ETHIOPATHOGENIC CORRELATIONS AND TREATMENT MEANS IN UPPER NON-VARICOSE GASTROINTESTINAL BLEEDINGS

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SUMMARY

Applying the scores according to the ethiopathogenesis of the upper gastrointestinal bleeding. Influencing the medication and surgical treatment according to prognosis. Development of a prognosis score modified for assessing the need or not for admission of some patients belonging to different risk groups, performing endoscopy or blood transfusions in patients with upper gastrointestinal bleeding of non-varicose origin. Prospective study on patients with upper non-varicose gastrointestinal bleeding, the group approximation being made based on the retrospective data gathered from the Emergency Department statistics and compared to the Surgery and Gastroenterology Departments discharge documents.

Key words: Upper gastrointestinal bleeding, ethiopathogenesis, treatment, Rockhall score

RÉSUMÉ

Corrélations étiopathogéniques et modalités de traitement dans les saignements gastro-intestinaux supérieurs de nature non-variqueuse


Mots-clés: saignement gastro-intestinal supérieur, éthiopathogénèse, traitement, score Rockhall

INTRODUCTION

Correlation of the ethiopathogenesis and medical and surgical treatment means. Outline the prognosis based on the upper gastrointestinal bleeding causes and influence it according to treatment. Evaluating and fitting the patients with upper gastrointestinal bleeding in certain risk group and validating the results using endoscopy, will decrease the morbidity and mortality rates, the days of hospitalization and implicitly the costs, and will even replace an useless hospitalization with the performance of some ambulatory additional investigation (endoscopy) for patients belonging to 0 risk group. Assessment of the influence exerted by the socio-economical or
ethnical factors on the treatment and obtained results (morbidity, mortality).

Collection and multi-disciplinary statistical analysis (medical, social, economical) of data, in order to identify some correlations, models or tendencies, which may be utilized to the benefit of public health politics reform or prioritization.

**Ethiopathogenic correlations and treatment means in upper non-varicose upper gastrointestinal bleedings**

**Epidemiology**

**Causes of upper gastrointestinal bleeding**

**Treatment**

**Prognostic scores**

Upper gastrointestinal bleeding is defined as an extravasation of blood, originating from the upper digestive tract, located above Treitz angle.

**Epidemiology**

The upper gastrointestinal bleeding represents a medico-surgical emergency and also a very frequently encountered worldwide pathology, being accompanied by a high incidence of complications and by a high rate of mortality.

It is recorded an incidence of 48-160 cases per 100000 people per year and a mortality rate which varies between 3-12% with great differences between countries: USA 3.3%, UK 7.4%, Hong Kong 7.1%, Japan 1.1%, Italy 6.9%, Denmark 11%. It’s been proved that patients do not die because of the hemorrhage, but because of the associated comorbidities. These difference may be owed to risk factors that depend on the patient, on the disease’s severity and on the health systems. Many studies have reported a decrease of incidence and mortality. [10,11]

The age and the presence of comorbidities are the main factors that significantly influence the morbidity in upper gastrointestinal bleeding.[4,5] With age, the frequency of hemorrhagic episodes increases significantly. It has been noted that the risk of upper gastrointestinal bleeding among people older than 70 years, exceeds 20-30 times that of people younger than 30 years.[4,5]

Another cause may be the change of upper gastrointestinal bleeding etiology. CORI’s (Clinical Outcome Research Initiative) data show the ratio change 2/3 duo-denal ulcer and 1/3 gastric ulcer in 56% gastric ulcers and 44% duodenal ulcers, gastric ulcers evaluating more severely comparing with duodenal ulcer.

Regarding the study realized under the guidance of the Romania Society of Digestive Endoscopy, in Romania there is a reduced mortality caused by non-varicose superior gastrointestinal bleeding (2.6%). The proportion of non-varicose upper gastrointestinal bleedings from the total number hemorrhages, was 74.7%, the most frequent cause being the duodenal ulcer, followed by: gastric ulcer, erosive gastroduodenitis, reflux esophagitis, Mallory Weiss syndrome, neoplasias.[6]

**Causes of upper gastrointestinal bleeding**

It has been noted that the most frequent cause is represented by the duodenal ulcer in proportion of 40%, followed by the gastric ulcer in approximately 10-20% of cases, diffuse gastritis 15-20%, esophageal varices 10%, Mallory-Weiss syndrome 10%, gastric carcinoma less than 5%.[1][2][3].

**Gastric and duodenal ulcer**

Despite of the numerous possibilities of medicamentous and endoscopic management, the duodenal ulcer continues to be a frequent cause of upper gastrointestinal bleeding. Hemorrhages caused by ulcer need surgical intervention in

<table>
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<tr>
<th>Table 1 - Digestive diseases</th>
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<tbody>
<tr>
<td>Esophageal</td>
</tr>
<tr>
<td>- esophageal varices, benign and malignant tumors, esophageal ulcer, erosive esophagitis, diverticula</td>
</tr>
<tr>
<td>- trauma caused by foreign bodies or iatrogenic (endoscopic explorations, biopsies, instrumental dilatation) Mallory-Weiss syndrome</td>
</tr>
<tr>
<td>Gastroduodenal</td>
</tr>
<tr>
<td>- ulcer, acute and hemorrhagic chronic gastritis, duodenitis, Menetrier’s disease</td>
</tr>
<tr>
<td>- hiatal hernia, benign and malignant tumors, diverticula</td>
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<tr>
<td>- gastric or duodenal mucosa prolapse</td>
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<tr>
<td>- trauma caused by foreign bodies or by endoscopy</td>
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<tr>
<td>- infections (fungal, CMV, TBC, syphilis), ampulla of Vater’s tumor, Crohn’s disease</td>
</tr>
<tr>
<td>- gastric volvulus, irradiation gastritis</td>
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</tbody>
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<tr>
<th>Table 2 - Other digestive diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>- hepatic cirrhosis, splenopathies, portal vein thrombosis, splenic artery thrombosis</td>
</tr>
<tr>
<td>- suprahepatic veins obstruction or thrombosis (Budd Chiari syndrome)</td>
</tr>
<tr>
<td>- hemobilia- bleeding’s cause may be hepatobiliary (trauma, hepatic artery broken aneurysm, biliary duct trauma) or pancreatic (acute or chronic pancreatitis, tumors)</td>
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<tr>
<td>- heterotopic gastric or pancreatic tissue, hemorrhagic celiac disease</td>
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4.3% of cases and hospital readmissions in 4.7% of cases [7]. The mortality is high but it varies between different countries: Canada 8.5%, Korea 2.2%, USA 2.5%, Turkey 2.8%, Spain 3.1%, Sweden 6.2%, Denmark 11% and Holland 14%.

The heterogeneity may be explained by the different prevalence of comorbidities, by the availability of endoscopy and by the usage of pharmacotherapy [10]. Some studies showed that the incidence had decreased and had stabilized. For example, in Sweden, the incidence is decreased from 64/100,000 in 1996 to 35/100,000 in 2014 and in Spain, from 55/100,000 to 25/100,000 [8]. This decrease may be partially explained by the prevalence’s decrease of Helicobacter Pylori [9].

Duodenal ulcers have a more severe prognostic compared to gastric ulcers, being associated to a higher rate of mortality, hospital readmission and surgical reintervention [11,12], probably because they are less endoscopically accessible, especially in rural areas [13,14]. It has been noticed that the upper gastrointestinal hemorrhage caused by ulcer, is accompanied by a more important blood loss, the conservative therapy and endoscopy have a lower efficacy and a higher necessity of surgical treatment, compared to other ways of treatment [3].

**Gastroesophageal reflux**

When a massive hemorrhage appears in patient suffering from gastroesophageal reflux disease, this is most likely caused by a penetrating esophageal ulcer, often distally localized. It has been observed that ordinarily, the esophageal ulcer develops from metaplastic epithelium and is localized at the border between normal epithelium and cylindrical Barrett epithelium. A particular form of upper gastrointestinal bleeding is that produced by an ulcer associated with a diaphragmatic hernia of the esophagus hiatus, also called Cameron ulcer. It’s supposed that the triggering mechanism of these lesions is represented by local trauma and gastric wall ischemia at diaphragm level. Frequently, the ulcer may remain undiagnosed [3].

**Tumors**

It has been observed that in majority of cases, the most frequent gastroduodenal benign tumors which cause upper gastrointestinal hemorrhage have mucosal (polyps) or muscular layer (leiomyomas) origin. They have in common the fact that are diagnosed at middle age and are more frequently located in gastric body or antrum. They may prolapse in lumen, or on the contrary, they may develop outwards. Small ulcerations orientated towards stomach lumen, may develop on their surface. From shallow ulcerations occult hemorrhages may produce which can frequently lead to iron deficiency anemia, while massive ulcerations may cause massive hemorrhage but also gastric ulcer like pain [3].

**Erosive gastritis**

It’s defined by multiple gastroduodenal mucosal defects. Commonly, stress lesions are localized in the fundic and corporeal region of stomach, while the hemorrhagic gastritis conditioned by the usage of NSAIDs, and affects the entire gastric mucosa, inclusively antral region. Erosive gastritis may result in severe acute hemorrhage [3].

**Mallory-Weiss syndrome**

In this case, the bleeding produces because of a linear laceration of the esophagogastric mucosa junction [15]. It most frequently appears in men with ages of 50-70 years, alcohol, acetylsalicylic acid or both consumers [17]. Among the rarer causes that can lead to the onset of the syndrome, the most popular are: anorexia, prolonged cough, epileptic convulsions, abdominal trauma, pregnancy and birth. Most of the patients initially have vomiting with gastric content, subsequently having vomiting with blood [15,16].

Most of the gastric cardial region hemorrhages stop by themselves while in the other patients, therapeutic endoscopy represents the elective method, surgery being reserved only for recurrences and transmural ruptures. The most efficient method is the guided through catheter angiographic embolization with gelfoam. Lethality in Mallory-Weiss syndrome constitutes 3-4% [15,3]. Some studies have shown that the endoscopic evidence of active bleeding and the shock as first manifestation, are risk factors for syndrome recurrence [18,19].

**Watermelon stomach (antral vascular ectasia)**

It represents about 4% of the cases of occult digestive hemorrhage, the main symptoms of patients being melena.

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### Table 3 - Extradigestive diseases

<table>
<thead>
<tr>
<th>Hemopathies</th>
<th>idiopathic thrombocytopenic purpura, hemophilia, Henoch purpura</th>
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<tbody>
<tr>
<td></td>
<td>allergic purpura, purpura vera, hemophilia, leukemia, Hodgkin disease</td>
</tr>
<tr>
<td></td>
<td>hypoprothrombinemia, hypofibrinogenemia, fibrinolysis</td>
</tr>
<tr>
<td></td>
<td>Glanzmann thrombastenina, pernicious anemia, Von Willebrand disease</td>
</tr>
<tr>
<td>Vasculopathies</td>
<td>arterial hypertension, aorto-enteric fistula, mesenteric or hepatic artery aneurysm, Rendu-Osler disease (hereditary hemorrhagic telangiectesia)</td>
</tr>
<tr>
<td></td>
<td>hemangiomas, intestinal varices, vasculitis</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>polyaarteritis nodosa, sarcoidosis, multiple myeloma, amyloidosis</td>
</tr>
<tr>
<td></td>
<td>systemic lupus erythematous, Ehler-Danlos syndrome, pseudoxantoma elasticum</td>
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<tr>
<td></td>
<td>scurvy</td>
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<tr>
<td>Renal diseases</td>
<td>those accompanied by uremia</td>
</tr>
</tbody>
</table>

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Hemopathies - idiopathic thrombocytopenic purpura, hemophilia, Henoch purpura, allergic purpura, purpura vera, hemophilia, leukemia, Hodgkin disease, hypoprothrombinemia, hypofibrinogenemia, fibrinolysis, Glanzmann thrombastenina, pernicious anemia, Von Willebrand disease

Vasculopathies - arterial hypertension, aorto-enteric fistula, mesenteric or hepatic artery aneurysm, Rendu-Osler disease (hereditary hemorrhagic telangiectesia), hemangiomas, intestinal varices, vasculitis

Systemic diseases - polyaarteritis nodosa, sarcoidosis, multiple myeloma, amyloidosis, systemic lupus erythematous, Ehler-Danlos syndrome, pseudoxantoma elasticum, scurvy

Renal diseases - those accompanied by uremia
and chronic anemia [20]. The affection appears more frequently in old women and is characterized by multiple dilated capillaries and corrugated vessels in the antral portion, which longitudinally cross the stomach towards pylorus [3].

Medication may be applied using tranexamic acid, corticotherapy, thalidomide, interferon, calcitonin, estrogeneric combinations or serotonin antagonists[21-25]. Endoscopic methods include sclerotherapy, thermocoagulation, endoscopic resection, banding [26]. Argon plasma coagulation, is the preferred method [3,26]. The surgical treatment is reserved to severe cases.

**Dieulafoy lesion**

Frequently occurs in the proximal portion of the stomach, close to the esogastric junction or on the small curvature of the stomach and represents about 1-2% of the upper gastrointestinal bleeding causes [26,27]. Its source is represented by the rupture of an artery belonging to the gastroduodenal wall submucosa, with an unusual large diameter (1-3 mm) and localized superficially in relation to the mucosa. Many patients are also NSAIDs consumers, oral anticoagulants or aspirin, alcohol, which may contribute to the onset of bleeding. Before the usage of endoscopy, the mortality had been of 80% but it decreased to 0-22%. The treatment combines endoscopic methods, injection of norepinephrine, of sclerosing agents, thermal coagulation, laser photocoagulation, banding, hemoclips etc. the recurrence is treated either in the same way as the first event, or surgically, by local excision or suture [3,27].

**Aorto-intestinal fistula**

It represents communications between aorta and gastrointestinal tract. There are known two types. The primary form is the most frequent and is produced by the rupture of an aneurysm of the abdominal aorta in the intestinal lumen[3]. The secondary form has an incidence of 1-4% and appears between the suture line of a vascular graft and bowel, after a long interval from the surgical intervention of vascular reconstruction [3,28]. In unstable hemodynamic patients, the emergency laparotomy is necessary. Even in those who undergo a reintervention, the mortality is of 60%[3,29].

**Hemobilia**

It’s among the less frequent sources of upper gastrointestinal bleeding and it appears when there is a fistula between vascular structures and the intrahepatic and extrahepatic biliary ducts. The most frequent causes are the iatrogenic and traumatic ones, in 50% of cases. Other causes are the hepatic and biliary neoplasms, inflammations, vascular causes, intrahepatic abscesses, choledocolithiasis and cholelithiasis. The patient presents for biliary (70%) of cases, jaundice (60%), digestive bleeding (100%), those composing Quincke triad which is present in 32-40% of cases [30,31].

The bleeding may spontaneously stop in patients who have undergone percutaneous angiography or hepatic biopsy. Some authors recommend prophylactic administra-

tion through puncture of clot forming promoters or absorbent gelatins Gelafon[34]. The aim of the treatment is to stop the bleeding and to reestablish the flow through the bile ducts. The most efficient method is the angiography with embolization. Other methods include endoscopic sphincterectomy and electrocoagulation. Surgery is required for the cases of hepatic trauma, when debridement, drainage and vessel ligation are necessary. It also has to be considered in cases of cholelithiasis, cholecystitis and resectable neoplasms. Although the surgical treatment is efficient in stopping hemobilia when the transcatheter embolization failed, this doesn’t rich the embolization’s efficacy if used as first way of treatment[31]. Among the complications of transcatheter embolization, are the hepatobiliary necrosis (6%), the formation of abscesses (9%) and the bleeding (6%)[31,32,33].

**Pancreatic pseudocyst and pseudoaneurysm**

They represent a rare cause, digestive hemorrhages producing in 10-15% of the patients with chronic pancreatitis and in 6-30% of those who develop pseudocyst. In case of an acute pancreatitis or in case of an inflammation due to a chronic pancreatitis, the visceral arteries may be injured, causing a pseudoaneurysm. Bleeding’s control may be obtained by radiological methods (bleeding’s source embolization – the celiac trunk or the superior mesenteric artery) or by surgical ones, in hemodynamically unstable patients. The studies have shown that a higher mortality in the pathology of acute pancreatitis 60% versus 22% in the case of chronic pathology, 43% in the case of cephalic localized lesions[39,40].

**Prognostic scores**

In emergency, it is necessary to sort the patients with acute upper gastrointestinal bleeding, to quickly recognize those patients who immediately need endoscopic exploration, to predict the possibility of appearance of a new bleeding and to choose the best treatment option. In order to achieve these goals, before performing any laboratory investigations, there may be used different variables, upon which, have been realized scores and classifications.

Blatchford score is based on this clinical and laboratory information, being used for predicting medical intervention of some kind. It consists of a scale of 0-23 points and the lowest score signifies the highest risk.

Rockall score is the most frequently used score in order to stratify the risk of upper gastrointestinal hemorrhage. It is calculated on the basis of the patient’s clinical parameters during his presentation to the hospital. Complete Rockall score associates both clinical observations and endoscopic criteria in order to determine the risk of a rebleeding or even of death caused by bleeding. The score may be between 0 and 11, 11 representing the highest risk.

**Treatment**

Upper digestive hemorrhage needs emergency evaluation and immediate treatment. Acid secretion suppression, endoscopic hemostasis techniques and H. Pylori identification as etiology have improved the treatment in superior digestive
hemorrhage. Nevertheless, the upper gastrointestinal bleedings have a high degree of mortality and morbidity. Neoadjuvant therapy with proton pump inhibitors have become the empirical standard treatment for superior digestive hemorrhages because their main cause is the gastric ulcer. It have been proved that their administration doesn’t affect the bleeding risk or the mortality, the last remaining between 7-14% in the USA.

For hemodynamically unstable patients the main goal of the initial management is the hydroelectrolitic and volume rebalancing. Risk stratification of patients is made according to clinical and endoscopic criteria. Unfavorable prognostic predictors include: age >65 years, shock, malaise, associated comorbidities, decreased hemoglobin/hematocrit levels at presentation, active bleeding, sepsis, increased creatinine and transaminases levels [42,43,44].

The optimum moment for endoscopy is frequently debated. After volume resuscitation and hemodynamic stabilization, the endoscopy should be made in 24 hours in all patients with signs of upper gastrointestinal bleeding, with both diagnostic and therapeutic purposes. Based on the endoscopy, it can be taken the decision of sending home those low-risk patients or hospitalizing those with severe lesions, for diagnostic and further treatment. The concurrent treatment with NSAIDs and antiplatelet agents like clopidogrel impact the etiology and the severity [42,43]. There are some scores used for this purpose: APACHE II, Forrest Classification, Blatchford, Rockall, Baylor, Cedars-Sinai Medical Center [46,47].

Theoretically, the presence of fresh red blood in the nasogastric suction probe, suggests active bleeding and necessitates emergency esophagogastroduodenoscopy, while the absence of blood in the nasogastric suction probe doesn’t exclude the superior digestive hemorrhage. According to a study realized by Al-jebreen, 15% of the patients without blood in the nasogastric suction probe had upper gastrointestinal bleeding [45]. Acid gastric secretion suppression has to be done using proton pump inhibitors, these offering a better gastric secretion suppression than antihistamine, which determines tachyphylaxis.

Proton pump inhibitors administration as neoadjuvant treatment before endoscopic therapy is frequently recommended, especially when the immediate access to endoscopy is limited [42]. It’s uncertain if the proton pump inhibitors administration before endoscopy influences the clinical evolution. One study had compared the administration of proton pump inhibitors versus placebo before endoscopy and revealed that a smaller number of the patients receiving proton pump inhibitors, had had active bleeding during endoscopy. There were no significant differences regarding the rate of rebleeding, the necessity of surgical intervention, or the mortality at 30 days. A meta-analysis has proved that neoadjuvant administration (before endoscopy) of proton pump inhibitors, has no benefit upon decreasing the risk of bleeding, necessity of surgery or mortality [49].

Adjuvant therapy administered after diagnostic and therapeutic endoscopy has proved efficient in decreasing the necessity of transfusion, the need of surgery and the duration of hospitalization. Yet, it hasn’t been proved an impact upon mortality [45,50,51]. The guides recommend the use of proton pump inhibitors intravenously 3 days after haemostatic endoscopy. In many studies, the increased dose of proton pump inhibitors is defined as an initial bolus of omeprazol 80 mg, followed by continuous perfusion of omeprazol 8 mg/h up to 72 hours [42].

Endoscopic evaluation represents an essential part in the management of superior digestive hemorrhage. Emergency endoscopy has been proposed as standard method in patients with high-risk lesions, but the execution moment is variably defined. The American Society of Gastrointestinal Endoscopy suggests that precocious endoscopy (in 24 hours) is the most efficient, but has no recommendations regarding the exact moment which should be chosen in this interval of 24 h [52].

More studies have tried to find an answer to these questions. In a study of Sarin, endoscopy was effectuated in 500 patients, in more time intervals: <6h, 6-24h and >24h. There was no significant difference in mortality or the need for surgery between the groups of <6h and 6-24h, but there was a difference between the groups of <24h and >24h [53].

The endoscopic techniques include 1) pharmacologic therapy, which presumes the injection of epinephrine, sclerosing substances, saline solution 2) clotting techniques which include mono or bipolar cautery or plasma argon coagulation 3) mechanical techniques which comprise hemoclips and banding. Each of these is efficient in different clinical situations.

Usually the choice is made basing on the clinical judgment and experience. There are data which suggest that epinephrine injection and a second endoscopic intervention is superior than administering only epinephrine. Even if endoscopy cannot realize ultimate hemostasis, it may have an important part in localizing the bleeding source and in choosing a non-endoscopic technique. Endoscopy repeat may assist the radiologic or surgical intervention. Second-look endoscopy decreases the rate of rebleeding but not also the risk of mortality or the necessity of surgery.

Blood in the superior digestive tract limits the ability of endoscopy to identify the bleeding source. Prokinetic agents stimulate the gastrointestinal tract’s motility. American Society of Gastroenterology recommends the use of erythromycin intravenously before endoscopy [52]. A recent meta-analysis shows that it can also be used metoclopramide, but none of them doesn’t influence the number of transfused blood units, the hospitalization period or the need of surgical intervention [55,56].

Long-term treatment with proton pump inhibitors is recommended for 6-8 weeks after endoscopy in order to allow mucosal healing. Some studies revealed proton pump inhibitors benefits in patients who use NSAIDs or to whom the presence of H. Pylori had been confirmed. Other studies have tried to prove that proton pump inhibitors may have a role in secondary prevention in patients belonging to these two categories [57]. Although is has
numerous benefits, it’s not completely risk-free. Chronic administration is associated with Clostridium Difficile infection, community-acquired pneumonia, calcium malabsorption and risk of fracture [41,58].

Emergency surgery or transcatheter embolization represent treatment options for recurrent or refractory hemorrhage. Surgery has the disadvantage of increased rates of mortality and morbidity. Embolization has the advantage of avoiding laparotomy in elderly patients, patients with associated comorbidities, patients with coagulopathy or anti-coagulant treatment. This method has the disadvantage that it associates a high risk of rebleeding compared to surgery. Other TAE complications are the ischemic ones, in 7-16% of cases, gastrointestinal wall necrosis, stenosis [57,58,41].

CONCLUSIONS

Correlation between ethiopathogenesis and ways of medical and surgical treatment, together with prognosis scores, may positively influence the mortality and morbidity in non-variceal upper gastrointestinal bleedings. In emergency, there is necessary the sorting of patients with acute superior digestive hemorrhages, the fast identification of those patients who immediately need endoscopic exploration, the prediction of the possibility to start a new bleeding and the choice of the best option of treatment. In order to achieve this, before effectuating any laboratory tests, there may be used clinical variables on which were made scores and classifications.

Rockall score is based on clinical and laboratory information, being used for predicting medical intervention of some kind. It consists of a scale of 0-23 points and the lowest score signifies the highest risk.

Rockall score is the most frequently used score in order to stratify the risk of upper gastrointestinal hemorrhage. It is calculated on the basis of the patient’s clinical parameters during his presentation to the hospital. Complete Rockall score associates both clinical observations and endoscopic criteria in order to determine the risk of a rebleeding or even of death caused by bleeding. The score may be between 0 and 11, 11 representing the highest risk.

Hemorrhages caused by esophageal varices in cirrhotic patients are evaluated using other scores (ex. Child-Pugh). Although Glasgow Blatchford Score correctly frames at presentation the patients with superior digestive hemorrhage of variceal origin, studies have shown that it’s not able to predict the clinical evolution of the patients belonging to this group.

Acknowledgement

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