinoma triangle"
  - Defined superiorly by the confluence of the cystic & common bile duct, inferiorly by the junction of the 2nd & 3rd portions of the duodenum & medially by the junction of the neck & body of the pancreas
  - 80% of the gastrinomas within the gastrinoma triangle are curable
- Gastrinomas in patients w/ MEN-1 commonly develop in the duodenum, are multiple, & <2 cm, while sporadic gastrinomas are found in the pancreas, are solitary, & >2 cm

Somatostatin Receptor Scintigraphy (SRS)

- Imaging method of choice because of its high sensitivity in detecting primary or metastatic lesions in ZES
- Detects extrahepatic & lymph node involvement more reliably than computed tomography (CT) & magnetic resonance imaging (MRI)
- Superior to bone scan in detecting bone metastases
- Able to distinguish hepatic hemangiomas from metastatic gastrinomas in ZES patients seen to have hepatic masses via other imaging modalities
- Able to differentiate between gastrinomas & coexisting carcinoid tumors of the stomach in patients w/ MEN-1-associated ZES
- Disadvantage: Does not give reliable data about tumor size & exact location (eg duodenum vs pancreatic head)
  - CT scan w/ contrast is therefore also recommended

Computed Tomography (CT)

- Helical CT is highly sensitive for the detection of primary pancreatic tumors & hepatic metastases
- May provide additional information about tumor size & location

Magnetic Resonance Imaging (MRI)

- Has a high sensitivity for detecting hepatic metastases
- Disadvantage: Less sensitive for detection of primary pancreatic tumors

Endoscopic Ultrasound (EUS)

- Has a sensitivity of 80-90% for the detection of pancreatic islet cell tumors
- Allows fine needle aspiration for histological identification
- Disadvantage: Often misses primary duodenal gastrinomas

Other Imaging Techniques

- Useful imaging studies for small gastrinomas may include hybrid scanning w/ SRS & CT or MRI, & use of PET scan w/ somatostatin analogs labeled w/ gallium-68

Common Sites of Gastrinoma Tumor Metastases

- Only the presence of metastases or gross invasion of normal tissues remains the generally accepted criterion for malignancy

Liver

- Site of major metastases for gastrinomas
- Pancreatic gastrinomas >3 cm in size are associated w/ a higher incidence of liver metastases
- Pancreatic tumors metastasize more frequently to the liver, compared to duodenal tumors

Bone

- Bone metastases (eg spine or sacrum) occur later in the course of illness
- Associated w/ aggressive tumor growth & decreased survival

Lymph Nodes

- Incidence of lymph node metastases is similar for pancreatic & duodenal gastrinomas

4 EVALUATION

The presence of MEN-1 in a patient w/ ZES has important consequences affecting prognosis & treatment

- MEN-1 is an autosomal dominant familial syndrome characterized by tumors in multiple endocrine organs, notably the parathyroid, pituitary & pancreas
  - Majority of MEN-1 endocrine tumors are benign, but pancreatic islet tumors & foregut carcinoids may be malignant
  - Gastrinomas develop in about 60% of MEN-1 patients
    - The presence of MEN-1 in ZES patients is associated w/ aggressive growth of gastrinoma
- MEN-1 should be considered in any ZES patient who manifests w/ hypercalcemia or its complications eg nephrolithiasis
- Serum calcium & parathyroid hormone measurements should be done in all ZES patients
- The attending physician should inquire about a family history of PUD & hypercalcemia
- Conversely, all patients diagnosed w/ MEN-1 should be screened for ZES using fasting serum gastrin w/ or without the secretin test

A CONTROL OF ACID HYPERSECRETION

Principles of Treatment

- Aggressive control of acid hypersecretion in ZES patients is of prime importance because of the risk of peptic ulcer complications & other acid-peptic disease including esophagitis
- Once gastric acid secretion is controlled, imaging studies can be performed to locate the tumor & to stage the disease
- Control of acid secretion remains mandatory in patients who have undergone successful gastrinoma resection & exhibit biochemical evidence of cure as gastric secretion may not return to normal level after resection due to residual excess gastric parietal cells which is a consequence of long-standing hypergastrinemia

Proton Pump Inhibitors (PPIs)

- Most effective drugs for controlling gastric acid hypersecretion in ZES patients
  - PPIs have been found to be safe even at high doses
- Act by irreversibly binding to & inhibiting the hydrogen/potassium ATPase found on the luminal surface of the parietal cells
- **Goal:** To maintain basal acid output (BAO) at <10 mEq/hr & at <5 mEq/hr in patients w/ previous acid-reducing gastric surgery
- Allow for once- to twice-daily dosing in about 95% of patients due to its long duration of action & potency
- Once adequate control of acid secretion is achieved, the dose may be decreased over time to about half the starting dose
- Dose reduction of PPIs should be done cautiously in the following patients since they require greater acid suppression:
  - Patients w/ MEN-1 or severe GERD
  - Patients who have previously undergone gastric surgery
- PPIs given the IV route may also be used to achieve uninterrupted control of gastric acid secretion in ZES patients who are vomiting & have gastric outlet obstruction, & in those who are about to undergo gastrinoma resection or receive chemotherapy
- Vitamin B_{12} levels should be monitored in patients receiving long-term PPI therapy because PPIs may lead to reduced Cobalamin absorption from food
- Yearly acid secretory control assessment is recommended after initial PPI treatment

Histamine$_2$-Receptor Antagonists (H_2RAs)

- May be effective for controlling gastric acid hypersecretion; however, higher-than-conventional doses are required
  - Failure to control acid hypersecretion w/ conventional doses often lead to a suspicion of ZES

B SURGERY

- Goal of surgery is primarily to prevent metastases
- Surgical cure is likely high for extrapancreatic gastrinomas (eg gastrinomas in the duodenum or peripancreatic lymph nodes)
- If preoperative imaging studies have shown clearly the location of the primary tumor & there are no metastases, extirpation should be attempted

B SURGERY (CONT'D)

- If preoperative imaging studies are equivocal or negative, then intraoperative exploration to locate the tumor will be necessary
- Patients w/ a sporadic gastrinoma without evidence of metastatic spread of disease should be offered exploratory laparotomy (regardless of imaging results) & resection w/ curative intent

Resection of Gastrinoma

Patients Who May Be Considered for Surgical Tumor Resection

- Patients w/ sporadic ZES without liver or distant metastases or concomitant disease increasing surgical risk or limiting life expectancy
- ZES patients who have MEN-1 & a gastrinoma >2 cm in size
  - Goal of surgery is to reduce risk of subsequent metastatic disease
  - Tumor size is a predictor of survival & development of liver metastases
  - Role of surgery is controversial since majority has multiple duodenal gastrinomas & often w/ lymph node metastases at the time of surgery
  - At present, surgery is still recommended only for lesions >2 cm on imaging & for persistent ZES after correction of hyperparathyroidism
  - For ZES patients who have MEN-1 w/ parathyroidism, it is recommended to have parathyroid surgery first
  - For MEN-1 patients whose ZES are controlled pharmacologically & who have not undergone surgery, monitoring of symptoms is important; imaging studies may be done as deemed important
- Patients w/ recurrent ZES in whom tumors are identified & localized

Types of Surgical Procedures

- Resection by enucleation is done for tumors that develop from the pancreatic head
  - Whipple procedure is not generally recommended & is only done for bigger tumors arising very near the pancreatic duct
- Distal pancreatectomy is done for pancreatic tail lesions
- Routine removal of pancreatic head lymph nodes & all regional lymph nodes is recommended
- Curative resection is also possible for duodenal gastrinomas
- Duodenotomy is recommended in all ZES patients undergoing surgery
  - Most effective method of identifying duodenal gastrinomas, which comprises 60% of all gastrinomas
  - Studies have shown that duodenotomy doubled the cure rate by 30-60% in ZES patients
- Exploratory laparotomy may be done to locate a primary gastrinoma
  - If a primary tumor cannot be located, a search for ectopic tumors should be done
    - Defer a Whipple procedure in favor of closure then monitor every 6 months w/ serial imaging to locate tumor
  - Common sites of ectopic gastrinomas: Pylorus, jejunum, liver, bile duct, ovary & omentum
  - Duodenectomy & intraoperative ultrasound may be done to help localize tumors

Parietal Cell Vagotomy

- Appears to reduce the need for medical treatment postoperatively in patients who have recurrent or persistent disease, especially when complete resection of gastrinoma is not possible

Surgery for Patients w/ Metastatic Disease to the Liver

- Hepatic resection is indicated for the treatment of metastatic liver disease in the absence of diffuse bilobar involvement, compromised liver function or extensive extrahepatic metastases
  - There is some evidence that resection of liver metastases improves survival
- Cytoreductive surgery may be considered in patients w/ limited liver metastases
  - Current recommendation is to attempt liver resection if ≥90% appears resectable on preoperative imaging studies
- Radiofrequency ablation (RFA) & cryoablation, done percutaneously or laparoscopically, are less morbid than hepatic resection & hepatic arterial embolization but may be applicable only to smaller lesions

Postoperative Assessment

- Assessment of cure should be performed postoperatively in patients without metastases who underwent tumor resection
  - Fasting serum gastrin measurement or the secretin stimulation test should be done
- History, PE, serum gastrin, & imaging w/ an abdominal multiphasic CT or MRI & a chest CT w/ or without contrast as clinically indicated are recommended 3-12 months postresection
  - Long-term surveillance includes history, PE, & tumor markers every 6-12 months for a max of 10 years; subsequent follow-up & imaging studies are as clinically indicated

C PALLIATIVE ANTITUMOR TREATMENT

- For patients w/ metastases of the liver, a rapidly growing tumor, those w/ bone metastases, ectopic Cushing's syndrome, or uncontrolled symptoms due to metastatic disease, antitumor treatment is indicated

Octreotide

- Octreotide is a somatostatin analog that may inhibit tumor growth by binding to somatostatin type-2 receptors (SST2) expressed by pancreatic islet cell tumors
- Octreotide w/ or without Interferon alfa is recommended as therapy
  - Octreotide plus Interferon alfa are associated w/ relatively less toxicity compared to chemotherapy
  - Effective in inhibiting further tumor growth in 50-60% of patients
- May be given to patients unresponsive to PPI therapy
- Effect is less predictable in gastrinomas compared w/ other pancreatic islet cell tumor
  - Nevertheless, it is effective in controlling gastrin secretion & may slow down tumor growth
- A long-acting preparation has largely eliminated the need for daily Octreotide injections
  - Used after a brief trial of short-acting formulation
  - Additional short-acting Octreotide may be used for breakthrough symptoms

Interferon alfa

- May be used in combination w/ Octreotide
- Based on past studies, reduces symptoms of hormonal hypersecretion in 40-50% of patients w/ neuroendocrine & carcinoid tumors
  - Induces tumor stabilization in 20-40%

Lanreotide

- A randomized study showed this somatostatin analog was associated w/ increased survival of patients w/ grade 1 or 2 metastatic enteropancreatic neuroendocrine tumors that are somatostatin positive

Radiation Therapy

- Case reports & series show that rates of symptom palliation & control of local progression are high w/ radiation therapy for nonsurgical candidates

D HEPATIC ARTERIAL EMBOLIZATION

- Palliative treatment for patient w/ symptomatic liver metastases who are not candidates for surgery
  - Liver metastases derive most of their blood supply from hepatic artery; therefore, embolization will cause metastatic necrosis
- Can be done either via infusion of gel foam powder (bland embolization) or in conjunction w/ chemotherapy (chemoembolization)
  - Cisplatin, Doxorubicin & Streptozocin may be used as chemoembolization agents
- A third technique (radioembolization) makes use of radioactive isotopes bound to glass or resin microspheres & selectively delivered to the tumor via hepatic artery
- Response rates are generally above 50% & are measured by radiographic regression, decreased hormone secretion & symptomatic improvement
- Proper patient selection must be done to minimize adverse effects which include fever, nausea, fatigue & elevated liver enzymes

E CHEMOTHERAPY

- Limited experience w/ systemic chemotherapy for patients w/ metastases
  - Choice of treatment regimen should be individualized
- Streptozocin & Doxorubicin have been the traditional treatment
  - Uncertainty w/ efficacy & associated toxicities (eg renal dysfunction, prolonged myelosuppression, nausea) limit their use
  - Radiologic response rate is estimated to be between 10% & 40%
- Single-agent therapy (eg Streptozocin, 5-fluorouracil, Doxorubicin alone) is associated w/ modest response rates
- Antineoplastic agents Everolimus & Sunitinib have been demonstrated in studies to increase the progression-free survival time of patients
- Temozolomide-based regimen has also shown antitumor activity

Dosage Guidelines

HISTAMINE$_2$-RECEPTOR ANTAGONISTS (H_2RAs)		
Drug	**Dosage**	**Remarks**
Cimetidine	300-400 mg PO 6 hrly **or** 200-400 mg PO 6-8 hrly after meals then 400 mg PO at bedtime **Max dose:** 2.4 g/day ***or*** 200 mg slow IV/IM 4-6 hrly **or** 300 mg slow IV/IM 6-8 hrly **Continuous IV infusion:** 50-100 mg/hr	**Adverse Reactions** • CNS effects (headache, dizziness, somnolence, agitation); GI effects (diarrhea, N/V); Other effects (rashes, myalgia, arthralgia) • Altered LFTs, reversible confusion in the elderly & those w/ renal failure have occasionally occurred • Rarely reported effects: Hepatotoxicity, hypersensitivity reactions, hematologic effects (leukopenia, thrombocytopenia, agranulocytosis); CV effects (tachycardia, bradycardia, hypotension); acute pancreatitis • Cimetidine has weak anti-androgenic effects; impotence & gynecomastia have occurred & are usually reversible **Special Instructions** • Intravenous injections should be given slowly; intravenous infusion is preferred (especially for high doses & in patients w/ CV impairment) • Use w/ caution in patients w/ hepatic & renal impairment; dose adjustment recommended • Cimetidine may reduce hepatic metabolism of some drugs through inhibition of cytochrome P450 isoenzymes; closely monitor those on oral anticoagulants, Lidocaine, Phenytoin or Theophylline; dose reduction may be necessary
Famotidine	**Initial dose:** 20 mg PO 6 hrly May increase up to 160 mg PO 6 hrly in severe cases **Max dose:** 800 mg/day ***or*** 20 mg IV 6 hrly	
Nizatidine	**Initial dose:** 150 mg PO 12 hrly **or** 300 mg PO 24 hrly in the evening ***or*** **Continuous IV infusion:** 10 mg/hr **Max dose:** 480 mg/day	
Ranitidine	150 mg PO 8-12 hrly **Max dose:** 6 g/day ***or*** 50 mg IM/slow IV 6-8 hrly **IV infusion:** Initially, 1 mg/kg/hr May increase by increments of 0.5 mg/kg/hr after 4 hr	
Roxatidine	75 mg PO 12 hrly	
Combination Product		
Ranitidine/ tripotassium bismuth dicitrate/ sucralfate	Ranitidine 84 mg/tripotassium bismuth dicitrate 100 mg/ sucralfate 300 mg Initially 2 tab PO 8 hrly, may be increased as necessary May increase Ranitidine dose up to 6 g/day in severe cases	**Adverse Reactions** • GI effects (constipation, diarrhea, dark stool color, tongue becomes dark); Other effects (itching, gynecomastia, impotence, sexuality abatement) **Special Instructions** • Use w/ caution in patients w/ renal & hepatic disorder, drug hypersensitivity; prolonged use • Observe progress sufficiently & use as minimally as needed in treatment • May mask gastric cancer • May give false-positive result in proteinuria test; use sulfosalicylic method

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
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Specific prescribing information may be found in the latest MIMS.

Dosage Guidelines

PROTON PUMP INHIBITORS (PPIs)		
Drug	**Dosage**	**Remarks**
Esomeprazole	**Initial dose:** 40 mg PO 12 hrly (adjusted as required) **Max dose:** 80-160 mg/day Doses >80 mg/day should be given in 2 divided doses	**Adverse Reactions** • Generally well tolerated; most commonly reported: Headache, diarrhea, rash • Less common: GI effects (constipation, flatulence, abdominal pain, N/V, dry mouth); Dermatologic effects (pruritus, urticaria); Musculoskeletal effects (arthralgia, myalgia); Other effects (dizziness, fatigue, insomnia, cough, upper resp tract infection) • Hypersensitivity reactions, elevated liver enzymes, & isolated cases of photosensitivity & hepatotoxicity have been reported **Special Instructions** • Use w/ caution in patients w/ hepatic impairment; dose adjustment recommended • Concomitant use w/ Atazanavir or Nelfinavir is not recommended (PPIs reduce exposure to these drugs) • Exclude possibility of gastric malignancy prior to treatment • Bone fracture: Several published observational studies suggest that PPI therapy may be associated w/ an increased risk for osteoporosis-related fractures of the hip, wrist or spine. Patients should use the lowest dose & shortest duration of PPI therapy appropriate to the condition being treated
Lansoprazole	**Initial dose:** 60 mg PO 24 hrly (adjusted as required) May increase up to 90 mg PO 12 hrly Doses >120 mg/day should be given in divided doses	
Omeprazole	**Initial dose:** 60 mg PO 24 hrly (adjusted as required) **Maintenance dose:** 20-120 mg PO/day Doses >80 mg/day should be given in 2 divided doses ***or*** 40 mg IV infusion over a period of 20-30 min 24 hrly **Max rate:** 4 mL/min	
Pantoprazole	80 mg/day PO (adjusted as required) Daily doses >80 mg should be given in 2 divided doses **Max dose:** 240 mg/day in divided doses ***or*** 40-80 mg IV 24 hrly, adjusted as required **Max dose:** 240 mg/day in divided doses (for a limited period of up to 7 days)	
Rabeprazole (Na rabeprazole, Sodium rabeprazole)	**Initial dose:** 60 mg PO/IV 24 hrly (adjusted as required) May increase to 60 mg PO/IV 12 hrly **or** 100 mg PO 24 hrly Daily doses >100 mg should be given in 2 divided doses	

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Dosage Guidelines

OTHER GASTROINTESTINAL DRUGS		
Drug	**Dosage**	**Remarks**
Somatostatin Analog		
Octreotide	**Immediate-release (SC dose)** **Initial dose:** 0.05-0.1 mg SC 12-24 hrly May increase up to 0.1-0.2 mg SC 8 hrly, as required **Long-acting release (LAR)** **Patients previously adequately controlled w/ immediate-release Octreotide:** **Initial dose**: 20 mg IM every 4 wk Continue SC dose x 2 wk after 1st LAR dose **Dose adjustment after 3 mth, as required:** 10-30 mg IM every 4 wk	**Adverse Reactions** • Transient local reaction at site of injection • GI effects (N/V, abdominal discomfort, flatulence, anorexia, diarrhea, steatorrhea), CV effects (flushing, edema, arrhythmia, bradycardia which may be due to underlying CV disease), cholelithiasis & biliary sludge (w/ prolonged use), hyperglycemia, hypoglycemia • Gallstones may develop on long-term therapy **Special Instructions** • Monitor for cholelithiasis prior to prolonged therapy & at 6-12 mth intervals during treatment • Monitor thyroid function during therapy due to possibility of hypothyroidism • **For Octreotide LAR:** Patients not previously treated w/ SC immediate-release Octreotide should receive the agent (0.1 mg SC 8 hrly) for 2 wk to assess systemic response & tolerance before starting Octreotide LAR

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