

# Management of acute gastrointestinal bleeding in the emergency medicine setting

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**MANAGEMENT OF ACUTE  
GASTROINTESTINAL BLEEDING IN THE  
EMERGENCY MEDICINE SETTING**

**GRADUATE THESIS**



Zagreb, 2019.

This graduate thesis was made at the Department of Gastroenterology at KBC Sisters of Mercy Hospital under the mentorship of Doc. dr. sc. Neven Baršić, and was submitted for evaluation in the academic year 2018/2019.

## **Abbreviations**

ASA- Aspirin  
BP- Blood Pressure  
BRBPR- Bright Red Blood Per Rectum  
BUN- Blood Urea Nitrogen  
CBC- Complete Blood Count  
Cr- Creatinine  
CMV- Cytomegalovirus  
EGD- Esophagogastroduodenoscopy  
ESGE- European Society of Gastrointestinal Endoscopy  
GERD- Gastroesophageal Reflux Disease  
GI- Gastrointestinal  
GIB- Gastrointestinal Bleeding  
HSV- Herpes Simplex Virus  
INR- International Normalized Ratio  
LGIB- Lower Gastrointestinal Bleed  
MCV- Mean Corpuscular Volume  
NVUGIH- Nonvariceal Upper Gastrointestinal Hemorrhage  
PPI- Proton Pump Inhibitor  
PRBC- Packed Red Blood Cells  
PUD- Peptic Ulcer Disease  
VKA- Vitamin K Antagonist  
UGIB- Upper Gastrointestinal Bleed  
WBC- White Blood Cell

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## **1. Abstract**

Title: MANAGEMENT OF ACUTE GASTROINTESTINAL BLEEDING IN THE EMERGENCY MEDICINE SETTING

Key words: Gastrointestinal Bleeding, Melena, Hematochezia, Hematemesis, Upper GI Bleeding, Lower GI Bleeding

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Gastrointestinal bleeding remains a significant cause of morbidity and mortality worldwide, and contributes significantly to health care costs. GI bleeding can be life threatening, and treatment of this condition remains a significant challenge. Mortality rates have persisted stubbornly for decades; however recent advances in guidelines, pre-endoscopic management, and endoscopic therapies has decreased the death rate for this condition. Gastrointestinal bleeding is commonly divided into upper and lower GI bleeding based on the location of the bleed in relation to the ligament of Treitz. Although expansive, this review seeks to succinctly explain the causes, clinical manifestations, and management of both upper and lower gastrointestinal bleeding. A brief discussion of the challenges and uncertainties physicians continue to face concludes this review.

## 2. Sažetak

Naslov: OBRADA I LIJEČENJE AKUTNOG GASTROINTESTINALNOG KRVARENJA U ODJELU HITNE MEDICINE

Ključne riječi: gastrointestinalno krvarenje, melena, hematokezija, hematemeza, krvarenje iz gornjeg probavnog trakta, krvarenje iz donjeg probavnog trakta

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Krvarenje iz probavnog trakta ostaje važan uzrok morbiditeta i mortaliteta diljem svijeta, te značajno doprinosi visokim troškovima zdravstvene skrbi. Ta vrsta krvarenja može često biti životno ugrožavajuća, a liječenje bolesnika s ovim stanjem ostaje i dalje značajan izazov. Stope smrtnosti su kod gastrointestinalnog krvarenja desetljećima uporno ostajale iste, no relativno recentnim pomacima u endoskopskom i medikamentoznom liječenju te razvojem smjernica prati se smanjenje mortaliteta kod ovih bolesnika. Krvarenje iz probavnog trakta obično se dijeli na krvarenje iz gornjeg i krvarenje iz donjeg trakta, na osnovu lokalizacije mjesta krvarenja u odnosu na Treitzov ligament. Iako opsežan, ovaj pregledni tekst nastoji sažeto obraditi uzroke, kliničke manifestacije i liječenje krvarenja iz oba dijela probavnog trakta. Pregled završava kratkom diskusijom o izazovima i nedoumicama s kojima se liječnici i dalje suočavaju pri zbrinjavanju ovih stanja.

### **3. Introduction**

Gastrointestinal bleeding (GIB) is a common medical condition that results in significant morbidity, mortality, and medical care cost. GIB remains a frequent cause of hospital admission in the United States, and is the most common cause of hospitalization due to gastrointestinal (GI) disease.<sup>1</sup> It is estimated that GIB contributes to more than 1,000,000 hospitalizations and \$4.85 billion in costs annually in the United States alone.<sup>2,3</sup> GIB is generally classified according to the origin of the bleed in relation to the ligament of Treitz. Upper GI bleeding (UGIB) is defined as intraluminal gastrointestinal blood loss that originates proximal to the ligament of Treitz, whereas lower GI bleeding (LGIB) is defined as intraluminal blood loss distal to the ligament of Treitz. Additional classifications include obscure overt gastrointestinal bleeding, obscure occult gastrointestinal bleeding, and iron deficiency bleeding. Overt bleeding refers to bleeding that has visible signs of blood loss, whereas occult refers to GI bleeding that is subclinical and not visible. The obscure designation signifies GI bleeding that is not apparent after routine esophagogastroduodenoscopy (EGD) and colonoscopy.<sup>2</sup>

The epidemiology, etiology, brief disease pathogenesis, clinical manifestations, approach to diagnosis, and management up to endoscopy of both upper and lower gastrointestinal bleeding is the principle focus of this review.

### **4. Epidemiology**

Previous bodies of literature agree, the majority of hospital admissions for GI bleeds have been upper in origin; approximately 30 to 40% of admissions for gastrointestinal bleeding are for lower GI bleeds, 40 to 50% are for upper GI bleeds, and 10% are for obscure bleeding.<sup>1,2</sup> Recent evidence however suggests the epidemiology surrounding GI bleeding is changing, with hospitalization rates for UGIB and LGIB becoming increasingly similar.<sup>4</sup>

The annual incidence of hospitalization for UGIB in the United States is higher in men, increases with age, and is estimated to be 65 per 100,000 individuals.<sup>5</sup> Current studies indicate the case fatality rate for UGIB in hospitalized patients has decreased over the past two decades; from 4.5% in 1989 to 2.1% in 2009.<sup>6</sup> Despite this improvement in care however, the death rate among patients who develop UGIB while hospitalized for another condition is approximately 3 to 4 times higher than patients who are admitted to the hospital for UGIB alone. Patients with particularly high mortality rates appear to be those who have diagnosed variceal bleeding or UGIB related to upper gastrointestinal malignancy.<sup>7</sup> Historically, studies have attributed peptic ulcer disease (PUD) as the cause for approximately half of upper GI bleed cases; new reports suggest the incidence of disorders such as upper GI neoplasm, Dieulafoy's lesion, angiodysplasia, and esophagitis have risen with an accompanying decline in the incidence of PUD and gastritis.<sup>5</sup>

The annual incidence of LGIB is approximately 20/100,000 population, with an increased risk in older adults.<sup>2</sup> As previously noted, over the past decade there has been a progressive change in the epidemiology of gastrointestinal bleeding resulting in hospitalization. The incidence of LGIB and UGIB have become increasingly commensurate owing to declining rates of upper GI bleeds, and rising rates of lower GI bleeds.<sup>8</sup> Overall, the mortality of lower GI bleeds has decreased;



current studies indicate the all-cause in-hospital mortality rate in lower GI bleeds is low (3.9%).<sup>8</sup> Complication events for LGIB have remained the same however, and the strongest predictors of mortality appear to be advanced age, intestinal ischemia, and comorbid illness.<sup>9</sup>

## 5. Etiologies and Pathogenesis

### 5.1 UGIB

From a pathophysiologic perspective, it is useful to categorize specific causes of UGIB into several broad categories based on anatomic and pathophysiologic factors. These categories include erosive or ulcerative lesions, complications of portal hypertension, vascular lesions, traumatic or iatrogenic lesions, tumors, and miscellaneous (Table 1). A brief discussion of the pathogenesis and associated risk factors of the most common causative agents of UGIB follows.

**Table 1.** Pathophysiologic Mechanisms of UGIB

Erosive or Ulcerative	Complications of portal hypertension	Vascular lesions	Traumatic or Iatrogenic	Tumors	Miscellaneous
Duodenal/ Gastric Ulcer	Esophagogastric varices	Angiodysplasia	Mallory-Weiss syndrome	Gastric cancer	Hemobilia
Esophagitis	Ectopic varices	Dieulafoy's lesion	Aortoenteric fistula	Esophageal adenocarcinoma	Hemosuccus pancreaticus
Gastritis/ Duodenitis	Portal hypertensive gastropathy	Gastric antral vascular ectasia (GAVE)	Cameron lesions	Esophageal squamous cell carcinoma	

*Modified according to Laine L, Yale School of Medicine. Upper Gastrointestinal Bleeding Due to a Peptic Ulcer. N Engl J Med 2016; 374:2367-2376*

Peptic ulcers, defined as mucosal defects that extend past the muscularis mucosae, remain the most frequent cause of upper gastrointestinal bleeding.<sup>4</sup> Risk factors for the development of PUD include *Helicobacter Pylori* infection, use of nonsteroidal antiinflammatory drugs (NSAIDs), physiologic stress, and excess gastric acid. *H. pylori*, a gram negative spiral bacterium, infects the superficial mucosa of the stomach and results in a disruption of mucosal defenses. This disruption in defense, coupled with a disturbance in gastric acid secretory physiology as a result of chronic inflammation, ultimately leads to ulcerative disease.<sup>10</sup> NSAIDs, which include low dose aspirin, disrupt gastric mucosal defenses by inhibiting the production of prostaglandins. This inhibition results in decreased mucosal mucous and bicarbonate secretion, as well as decreased mucosal blood flow. Taken together these changes, in addition to the harsh acidity of the stomach, result in the formation of an ulcer.<sup>11</sup> Ulcerative lesions can occur both in the duodenum and stomach, and recent studies indicate that among patients with bleeding ulcers, gastric ulcers are more common.<sup>12</sup> Interestingly, a sizeable amount of evidence has indicated that gastroduodenal ulcers associated with different risk factors behave different clinically. In a recent study of 575 patients in North America with gastroduodenal ulcers, approximately half had evidence of *H. pylori* infection and half did not. Patients with *H. pylori* positive ulcers had the lowest rate of rebleeding and mortality, whereas patients with *H. pylori* negative ulcers had

poorer outcomes. The patients with the worst outcomes and more severe systemic disease were those who had ulcers negative for *H. pylori* and no history of NSAID use.<sup>13</sup>

Esophagitis is recognized as a fairly common cause of upper GI bleeding, as one recent cohort study by *Balderas et al* indicates. Of the 920 patients diagnosed with UGIB, approximately 123 (13%) were found to have esophagitis on endoscopy (similar to the incidence of duodenal ulcers).<sup>14</sup> Risk factors for the development of esophagitis include gastroesophageal reflux disease (GERD), medications (e.g., tetracyclines, oral bisphosphonates), and infections (e.g., *Candida*, CMV, and HSV). Typically, patients with UGIB due to esophagitis have a comparatively favorable outcome; shorter hospital stays, lower rebleeding rates, and lower mortality rates.<sup>15</sup>

Complications of portal hypertension (e.g., esophagogastric varices, and portal hypertensive gastropathy) most commonly develop in the setting of cirrhosis. However, it is important to recognize that patients without cirrhosis can still develop portal hypertension due to portal vein thrombosis and schistosomiasis. Varices, which represent dilated veins where the systemic and portal circulations share capillary beds, can be found principally in the cardioesophageal junction.<sup>11</sup> Risk factors for the development of variceal hemorrhage include increasing severity of liver disease, increasing Child-Pugh class, and increasing variceal size.<sup>16,17</sup> The proportion of upper gastrointestinal bleeding attributable to varices varies widely, from 1.9% to more than 30%, depending on the characteristics of the patient population (e.g., the prevalence of drug or alcohol use and the country of origin).<sup>4,18</sup> Significant portal hypertension, which is typically seen with advanced liver disease (Child-Pugh Class B or C), is associated with the onset of bleeding from varices.

It is important to note that in approximately 10-15% of patients with UGIB, the causative lesion cannot be identified for a variety of reasons: difficulty finding the lesion on endoscopy (Dieulafoy's lesion), the lesion is obscured by a retained blood clot, or the culprit lesion has healed by the time endoscopy is performed.<sup>2</sup>

## 5.2 LGIB

Similar to UGIB, the causes of LGIB can be succinctly grouped into several categories: anatomic, vascular, inflammatory, and neoplastic (Table 2). A brief discussion of the pathogenesis and risk factors associated with the most common etiologies follows.

<b>Anatomic</b>	<b>Vascular</b>	<b>Inflammatory</b>	<b>Neoplastic</b>
	Angiodysplasia (5-10)	Infectious (2-5)	Colonic polyps (2-15)
Diverticulosis (30-65)	Hemorrhoids (5-20)	IBD (3-5)	Colonic Adenocarcinoma (2-15)
	Ischemic (5-20)	Ulceration (0-5)	

*Adapted from Gralnek IM, Neeman Z, Strate LL, University of Washington School of Medicine. Acute Lower Gastrointestinal Bleeding. N Engl J Med 2017; 376:1054-1063*

Anatomically, colonic diverticuli represent small, dome-like outpouchings of the mucosa and submucosa, usually 0.5 to 1cm in diameter, that occur in a regular distribution between the taeniae coli. Diverticula generally are multiple, and this condition is referred to as *diverticulosis*. Diverticula tend to occur primarily in the sigmoid colon under conditions of elevated intraluminal pressure, however they may be in other regions of the colon in severe cases. Although high luminal pressures may be exaggerated by diets low in fiber, which reduces stool bulk, it is still unclear whether a high-fiber diet prevents progression of this disease.<sup>11</sup> Diverticular bleeding occurs when penetrating vessels, which are draped over the dome of the diverticula, rupture due to chronic injury along their luminal aspect. This bleeding may be overt and life-threatening, as the aforementioned penetrating vessels are often arterial. Risk factors for the development of diverticular bleeding include ASA or NSAID use, obesity, advanced age, physical inactivity, and hypertension.<sup>19</sup> The high prevalence of diverticulosis, particularly among individuals between 40 and 60,<sup>20</sup> explains why it is the most common cause of lower gastrointestinal bleeding.

Ischemic damage to the bowel can range from mucosal infarction, in which damage does not extend farther than the muscularis mucosa, to transmural infarction involving all three layers of the bowel wall. While mucosal infarctions are often secondary to acute or chronic states of hypoperfusion, transmural infarcts most frequently occur in the background of acute vascular obstruction. Intestinal hypoperfusion is most commonly associated with conditions such as shock, cardiac failure, or vasoconstrictive drugs. Frequently, this condition is confused with inflammatory bowel disease (IBD) with episodes of bloody diarrhea interspersed with periods of healing. Acute vascular obstruction, which often constitutes a life-threatening surgical emergency, commonly results from severe atherosclerosis and overlying thrombosis, embolization, and hypercoagulable states. The disparity in clinical presentation between acute vessel occlusion and chronic states of hypoperfusion can be explained by the presence or absence of collateral circulation in the GI tract; chronic low states of hypoperfusion provide adequate time for collateral vessels to develop. These collateral vessels make it possible for the intestine and colon to tolerate slowly progressive losses of blood supply. Ischemic damage of the colon tends to occur in watershed zones, which are regions of tissue that are situated along the border zones between the territories of two major arteries. The corresponding regions in the colon include the splenic flexure, the sigmoid colon, and the rectum.<sup>11</sup>

Hemorrhoids represent dilated anal and perianal collaterals that connect the portal and caval venous systems. Hemorrhoids can be classified as internal or external depending on their relation to the pectinate line; the former lying proximal and the latter lying distal to the pectinate line. Factors that predispose to the development of hemorrhoids include constipation and associated straining, venous stasis of pregnancy, and portal hypertension. Except in pregnancy, the development of hemorrhoids in patients under the age of 30 is uncommon, and bleeding events are rarely a medical-emergency. Notably however, patients on anticoagulants or with known coagulopathy are at significantly higher risk of serious bleeding.<sup>11,21</sup>

## 6. Clinical Manifestations

Several signs of gastrointestinal bleeding warrant special attention as they are common manifestations of this clinical condition, often aid decision making, and assist in determining the site of bleeding. These signs are hematemesis, melena, and hematochezia. Hematemesis is defined as the vomiting of blood, which can be both bright red (suggesting recent or ongoing bleeding), and dark or coffee ground (suggesting bleeding that has recently stopped). Clinical presentation of hematemesis, coffee-ground emesis, or nasogastric lavage with return of blood indicates a gastrointestinal bleed that is proximal to the ligament of Treitz. Melena is defined as black tarry stool that results from degradation of blood to hematin by intestinal bacteria. Melena generally occurs after approximately 50 to 100 mL of blood has been delivered to the GI tract, with passage of characteristic stool occurring several hours after the bleeding event.<sup>2</sup> Although often indicative of GI bleeding, it is important to note that black discoloration of stools can also result secondarily to both iron or bismuth ingestion.<sup>22</sup> Furthermore, although the presence of melena generally implies GI bleeding proximal to the ligament of Treitz, melena due to bleeding in the small intestine and proximal colon occurs in approximately 10% of cases.<sup>22</sup> Hematochezia refers to bright red blood per rectum (BRBPR) and can be indicative of either UGIB or LGIB; lower GI sources are frequently colonic or anorectal. Hematochezia from an upper GI source should be suspected when fresh rectal bleeding is accompanied by signs of hypovolemia or hypoperfusion.<sup>22</sup> While these clinical signs collectively may provide clues to the origin of a GI bleed, it is often impossible to determine the site of bleeding on clinical grounds alone.<sup>23</sup> Almost invariably, an interventional procedure such as colonoscopy or endoscopy is needed to confirm the diagnosis.

## 7. Initial Assessment

The initial assessment of patients with GI bleeding includes medical history taking, an assessment of vital signs (including postural changes), performance of physical and rectal exams, risk stratification, and, in some cases, nasogastric lavage. The information gathered from this initial evaluation is used to guide decisions regarding triage, resuscitation, empiric medical therapy, and diagnostic testing.

History taking should provide clues to the source of the GI bleed by determining relevant patient risk factors and historical features. Important elements of the medical history include inquiring about previous episodes of GIB and their causes, alcohol abuse, cigarette smoking (duodenal ulcers recur more frequently, and heal more slowly, in smokers than in nonsmokers),<sup>24</sup> usage of relevant medications (e.g., NSAIDs, ASA, anticoagulants), prior infection with *H. pylori* and treatment, history of liver disease or coagulopathy, and prior aortic surgery (strongly associated with Aortoenteric fistula). Indicators of GI malignancy as the cause for bleeding that are often uncovered in the medical history include recent unintended weight loss, loss of appetite, change in stool caliber, and abdominal pain.<sup>2</sup>

Physical examination is initially directed at determining hemodynamic status in order to assess the severity of blood loss. Resting tachycardia (heart rate  $\geq 100$  beats per minute), orthostasis (defined as a decrease in systolic blood pressure by more than 20 mm Hg from recumbency to standing), and shock roughly correspond to 10, 20, and  $>30\%$  loss of blood volume respectively.

The abdomen should be auscultated and examined for surgical scars, tenderness, and masses. Hyperactive bowel sounds are often seen in UGIB as a result of the irritating effect blood has on the peristaltic activity of the GI tract. Tenderness of the abdomen is an uncommon finding in patients with GIB, and severe tenderness with guarding or rebound should raise suspicion for a perforated viscus. Rectal exam should be performed to assess for frank bleeding, external hemorrhoids, anal fissures, and to determine changes in stool color.<sup>22</sup> Providers should note however, the subjective description of stool color varies greatly amongst both patients and physicians.<sup>2</sup>

Risk stratification tools have been developed to identify patients with nonvariceal upper GI bleeding who are at greatest risk for rebleeding and mortality. These tools can also assist with triage, determine the urgency of endoscopy, and estimate the length of hospital stay.<sup>2</sup> A number of scoring tools have been developed, with the Glasgow-Blatchford Score (GBS) (Table 3) and the Rockall score being the most widely evaluated and adopted.<sup>25</sup> No single scoring tool has been shown to excel at predicting all relevant clinical outcomes in acute upper GI bleeding, as most risk scores were derived to assess a specific UGIB outcome (i.e. mortality with the Rockall score and the need for intervention with the GBS). The ESGE currently recommends the GBS for pre-endoscopy risk stratification. Patients who are found to be very low risk (GBS score of 0-1) do not require early endoscopy nor hospitalization.<sup>25</sup>

Table 4 below shows clinical factors that are predictive of severe lower GI bleeding or recurrent bleeding after 24 hours of stability. Severe lower GI bleeding is defined as continued bleeding within the first 24 hours of hospitalization, with a transfusion requirement of at least 2 units of packed red blood cells or a decrease in the hematocrit value of 20% or more.<sup>2</sup> Recurrent bleeding is defined as the need for additional transfusions, a further decrease in the hematocrit value of at least 20%, or readmission within 1 week of discharge. Risk factor models for acute lower GI bleeding have been shown to have limited ability to predict patient outcomes, and have been less well studied than models for upper GI bleeding.<sup>1</sup>

<b>Table 3. Glasgow-Blatchford Score</b>	
	<b>Points</b>
<b>Systolic BP, mm Hg</b>	
100 - 109	1
90 - 99	2
< 90	3
<b>BUN, mmol/L</b>	
6.5 - 7.9	2
8.0 - 9.9	3
10.0 - 24.9	4
≥ 25.0	6
<b>Hemoglobin for men, g/dL</b>	
12.0 - 12.9	1
10.0 - 11.9	3
< 10.0	6
<b>Hemoglobin for women, g/dL</b>	
10.0 - 11.9	1
< 10.0	6
<b>Other risk variables</b>	
Pulse ≥ 100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2
Total GBS: _____	
GBS restricted for use only in nonhospitalized, ambulatory patients	
Risk variables measured at time of patient presentation	
GBS = 0 - 1 denotes "low-risk"	
<i>Adapted from ESGE guidelines for the Management of Nonvariceal Upper Gastrointestinal Hemorrhage 2015</i>	

**Table 4.** Clinical Prediction Score and Outcomes of Severe Acute LGIB

Total Risk Points*	Frequency (%)	Risk of Severe Bleeding (%)	Need for Surgery (%)	Mortality Rate (%)	Hospital Days	Mean # of Units Transfused (pRBCs)
0	6	6	0	0	2.8	0
1-3	75	43	1.5	2.9	3.1	1
≥ 4	19	79	7.7	9.6	4.6	3

\*Risk factors (1 point each): ASA use; more than 2 comorbid illnesses; heart rate ≥ 100 bpm; nontender abdominal exam; rectal bleeding within the first 4 hr of evaluation; syncope; systolic BP ≤ 115 mm Hg.

*Adapted from Sleisenger and Fordtran's Gastrointestinal and Liver Disease 10<sup>th</sup> e Vol. 1; page 321*

The necessity of nasogastric lavage in the initial assessment of GIB is a subject of debate, as studies have failed to demonstrate a benefit with regard to clinical outcomes.<sup>26</sup> Theoretically, lavage could be used to clear the stomach of particulate matter, clots, and fresh blood to facilitate endoscopy; indeed failure to clear the fundus of blood before endoscopy often results in missed pathology due to poor visibility, and often necessitates repeat endoscopy.<sup>27</sup> However, it remains unclear whether standard-bore nasogastric tubes allow sufficient clearance of debris to substantially improve visualization of the gastric mucosa.<sup>28</sup> Complicating the matter further is the possibility of trauma induced bleeding (epistaxis and gastric erosion) from nasogastric tube insertion and suction, resulting in a false positive gastric lavage. These complications, however, are relatively rare, as illustrated by a review of 152 nasogastric tube insertions for gastrointestinal bleeding which reported only two cases (1.3% rate) of clinically significant complications.<sup>22</sup> Despite the rarity of these complications it is important to consider that nasogastric tube insertion is a procedure that is not well tolerated or desired by patients.<sup>25</sup> Currently, the European Society of Gastrointestinal Endoscopy makes a strong recommendation *against* the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIB.<sup>25</sup>

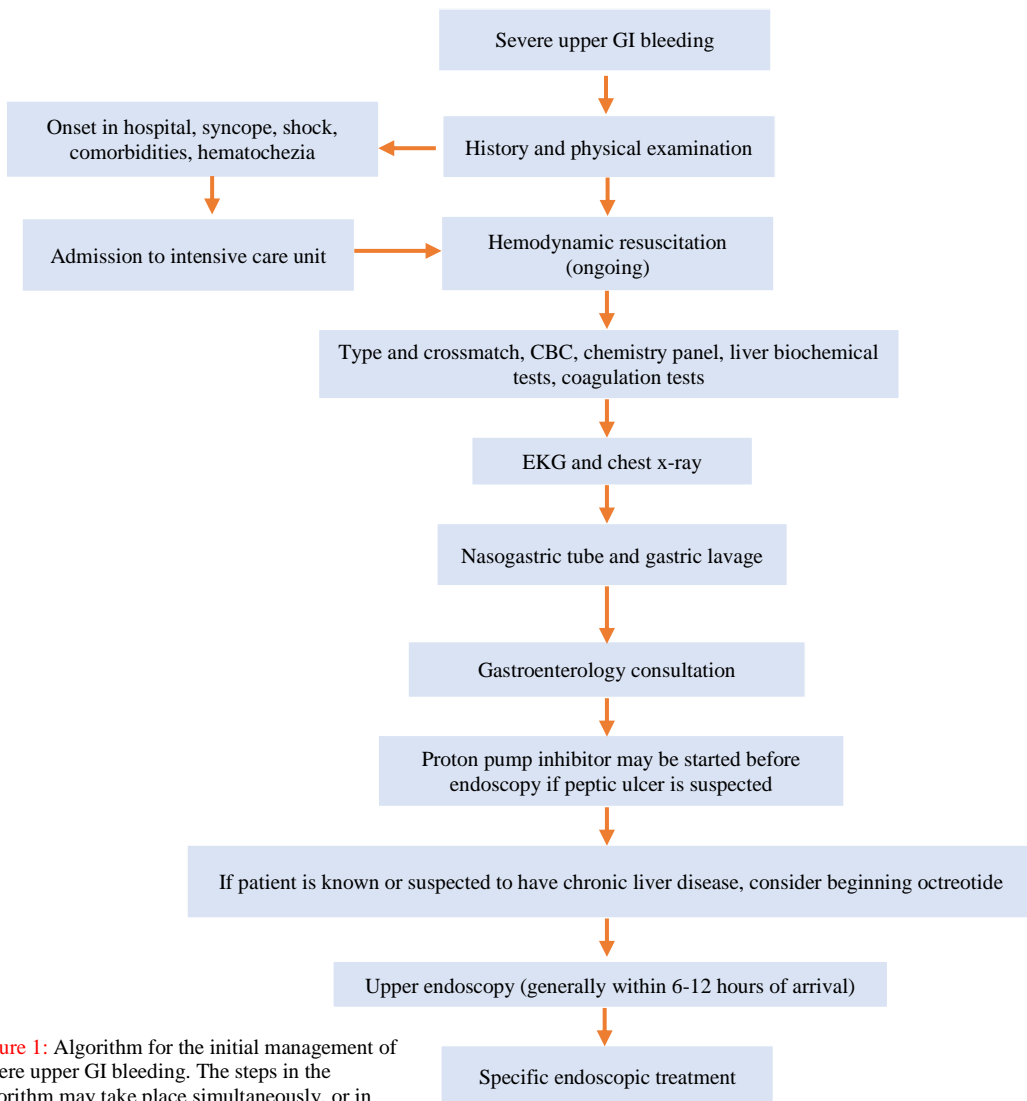
## 8. Laboratory Studies

Blood from patients with acute GI bleeding should be sent for standard hematology, chemistry, liver function testing, coagulation studies, and for type and crossmatching for packed red blood cells. Hemoglobin values should be monitored, and are most accurately interpreted when a prior baseline value is available for comparison. Unlike blood pressure and heart rate however, hemoglobin measurements are initially poor indicators of blood loss severity. At the onset of bleeding, patients lose whole blood resulting in a proportionate decrease in both erythrocytes and plasma. It may take 24-72 hours for the vascular space to equilibrate with extravascular fluid, resulting in the anticipated dilutional decline in hemoglobin.<sup>2</sup> It should be noted that volume resuscitation with normal saline can exaggerate this dilutional process and result in falsely depressed hemoglobin concentrations. Patients with an acute GI bleed typically have a normocytic anemia (MCV 80 – 100 fL); a microcytic anemia (MCV < 80 fL) suggests a chronic GI bleed. An elevated WBC count may occur in more than half of patients with upper GI bleeding, and its presence has been associated with a greater severity of bleeding.<sup>2</sup> Patients with an upper GI bleed typically have a BUN/Cr ratio > 30; the higher the ratio the more likely the bleeding is from an upper GI source.<sup>2</sup> This ratio increases for two reasons: intestinal bacteria

break down blood proteins into urea which is subsequently absorbed by the GI tract, and hypovolemia results in pre-renal azotemia which increases both BUN and Cr.<sup>29</sup> Platelet counts should be assessed, as low levels can contribute to the severity of the bleed. Platelet counts  $>50,000/\text{mm}^3$  are generally regarded as safe for endoscopic procedures. The prothrombin time and INR should be measured to determine whether the patient is on anti-coagulants (i.e. warfarin) and if the patient has an impairment in the extrinsic coagulation pathway.

## 9. Pre-Endoscopy Management

Figures 1 and 2 below represent algorithms for the initial management of acute, severe upper and lower gastrointestinal bleeding. Severe bleeding in this context is defined as documented gastrointestinal bleeding accompanied by shock or orthostatic hypotension, a decrease in hematocrit by at least 6%, or transfusion of at least two units of packed red blood cells.<sup>2</sup>



**Figure 1:** Algorithm for the initial management of severe upper GI bleeding. The steps in the algorithm may take place simultaneously, or in varying orders depending on the clinical situation.

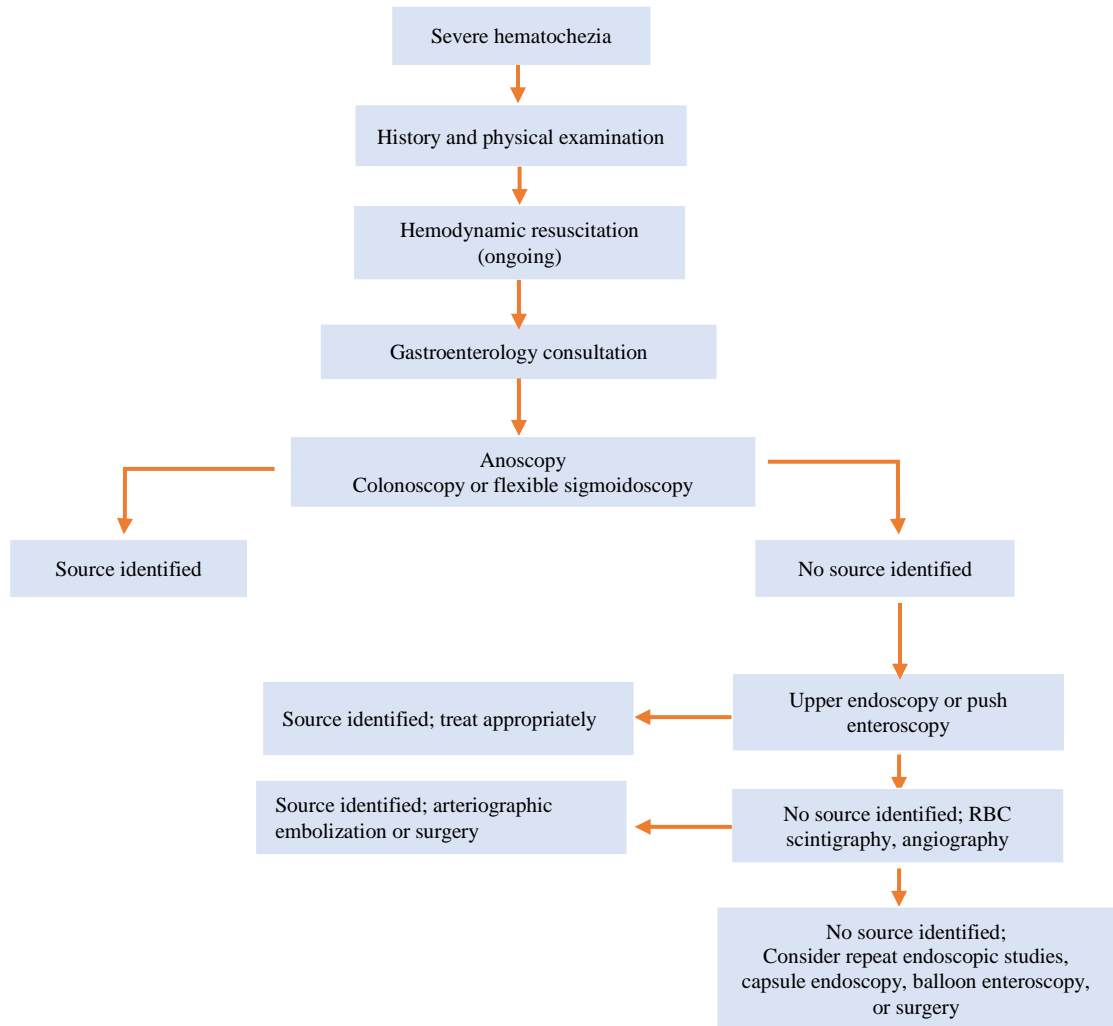


Figure 2: Algorithm for the initial management of severe hematochezia.

Adapted from Sleisenger and Fordtran's *Gastrointestinal and Liver Disease 9<sup>th</sup> ed.*; page 289

## 9.1 Resuscitation

Patients generally receive supplemental oxygen via nasal cannula to improve their diminished oxygen carrying capacity due to loss of erythrocytes. Endotracheal intubation should be considered in any patient who has active hematemesis, hypoxia, severe tachypnea, or altered mental status. The purpose of intubation is to protect the airway, supplement tissue oxygenation, and prevent aspiration pneumonia.<sup>22</sup>

The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent multi-organ failure. Early intensive hemodynamic resuscitation of patients with acute upper GI bleeding has been shown to significantly improve outcomes; an observational study of patients with acute upper GI bleeding and hemodynamic instability showed significantly fewer myocardial infarctions and lower mortality in those



patients who received intensive hemodynamic resuscitation.<sup>30</sup> During the initial assessment in the emergency department patients should have two intravenous access sites secured with two large-bore (18-gauge or larger) catheters. Fluid is infused as fast as needed to keep the patient's systolic BP higher than 100 mm Hg and pulse lower than 100 beats/min.<sup>2</sup> The selection of fluid type (crystalloids or colloids) remains an area of ongoing uncertainty, particularly amongst critically ill patients.<sup>31</sup> The ESGE currently makes a strong recommendation for the use of crystalloids as the initial intravascular volume replacement in hemodynamically unstable patients.<sup>25</sup>

The use of red blood cell transfusions may be lifesaving following a massive GI bleed. Packed erythrocytes are transfused in order to improve tissue oxygenation and to prevent end-organ damage. The need for blood transfusion is individualized according to multiple patient factors: age, presence of comorbidity, cardiovascular status, baseline hematocrit, and tempo of bleeding.<sup>22</sup> The lack of an absolute hemoglobin level required to preserve life and organ function has resulted in uncertainty regarding the hemoglobin threshold at which blood transfusions should be initiated. This uncertainty is reflected in recent gastroenterology and critical care literature which reports poorer outcomes in patients managed with a liberal (target hemoglobin between 9 and 11 g/dL) RBC transfusion strategy.<sup>32,33</sup> Currently, the ESGE makes a strong recommendation for the use of a restrictive blood transfusion strategy (target hemoglobin between 7 and 9 g/dL) in patients with nonvariceal upper GI bleeding without significant comorbidity.<sup>25</sup> Exceptions are made in those individuals with relevant co-morbidities (particularly ischemic cardiovascular disease), in which a more liberal transfusion strategy is endorsed (transfusion at a hemoglobin level of less than 8 g/dL). Randomized trials of transfusion thresholds have not been performed for patient populations with acute lower GI bleeding; current management guidelines for lower GI bleeding similarly endorse a blood transfusion approach that minimizes the administration of blood products.<sup>1</sup>

## **9.2 Medical Therapy**

### **9.2.1 UGIB**

Administration of a proton pump inhibitor (PPI) prior to endoscopy has become routine practice, particularly in patients with suspected peptic ulcer disease. The rationale for PPI therapy is that common causes of UGIB (e.g., ulcers, gastritis, duodenitis, esophagitis) are medically treated with acid suppression. Moreover, recent evidence suggests that PPI's may play a hemostatic role in therapy by stabilizing intraluminal blood clots.<sup>34</sup> A meta-analysis of six randomized trials showed that a PPI administered to patients with upper GI bleeding soon after presentation was associated with a decrease in the frequency of high-risk endoscopic findings (active bleeding, a nonbleeding visible vessel, or an adherent clot) and the need for endoscopic therapy. Importantly however, use of PPI's did not reduce the risks of further bleeding, surgery, or mortality.<sup>35</sup> The benefit of therapy appears to be greatest in individuals who have high-risk stigmata of recent bleeding, such as a visible vessel.<sup>22</sup> The ESGE currently makes a strong recommendation for initiating high dose intravenous PPI's, bolus followed by continuous infusion (80 mg then 8 mg/hour), in patients with acute upper GI bleeding awaiting endoscopy. However, PPI infusion should not delay the performance of early endoscopy.<sup>25</sup>

Octreotide, a somatostatin analog, is used to reduce the risk of bleeding from esophageal varices by inhibiting the actions of glucagon on splanchnic vessels where glucagon plays a vasodilatory role.<sup>22</sup> Moreover, octreotide has been shown to inhibit both acid and pepsin secretion fueling speculation of its use in the management of nonvariceal upper GI hemorrhage (NVUGIH), particularly in patients with peptic ulcers. A meta-analysis of 30 randomized control trials showed that the use of vasoactive agents (e.g., somatostatin, octreotide, terlipressin) in acute variceal hemorrhage was associated with lower all-cause mortality and lower transfusion requirements.<sup>36</sup> The selection of which vasoactive agent to use appears to be governed by availability and cost; a recent study comparing the three most widely used agents, referenced above, found no significant differences among them.<sup>37</sup> The American Association for the Study of Liver Diseases currently recommends initiating octreotide (initial IV bolus of 50 micrograms followed by continuous IV infusion of 50 micrograms/hr) as soon as variceal hemorrhage is suspected for a duration of 2-5 days.<sup>38</sup> Published data show little or no benefit for the use of somatostatin and its analogues in the management of NVUGIH; the ESGE currently makes a strong recommendation against the use of somatostatin, or its analogue octreotide, in patients with NVUGIH.<sup>25</sup>

Erythromycin is a gastric prokinetic agent which is administered intravenously (most commonly at a dose of 250 mg) approximately 30 to 120 minutes before upper endoscopy. This agent induces gastric contraction and pushes blood from the stomach into the small intestine to improve endoscopic visualization.<sup>2</sup> The most recent published meta-analysis for the use of prokinetic agent infusion prior to upper GI endoscopy showed significant improvement in gastric mucosal visualization, and decreased the need for second-look endoscopy, RBC units transfused, and duration of hospital stay.<sup>39</sup> These studies included patients who were admitted to the intensive care unit because of UGIB with clinical evidence of active bleeding or hematemesis. Patients similar to those included in the study are most likely to benefit from erythromycin infusion prior to endoscopy. Contraindications to the use of erythromycin include sensitivity to macrolide antibiotics and prolonged QT interval.

### **9.2.2 LGIB**

In patients presenting with active lower GI bleeding, urgent colonoscopy can be performed after adequate bowel preparation. Preparation of the colon is important for endoscopic visualization, diagnosis, and treatment; studies using large volume (4 to 6 liters), rapid (3-4 h) purge protocols with colonoscopy performed within one to two hours of preparation completion report high rates of definitive diagnosis (22-42%) and hemostasis (34%).<sup>40</sup> Colonoscopy or flexible sigmoidoscopy without preparation should generally be avoided but can be considered in select cases (e.g., suspected bleeding from the distal left colon), with careful cleaning and inspection of the colon during the procedure.<sup>40,41</sup> Once hemodynamically stable, the patient should receive 4 to 6 liters of a polyethylene glycol-based solution or the equivalent over three to four hours until the rectal effluent is clear of blood and stool. A nasogastric tube can be considered to facilitate colon preparation in patients with ongoing bleeding who are intolerant to oral intake and are at low risk of aspiration.<sup>40</sup> In addition, administration of a prokinetic/antiemetic agent (e.g., metoclopramide) immediately prior to colon preparation may reduce nausea and facilitate gastric emptying.<sup>40</sup> Although rare, complications of colon preparation with polyethylene glycol include aspiration pneumonia, as well as fluid and electrolyte abnormalities.<sup>40</sup>

## 10. Endoscopy

In most patients with gastrointestinal bleeding, endoscopy will identify the bleeding site and permit therapeutic hemostasis. Endoscopy should be performed when it is safe to do so; patients should have a heart rate less than 100 beats/minute and a systolic blood pressure higher than 100 mm Hg.<sup>2</sup> Correction of coagulopathies and thrombocytopenia prior to endoscopy has become the standard of care in patients with clinically significant GI bleeding; adequate coagulation profiles and thrombocyte counts assure sufficient therapeutic hemostasis and promote safer endoscopy. Currently, the ESGE endorses withholding vitamin K antagonists while taking into account the patient's cardiovascular risk in consultation with a cardiologist. Urgent reversal is indicated in patients presenting with serious, life-threatening bleeding (i.e., hemodynamic instability or shock). Reversal can be achieved with either intravenous vitamin K, or, when more immediate reversal is required, fresh frozen plasma.<sup>25</sup> Thrombocyte counts can be improved with platelet transfusions; the American College of Gastroenterology (ACG) recommends transfusing platelets to achieve a level  $\geq 50 \times 10^9/l$  in patients with massive bleeding from any source.<sup>40</sup> Unfortunately, data are limited to guide a platelet count threshold specific for gastrointestinal bleeding. Complications related to endoscopy are rare and depend on the type of endoscopy and treatment performed. The most common complications, occurring in up to 1% of patients, include: GI tract perforation, aspiration pneumonia, induced hemorrhage, adverse medication reaction, hypotension, and hypoxia.<sup>2</sup>

EGD is the prime diagnostic and therapeutic tool for upper gastrointestinal bleeding. It is the procedure of choice. The multitude of benefits EGD provides includes: rational basis for triage of patients for routine hospital admission versus ICU admission, assessing the need for surgery, obtaining prognostic information, and endoscopic therapy.<sup>22</sup> Available therapies include injection therapy such as epinephrine, ablative therapy such as electrocautery or argon plasma coagulation, and mechanical therapy such as endoclips or banding. As previously stated, correction of coagulopathy holds a position of primacy prior to endoscopy. Currently the ESGE recommends an INR value  $< 2.5$ , if the clinical situation permits, prior to upper endoscopy with or without endoscopic hemostasis.<sup>25</sup> Most patients who are hospitalized with UGIB should undergo endoscopy within 24 hours; recent observational studies suggest prompt endoscopy, as compared with endoscopy after 24 hours, is associated with reductions in the need for surgery, length of hospitalization, and mortality.<sup>42</sup> Prompt endoscopy is further supported by cost effectiveness studies; approximately 40 to 45% of patients who undergo endoscopy within 2 to 6 hours have low-risk endoscopic findings that allow immediate discharge.<sup>42</sup> In Europe there is widespread variation regarding the timing of endoscopy; one large observational study that included 123 centers in 7 countries showed anywhere from 70 to 93% of 2660 patients with upper GI hemorrhage underwent upper endoscopy within 24 hours of hospital admission.<sup>8</sup> The ESGE currently makes a strong recommendation for early ( $\leq 24$  hours) upper GI endoscopy following hemodynamic resuscitation. Very early ( $< 12$  hours) endoscopy may be considered in patients with high risk clinical features (Glasgow-Blatchford score  $\geq 12$ ).<sup>25</sup> Moreover, discharging patients with low risk suspected NVUGIH (GBS = 0) directly from the emergency department without undergoing upper GI endoscopy has been proposed as a safe and cost-saving option in multiple studies.<sup>25</sup>

Colonoscopy is the initial procedure for nearly all patients presenting with acute lower gastrointestinal bleeding because it serves diagnostic and potentially therapeutic purposes.<sup>1</sup> The goal of colonoscopy is to identify the site of bleeding and perform hemostasis, if indicated. The diagnostic yield of colonoscopy ranges from 49 to 90% depending on the patient population in question.<sup>8,43</sup> Low rates of diagnostic yields may be explained by the intermittent nature of active lower GI bleeding.<sup>1</sup> Studies to determine the appropriate timing of colonoscopy in the setting of acute LGIB are limited. Observational studies have shown a higher frequency of definitive diagnoses and a shorter length of hospital stay amongst patients with LGIB undergoing early colonoscopy (within 12 to 24 hours after presentation) than among those undergoing colonoscopy at a later time.<sup>44,45</sup> It is unclear whether early colonoscopy improves important clinical outcomes such as rebleeding and the need for surgery; despite this claim, the ACG recommends patients with high-risk clinical features receive colonoscopy within 24 h of patient presentation after adequate bowel preparation to potentially improve diagnostic and therapeutic yield.<sup>40</sup> Additionally, patients without high-risk clinical features or serious comorbid disease should receive next available colonoscopy after a colon purge.<sup>40</sup>

## 11. Areas of Uncertainty and Challenges

Gastrointestinal bleeding remains a relatively common, potentially life threatening condition that requires rapid assessment of clinical presentation, resuscitative measures, and appropriate diagnostic and therapeutic interventions. Administration of PPI's is an important adjunctive therapy for nonvariceal upper GI bleeding, however the appropriate dosing of PPI's to treat ulcers in patients with high-risk findings requires further study. Although they are based on the same data, guidelines vary substantively regarding the use of PPI's before endoscopy. Some recommend high-dose PPI's, others indicate that PPI's "may be considered", and still others recommend that clinicians not administer PPI's at all. Hesitancy toward administration of proton pump inhibitors is justified by observational studies which show associations between PPI's and adverse outcomes such as dementia, chronic kidney disease, cardiovascular events, fractures, pneumonia, and enteric infections.<sup>46-48</sup> The strengths of these associations are modest, and it is not known whether or not they are causal. Transfusion of blood products remains an important resuscitative measure for patients with ongoing overt GI bleeding, particularly in those with coexisting heart disease. Importantly however, transfusions are associated with rare but severe side effects. Despite screening of blood donors, HIV, human T-cell lymphotropic virus types 1 and 2, hepatitis B and C, and parvovirus are still rarely transmitted by blood transfusions. Moreover, bacterial infections, particularly *Y. Enterocolitica* and *S. Aureus*, are an important, albeit rare, complication of erythrocyte and platelet transfusion respectively.<sup>22</sup> These rare side effects are important causes of morbidity and mortality during resuscitation of patients with GI bleeding. Coagulopathy is a frequent and adverse prognostic factor for patients with GIB. Published data for the management of coagulopathy are limited and inconclusive. Currently no available evidence has been shown to help guide coagulopathy correction in critically ill patients, and wide variation in practice exists in this area. Further complicating matters is the lack of high quality evidence to guide platelet transfusion thresholds, although a platelet transfusion threshold of  $50 \times 10^9/l$  has been proposed for most patients.<sup>25</sup> Patients who are anticoagulated as a result of medication, particularly non-VKA oral anticoagulants (NOACs), face a significantly increased risk of GI bleeding similar to or greater than that reported for warfarin.<sup>25</sup> Importantly, NOACs differ in comparison to warfarin and heparin in that there is currently no specific reversal

agent/antidote for emergency use with any NOAC. Since their half-life is so short, time is the only antidote currently available. Preliminary strategies to accelerate reversal (using substances such as prothrombin complex concentrates or hemodialysis) urgently require additional data on clinical effectiveness.<sup>25</sup> Moreover, there are no published clinical trials addressing the management of GI bleeding in patients using NOACs, and current recommendations are based on expert opinion or laboratory end-points.<sup>25</sup> The ESGE currently recommends withholding NOACs at the time of patient presentation, however the quality of the evidence to support this claim is low.<sup>25</sup>

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#### **14. Biography**

Marko Alavanja comes from the state of New Jersey in the United States of America. He finished highschool at Bergen Catholic and went on to receive his B.S. in chemistry at New York University. Upon graduating medical school at the University of Zagreb School of Medicine he plans to take his talents to Sweden to begin residency in Gastroenterology.