Gastroduodenal major haemorrhages in critical patients

An original surgical technique

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Francesco Cortese, Sara Colozzi, Roberto Marcello*, Irnerio Angelo Muttillo, Francesco Giacovazzo, Matteo Nardi, Alessandro Mero

A.C.O. "San Filippo Neri", Rome, Italy
U.O.C. di chirurgia d'urgenza (Chair: dr. A. Mero)
**U.O.C. di radiologia (Chair: f.f. dr A. Perozzi)*

Gastrointestinal major haemorrhages in critical patients. An original surgical technique

AIM: *Upper gastrointestinal bleeding represents today a serious pathology with two important problems: mortality and correct management. Our study is a review of recent and past licterature about causes, diagnosis and treatment of upper gastrointestinal bleeding.*

PERSONAL EXPERIENCE: *The Authors describe an original surgical technique in treating patients with gastroduodenal haemorrhages and critical circulatory-coagulative conditions. Any surgical resective procedure could be absolutely inacceptable for the rates in morbility and mortality in these absolutely instable patients. We approached the problem with a control damage surgery by endoluminal packing of the stomach or the duodenum.*

KEY WORDS: Damage control surgery, Endoluminal packing, Gastroduodenal haemorrhages, Haemorrhagic shock, Nonvariceal upper gastrointestinal bleeding.

Introduction

Nonvariceal upper gastrointestinal bleeding (NVUGIB) has a major impact on daily clinical practice, and is one of the most common reasons for urgent surgical consultation [1-3] with an incidence in the western countries estimated to be 50-150 cases per 100.000 persons [1-3]. NVUGIB, although less critical than variceal hemorrhage, is nevertheless a very serious condition with mortaliy rates ranging from 6-11%[4,5]. The most common causes of NVUGIB[4-12], occurring in patients of all ages [13], are peptic ulcer disease (35-50%) and/or erosive gastroduodenitis[4-12,14] (8-15%), neoplasia[15,16] (1%), Mallory Weiss Syndrome[4-17] (15%), aortoenteric fistulae[18] (5%), gastric and duodenal diverticulae[6-7] (5%), the latter being especially serious, sequelae of bariatric surgery[8-11] (3%), angiodysplasia[19,20]. Other causes include Dieulafoy's disease[21-26] (2%), cytomegalovirus[27-30] (2%), helicobacter pylori or human herpes virus 6[31-36], changes in coagulation status either due to pathology or specific therapy, steroids, nonsteroidal anti-inflammatory drugs (NSAIDS), the sequelae, even late sequelae, of surgery[37,38], Dengue virus[39] and the GAVE[40].

Treatment of NVUGIB in patients with important comorbidities (cardiac, respiratory and metabolic) is especially complicated. Due partly to the aging of the population the number of patients with chronic diseases has

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Correspondence to: Francesco Cortese, MD, via G. Martinotti 20, 00135 Rome, Italy (e-mail: francesco.cortese@sichirurgia.org)

increased[41-44], with the result that there are many patients receiving chronic and complex medical treatment. According to the Italian Drug Regulation Agency (Agenzia Italiana del Farmaco - AIFA) 55-60% of patients are not on "me-too" drugs. The Italian Federation of Centers for the Surveillance of Anticoagulant Therapy (Federazione Centri Sorveglianza Anticoagulanti) reports that there are 1.000.000 - 1.500.000 patients treated with oral anticoagulants, but there are no exact data on patients taking platelet aggregation inhibitors, whether clopidogrel or ticlopidine/ salycilates. The management of these patients is fraught with problems due to the characteristics of NVUGIB. The basic treatment algorithm for NVUGIB has been well described in the literature[3-5,45-55]. Surgery[54-75], once considered obligatory, has been replaced by endoscopy[76-86] and angiography[87-93] which, due to success rates of 80% and 95% respectively, are first-line treatment either singly or combined. In our opinion this algorithm has a grey zone: the clinical and logistic approach to patients who are hemodynamically unstable, who have blood-clotting abnormalities, who are in hospitals where neither operative endoscopy nor interventional radiology are available, or have already been treated unsuccessfully with both methods and therefore require surgery. For this reason at our unit of emergency surgery we have developed the technique of "endoluminal packing". This technique, associated with primary control of bleeding, has enabled us to treat patients in severe hemorrhagic shock, who could not be treated with any type of surgical resection due to absolute severe clinical instability.

Methods

In the period from February 2010 to December 2011 5 patients were treated with this technique at our unit. There were 2 males and 3 females, with an average age of 74.8 years (RANGE:64-86 YEARS). All 5 patients were in a state of severe hemodynamic instability with an average hemoglobin level of 6.5 g/dl and an average international normalized ratio (INR) of 3. One patient (20%) had alcholol-related cirrhosis of the liver and full-blown portal hypertension, 3 patients (60%) were on vitamin K antagonists because of chronic atrial fibrillation, 1 patient (20%) had a history of pulmonary embolism, 4 patients (80%) had arterial hypertension, 1 patient (20%) had an abdominal aortic aneurysm, 2 patients (40%) had chronic obstructive pulmonary disease, 1 patient(20%) had mitral regurgitation, and one (20%) had a history of stroke.

Two patients were transferred to our unit from another hospital for an EGD, 2 patients were transferred from the emergency department after resuscitation of hemorrhagic shock, and 1 patient had been admitted to the gastroenterology unit for recurrent melena.

All patients underwent esophagogastroduodenoscopy (EGD) and 2 patients also underwent arteriography. The

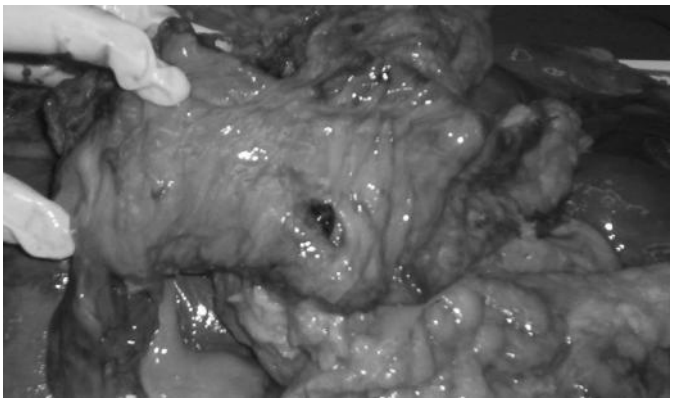

Fig. 1: Autopsy specimen of patient who died on postoperative day I with a diverticulum on the posterior wall of the duodenum.

TABLE I - *Patient characteristics*

Name	Age (years)	Sex	BMI (kg/m²)	Transferred from	Comorbidity	Prognosis
GT	86	F	27	Intensive care	HTN, MR, history of PE	Discharge on PO day XV
GG	71	M	32	Gastroenterology	HTN, AAA, history of stroke	Death on PO day I
AT	64	M	26	Other hospital for EGD	Alchohol-related cirrhosis, portal hypertension	Death on PO day XXX
AMG	81	F	28	Other hospital for EGD	HTN, COPD (pulmonary emphysema)	Discharge on PO day XXVI
CG	72	F	26	Intensive care	HTN / COPD Treated with steroids and ASA	Discharge on PO day XXIII

Legend: PE: pulmonary embolism; HTN: arterial hypertension:MR: mitral regurgitation; AAA: abdominal aortic aneurysm; ASA: acetylsalicylate; COPD: chronic obstructive pulmonary disease; BMI: body mass index; EGD. Esophagoduodenoscopy; PO: postoperative.

TABLE II - *Diagnostic and treatment pathways*

N	Patient	Forrest class	HB/INR on admission	Diagnostic EGD	Operative EGD	Diagnostic arteriography	Operative arteriography
1	GT	1 A	7,3/3,2	YES	NO	NO	NO
2	GG	III 4th part of duodenum	7,1/3	YES	NO	YES/+	NO
3	AT	1 A		YEs	YES	NO	NO
4	AMG	1 A	7/4	YES 2	YES	NO	NO
5	CG	1 A	5/3	YES 2	NO	YES/-	NO

Legend: HB: hemoglobin; INR: International normalized ratio.

following surgical procedures were performed: gastrotomy (n=2), duodenotomy (n=3). In 4 cases primary control of bleeding was performed, suturing an ulcer in 3 cases and resection of a polyp in 1, followed by endoluminal packing with laparotomy gauzes without any vessel ligation. In 2 patients a Petzer tube was left in the duodenum. Due to the extremely serious clinical condition of the remaining patient and inability to identify the source of bleeding, only endoluminal packing of segments 2-4 of the duodenum was performed with proximal and distal ligation of this section of the intestine.

TABLE III - *Transfusions:Blood/Plasma*

N	Patient	Pre	Intra	Peri	Post
1	GT	4/4	2/2	1/1	1/3
2	GG	3/4	3/2	2/2	Death 20 hours after surgery
3	AT	4/4	3/0	2/1	Death on PO day XXX *
4	AMG	2/1	4/5	3/5	2/1
5	CG	7/10	4/1	4/9	1/1

*further transfusions in postoperative period; PO: postoperative

Results

Satisfactory hemostasis was obtained in all cases. One patient died of acute myocardial infarction 19 hours after surgery (Fig. 1). In the other 4 cases relaparotomy for de-packing was programmed and performed 48-72 hours after primary surgery with all patients in good clinical conditions with coagulative and haemodynamic stable parameters. No resection or improvement of haemostasis was necessary. No vascular ligation was performed. A right hemicolectomy was required in only one patient due to neoplastic stenosis. This patient, who also had alchohol-related cirrhosis of the liver and portal hypertension, died of liver failure due to cirrhosis on postoperative day 30.
Patient characteristics and diagnostic/therapeutic procedures are shown in Tables I, II, III.

Discussion

NVUGIB is well-known to be an extremely serious condition. Despite the worldwide available well structured clinical algorithms[3-5,45-54,94-98] they seems not applicable because not all institutions provide operative endoscopy and angiography. The seriousness of NVUGIB stems from the fact that blood can accumulate in the gastrointestinal tract like in a reservoir, so that if the patient has no hematemesis the other two pathognomic symptoms of the condition, melena and rectal bleeding, become evident much later than in patients with lower gastrointestinal bleeding (LGIB).
The most important clinical classification systems for NVUGIB are the Forrest classification, the Rockall score and the Blatchford score[99-104] (Tables IV-V). The first, related to the endoscopic appearance of peptic ulcers, permits stratification of risk for mortality and re-bleeding. In class Ia and Ib the mortality risk is 55%, and the risk of reoperation is 35%, in class IIa 43% and 34% respectively, in class IIb 22% and 10% respectively and in class III 10% and 6% respectively for ulcers with an adherent clot and 55 and 0.5% respectively in ulcers without active bleeding[68,93].
The clinical Rockall score is based on clinical data at presentation and the score is calculated using clinical and endoscopic criteria (Table VI).
The Blatchford scoring system (Table VII) does not involve endoscopic evaluation and the risk variables are clinical and serum biochemical parameters. All three classification systems, which are used worldwide, make it possible to quantify in a reliable manner mortality and morbidity risks.

TABLE VI - *The Blatchford Scoring System*

Variable	Score
BUN (mmol/l)	
> 6.5< 8.0	2
> 8 < 10	3
> 10 < 25	4
> 25	6
Hemoglobin (g/dl)	
Men	
> 12 < 13	1
> 10 < 12	3
< 10	6
Women	
> 12 < 13	1
< 10	6
Systolic BP (mmHg)	
100–109	1
90–99	2
< 90	3
HR > 100	1
Melena	1
Syncope	2
Liver disease	2
Heart failure	2

Legend: BUN: Blood urea nitrogen; BP: blood pressure; HR=heart rate.

A global evaluation of NVUGIB patients, more than the bleeding lesion itself, must be made immediately. It is of the utmost importance to consider both the morphology of the disease (Forrest classification[7]) and the patient-specific factors used for specific risk scoring systems. In the case of NVUGIB patients, as other surgical patients, general clinical conditions are currently the essential considerations in determining the most appropriate clinical approach[94-106]. An Acute Physiology and Chronic Health Evaluation (APACHE) score >11, signs of recent bleeding, the presence/absence of cirrhosis, INR >1.3, serum creatinine >1.5 mg/dl, albumin <2.5 mg/dl and BUN >50mg/dl are of primary clinical importance[95-100]. These clinical and metabolic data are at least, if not more important than correct surgical management, and the experience and specialized training of the operating surgeon[95-100]. Although the classification systems and clinical protocols are standardized and widely used, the timing and performance of the procedures (as the number of transfusions, time until the procedure and operative time, flexible or rigorous application of management algorithms, presence/absence of the surgeon at the individual procedures) varies from one hospital to another.

The priority in clinical treatment pathways in clinical practice is often transferring the patient, when hemodynamic and metabolic stabilization of the patient should take precedence over any diagnostic and treatment maneuvers[99-106]. There is agreement in the literature that early, intensive stabilization reduces mortality[105-108]. A bloods transfusion policy is required for otherwise healthy NVUGIB patients with a hemoglobin level <7 g/dl and for cardiopathic and/or elderly patients with a hemoglobin level of <10g/dl[99-106]. However transfusion alone, without endoscopical, angigraphic or surgical treatment is useless and dangerous. Therapy with proton pump inhibitors[107-108] and antibiotics[109], standardized and universally accepted in elective surgery, does not have a key role in NVUGIB patients, although it should be started early and continued throughout diagnosis and treatment. There should be such close collaboration between endoscopists, interventional radiologists, and surgeons that a gastrointestinal bleeding unit is formed and fast-track clinical pathways adapted to each individual hospital setting, and widely accepted are implemented[110-116]. The introduction into clinical practice of first of H_2blockers and then of proton pump inhibitors, has notably reduced the incidence of peptic ulcer disease and the main associated complications (perforation and bleeding). In particular, according to Sreedharan and colleagues[112] therapy with proton pump inhibitors reduces

TABLE V - *The Rockall Scoring System (Definitive score)*

Variable	Score 0	Score 1	Score 2	Score 3
Diagnosis	No	—	Gastric/ esophageal cancer	—
Age	<60	60 – 79	> 80	—
Shock	No	HR > 100'	Average BP <100 mmHg	—
Comorbidity	No	—	Cardiac comorbidity or other major pathology	Liver or kidney failure Advanced cancer
	No signs of recent bleeding *Mallory–Weiss*			
Signs of recent bleeding	No	—	Blood in the lumen Clot	—
	Black spots		Non-bleeding visible vessel Active bleeding	

Legend: Liver HR: heart rate; BP: blood pressure.

TABLE IV - *Forrest classification*

Ulcer Characteristics	Risk Of Bleeding
ACTIVE BLEEDING	
I A spurting bleeding	55%
IB non-spurting active bleeding	55%
SIGNS OF RECENT BLEEDING	
II A non-bleeding visible vessel,	43%
II B non- bleeding ulcer with adherent clot	22%
IIC ulcer with hematin-covered base	10%
III NO SIGNS OF BLEEDING	
III clean base	5%

the incidence of recurrent bleeding by 13.9%, which is similar to the results of Leontidas[95] who reported 10% recurrent bleeding. In contrast to this overall reduction in rebleeding, the incidence of complications and of hemorrhage in particular, has not been reduced. This means that surgery for perforation and bleeding of the stomach and duodenum, except for cancer surgery, is almost exclusively in the hands of the emergency department. In fact, a Finnish study from 2009 showed that between 1987 and 1999 the number of patients undergoing elective surgery of the stomach and duodenum decreased while the number of patients undergoing emergency procedures increased from 25% to 90%[114].

The reason for this is that although drugs for treating peptic ulcers are now available, there has not been a reduction in the incidence of complications (i.e. bleeding) associated with the disease and not-responders are at risk of more severe complications[41-44,50,61,64,66-72,75,78,97-101,114-116]. It is necessary to establish simple key clinical points such as the number of units of blood to be transfused before proceeding to the next step. In the search for optimal clinical management of NVUGIB patients it becomes clear that at times for clinical and logistical reasons surgery is the default approach if operative endoscopy is not available 24 hours a day, 365 days a year, if there is no interventional radiology on hand and, last but not least, when the clinical condition of the patient is such that surgical management is unavoidable. This modification of the standard algorithm is then the best possible treatment. The inter-hospital transfer of a patient with massive gastroduodenal hemorrhage so that he/she can undergo operative endoscopy or arteriography is an immoral practice. Surgical control of the hemorrhage needs to be facilitated as soon as possible. Transfusing 5 units of blood as a preliminary to an inter-hospital transfer results in delayed treatment and thus puts the patient at very great risk of a catastrophic out come. Transfers, if insisted upon by obstinate consultants, must be organized without any loss of time, with clinical and haematological parameters stable.

First-line treatment, endoscopy, whether diagnostic or operative, must be performed early not too. The diagnosis must include Forrest classification of the lesion, as the starting point of the clinical algorithm. The literature unequivocally links prognosis to the quality rather than the quantity of treatment measures. Laine e McQuaid[83] describe the efficacy of endoscopic treatment of both active bleeding and non-bleeding visible vessels. They also report that outcome was significantly better if endoscopy was associated with a continuous infusion of proton pump inhibitors than if patients received a placebo/had no therapy (RR:0.40). The rate of recurrent bleeding is not significantly reduced by any other monotherapy (RR:0.058), epinephrine followed by other therapy (RR:0.34), heat probe coagulation (RR:0.44), or sclerotherapy (RR.0.56). Hemoclips are more effective than epinephrine (RR:0.22).

As regards the timing of endoscopy, the literature indicates that the procedure should not be performed too early. The Odds Ratio of mortality and surgical option in patients with endoscopy performed before <6 hours vs >24 hours is 3.6, in patients with endoscopy >6hrs/<24hrs is 2.8[86]. Same Authors describe the hypotension state period, haemoglobin levels and the endoscopy time <6 hours or 6/24 hours the risk factors for the prognosis[86]. The second option, angiographic management, is less invasive and makes it possible to significantly reduce gastroduodenal vascularization and to control bleeding with results almost as good as those obtained with surgery. In the literature the efficacy of angiographic treatment in controlling bleeding is reported to be 48%-90% and the incidence of recurrent bleeding 0%-40%[52].

Surgery is indicated when:

1) Failure of endoscopic treatment;
2) Recurrent hemorrhage after 2 attempts at endoscopic hemostasis;
3) Shock associated with recurrent hemorrhage;
4) Patient unstable after rapid transfusion of at least 5 units of blood or blood loss >2500 ml in 24 hours;
5) Continuous bleeding requiring the transfusion of more than 3 units of blood per day.

The standardized surgical procedures used for patients with NVUGIB are gastroduodenal and gastroepiploic arteries ligation, vagotomy, duodenotomy with placement of hemostatic sutures, excision of the ulcer and suturing, and gastric resection. It is important to note that the reduction in the risk of rebleeding after ligation of the gastroduodenal and gastroepiploic arteries is about the same as after gastrectomy[46-51]. Total or subtotal gastrectomy is the surgical procedure of choice in patients with NVUGIB when the double parasurgical treatment has failed. The indications for gastrectomy must be related to the hemodynamic status of the patient. It should always be kept in mind that patients who have undergone gastrectomy to remove the ulcer followed by

Billroth I or II reconstruction the risk of bleeding is lower than in patients who undergo a conservative procedure, even though the former is associated with a greater risk of bile reflux[15]. During gastric resection haemostatic agents and tissue sealants can be used to better control the bleeding[54,72,76,85]. Vagotomy (truncal, selective or superselective) can be combined with placement of drains or resection. De la Fuente and colleagues[57] compared the two procedures in a retrospective study. The postoperative mortality, morbidity and bleeding rates were similar while the patients who underwent resection had a longer postoperative hospital stay. If NVUGIB is known or suspected to be due to cancer, the surgical procedure of choice is partial or total gastrectomy[3,15-16,46,49].

Conclusions

In view of what is mentioned above our method must not be considered a standard approach to all patients with gastroduodenal bleeding but an emergency option for treating patients in extremely critical condition for whom Damage Control Surgery[115], in which less is more, is currently the procedure of choice. Performing more or less extensive gastroduodenal resections on patients in hemorrhagic shock would have led to unacceptably high morbidity and mortality rates without any real increase in curative potential.
Our approach with treatment kept to a minimum, rapid and effective, allowed complete control of bleeding and clinical stabilization of the patient. Essential to our treatment method and absolutely indicated were:
1) Extensive use of endoluminal drains (i.e. Petzer catheter, urinary catheter, gastrostomy kit);
2) Open abdomen or closure only of the skin layer.
The latter served both to prevent the development of compartment syndrome and to permit rapid reaccessing of the abdominal cavity if necessary which was never the case in our experience. None of the patients had particular surgical problems, bleeding was controlled in all cases, and depacking was almost always performed as an elective procedure.
This suggests that the clinical rationale and indications for our approach were correct.

Riassunto

Le emorragie non varicose del tratto gastrointestinale alto rappresentano ancora oggi una patologia importante, gravata da mortalità e morbilità elevate e di non sempre facile gestione. In particolare il verificarsi di questi eventi in pazienti anziani, con comorbilità importanti e con alterazioni della coagulazione sia per terapie sia da scompenso metabolico-ematologico, pone problemi di gestione clinica non facili. In quest'ottica abbiamo ideato una tecnica chirurgica, modulata dal concetto della *Control Damage Surgery*, di *packing* endoluminale che qui descriviamo insieme ad una revisione della letteratura riguardo le cause ed i protocolli clinico gestionali.

References

1. Van Leerdam EE: *Epidemiology of acute upper gastrointestinal bleeding.* Best Pract Res Clin Gastroenterol, 2008; 22:209-24.

2. Strano S, Biondi A, Caruso GB, et al:. *Il trattamento chirurgico delle lesioni peptiche sanguinanti: Nostra esperienza.* Ann It Chir, 2002; 67:267-71.

3. Hungness ES: *Gastrointestinal bleeding*. In Cance WG, Valentine RJ, Jurkovich GJ, Swanson SJ, Napolitano LM, Pemberton JH, Chen H, Soper NJ (eds): *ACS Surgery: Principles and Practice*. New York: Decker Inc., 2009.

4. Rockall TA, Logan RF, Devlin HB. et al.: *Incidence and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage*. BMJ, 1995; 311:222-26.

5. Barkun A. et al.: *Consensus recommendations for managing patients with nonvariceal upper gastrointestinal.* Ann Intern Med, 2003; 139:843-57.

6. Thorson CM, Ruiz PS, Roeder RA, et al.: *The perforated duodenal diverticula.* Arch Surg, 2012; 147:81-88.

7. Monig SP, Lubke T, Baldus S et al.: *Early elective surgery for bleeding ulcer in the posterior duodenal bulb. Our results and review of the literature.* Hepatogastroenterology, 2002; 49:416-18.

8. Csendes A, Burgos AM, Altuve J, et al.: *Incidence of marginal ulcer 1 month and 1 to 2 years after gastric bypass: a prospective consecutive endoscopic evaluation of 442 patients with morbid obesity.* Obes Surg 2009; 19:135-38.

9. Kyzer S, Gelber E, Rabinovich Y, et al.: *Massively bleeding gastric pouch ulcer after silastic ring vertical gastroplasty successfully treated endoscopically: A report of two cases.* Obes Surg, 1997; 7:158-60.

10. Husain S, Ahmed AR, Johnson J, et al.: *CT scan diagnosis of bleeding peptic ulcer after gastric bypass.* Obes Surg, 2007; 17:1520-522.

11. Mehran A, Szomstein S, Zundel N, et al.: *Management of acute bleeding after laparoscopic Roux-en-Y gastric bypass.* Obes Surg, 2003; 13:842-47.

12. *Yang CS, Lee WJ, Wang HH et al.*: *The influence of Helicobacter pylori infection on the development of gastric ulcer in symptomatic patients after bariatric surgery.* Obes Surg, 2006; 16:735-39.

13. Wilcox DT, Jacobson A, Bruce J:. *Haemorrhage from a duodenal ulcer in a neonate.* Pediatr Surg Int, 1997; 12:202-03.

14. Sapala JA, Wood MH, Schuhknecht MP, et al.: *Peptic ulcer after gastric bypass: Should a paracrine pathway be invoked?* Obes Surg, 2002; 12:419-20.

15. Karpeh MS, Kelsen DP, Tepper JE*: Cancer of the stomach.* In: DeVita VT Jr, Hellman S, Rosenberg SA (eds*)): Cancer. Principles e Practice of Oncology*. Philadelphia: Lippincott, 2001:1092-126.

16. Gunderson LL, Donhoue JH, Burch PA*: Stomach.* In: Abeloff

MD, Armitage JO, Lichter AS, Niederhuber JE (eds)*: Clinical Oncology,* 2nd ed,. New York:Churchill Livingstone, 2000: 1545-585.

17. La Greca G, Grasso E, Sofia M, Fagliardo S, Barbagallo F: *La fistola duodenobiliare complicata nell'ulcera duodenale sanguinante. Caso clinico e revisione della letteratura*. Ann It Chir, 2008; 79:57-61.

18. Fancellu A, Giuliani G, Feo CF, Scanu AM, Porcu A: *Su un caso di fistola aortoenterica primitiva*. Ann It Chir, 2004; 75:373-78.

19. Montesano G, Bertagni A, Gallinaro LS, Nasti AG, Bezzi C, Forte A, Palumbo P, Soda G, Buzzi M: *L'angiodisplasia del grosso intestino: Una rara localizzazione rettale.* Ann It Chir, 2000; 71:609-14.

20. Mattioli FP, Torre GC, Puglisi M: *Su 13 casi di angiodisplasia dell'apparato digerente.* Ann It Chir, 2002; 73:25-30.

21. Baettig B, Haecki W, Lammer F et al.:*Dieulafoy's disease: Endoscopic Treatment and follow up.* Gut, 1993; 34:1418-421.

22. Norton ID, Petersen BT, Sorbi D, et al.: *Management and long-term prognosis of Dieulafoy lesion.* Gastrointest Endoscop, 1999; 50:762.

23. Veldhuyzen van Zanten SJ, Bartelsman JF, Schipper ME, et al.: *Recurrent massive haematemesis from Dieulafoy vascular malformations: A review of 101 cases*. Gut, 1986; 27:213-22.

24. Ibrarullah M, Wagholikar GD: *Dieulafoy's lesion of duodenum: A case report.* BMC Gastroenterol, 2003; 3:2.

25. Lee FI: *Dieulafoy vascular malformation.* Gut, 1986; 27:746-47.

26. Sciumè C, Di Vita G, Geraci G, Pisello F, Modica G: *L'ulcera di Dieulafoy: Causa rara di emorragia del tratto gastroenterico superiore. Nostra esperienza.* Ann It Chir, 2001; 72:233-38.

27. Bobak DA: *Gastrointestinal infections caused by Cytomegalovirus.* Curr Infect Dis Rep, 2003; 5:101-07.

28. Page MJ, Dreese JC, Poritz LS et al.: *Cytomegalovirus enteritis: a highly lethal condition requiring early detection and intervention.* Dis Colon Rectum, 1998; 41:619-23.

29. Razonable RR: *Cytomegalovirus infection after liver transplantation: current concepts and challenges.* World J Gastroenterol, 2008; 14:4849-60.

30. Franzin G, Muolo A, Griminelli T*: Cytomegalovirus inclusions in the gastroduodenal mucosa of patients after renal transplantation.* Gut, 1981; 22:698-701.

31. Halme L, Arola J, Höckerstedt K et al.: *Human herpesvirus 6 infection of the gastroduodenal mucosa.* Clin Infect Dis, 2008; 46:434-39.

32. Callicutt CS, Behrman SW: *Incidence of Helicobacter pylori in operatively managed acute nonvariceal upper gastrointestinal bleeding.* J Gastrointest Surg, 2001; 5:614-19.

33. Tørring ML, Riis A, Christensen S et al.: *Perforated peptic ulcer and short-term mortality among tramadol users.* Br J Clin Pharmacol, 2008; 65:565-72.

34. Stabile BE: *Hemorrhagic complications of pancreatitis and pancreatic pseudocysts. The pancreas: A clinical textbook*. Oxford: Oxford Press, 1998; 606-13

35. Hirata M, Kita Y, Harihara Y, Hisatomi S et al.: *Gastrointestinal bleeding after living-related liver transplantation.* Dig Dis Sci, 2002; 47:2386-388.

36. Owens ML, Passaro E Jr, Wilson S, et al.: *Treatment of peptic ulcer disease in the renal transplant patient*. Ann Surg, 1977; 186:17-21.

37. Takebayashi T, Okushiba S, Ohno K, et al.: *Peptic ulcer-induced acute aortogastric fistula occurring 7 years after a pharyngogastrostomy following a resection for carcinoma of the esophagus: Report of a case.* Surg Today, 2004; 34:777-79.

38. Bianchi P, Dalainas I, Ramponi F et al.: *Late gastrointestinal bleeding after infrarenal aortic grafting: A 16-year experience.* Surg Today, 2007; 37:1053-59.

39. Chiu LN, Wu KL, Cuo CH et al.: *Endoscopic findings and management of dengue patients with upper gastrointestinal bleeding.* Am J Trop Med Hyg, 2005; 73:441-44.

40. Sciumè C, Geraci G, Pisello F, Facella T, Pinto G, Fernandez P, Licata G, Modica G: *Ectasia vascolare gastrica antrale (GAVE) e "Watermelon Stomach Syndrome": Report di 3 casi ed indicazioni cliniche e terapeutiche*. Ann It Chir, 2004; 74:477-84.

41. Higham J, Kang JY, Majeed A: *Recent trends in admissions and mortality due to peptic ulcer in England: increasing frequency of haemorrhage among older subjects.* Gut, 2002; 50:460-64.

42. Cullen DJ, Hawkey GM, Greenwood DC et al.: *Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs.* Gut, 1997; 41:459-62.

43. Christensen S, Thomsen RW, Tørring ML, et al.: *Impact of COPD on outcome among patients with complicated peptic ulcer.* Chest, 2008; 133:1360-366.

44. Thomsen RW, Riis A, Christensen S, et al.: *Diabetes and 30-day mortality from peptic ulcer bleeding and perforation: A Danish population-based cohort study.* Diabetes Care, 2006; 29:805-10.

45. Gralnek IM, Barkun AN, Bardou M: *Management of acute bleeding from a peptic ulcer.* N Engl J Med 2008; 359:928-37.

46. Bardou M, Benhaberou-Brun D, Le Ray L, et al.: *Diagnosis and management of nonvariceal upper gastrointestinal bleeding.* Nat Rev Gastroenterol Hepatol, 2012; 9:97-104.

47. Tsoi KK, Chiu PW, Sung JJ: *Endoscopy for upper gastrointestinal bleeding: Is routine second-look necessary*? Nat Rev Gastroenterol Hepatol, 2009; 6:717-22.

48. Wee E: *Management of nonvariceal upper gastrointestinal bleeding.* J Postgrad Med, 2011; 57:161-67.

49. Koenig AM, Gawad K, Yekebas E, et al.: *Timing and concepts of surgical treatment of upper gastrointestinal haemorrhage.* Zentralbl Chir, 2010; 135:65-69.

50. Zittel TT, Jehle JC, Hecker HD: *Surgical management of peptic ulcer disease today-indication, technique and outcome.* Langerback's Arch Surg, 2000; 384:84-96.

51. Barkun AN, Bardou M, Kuipers EJ, et al.: *International consensus recommendations on the management of patient with nonvariceal upper gastrointestinal bleeding.* Ann Intern Med, 2010; 152:101-13.

52. Van Lanschot JJB, van Leerdam M, van Delden OM et al.: *Management of bleeding gastroduodenal ulcers.* Dig Surg, 2002; 19:99-104.

53. Ghosh S, Watts D, Kinnear M: *Management of gastrointestinal hemorrhage.* Postgrad Med J, 2002; 78:4-14.

54. Pais SA, Yang R: *Diagnostic and therapeutic options in the management of nonvariceal upper gastrointestinal bleeding*. Curr Gastroenterol Rep, 2003; 5:476-81.

55. Palmer KR: *Non-variceal upper gastrointestinal haemorrhage: guidelines.* Gut, 2002; 51; iv1-iv6.

56. Robustelli U, Armellino MF, De Stefano G, et al.: *Surgical treatment of non-variceal upper gastrointestinal bleeding: our experience with 1482 patients.* Chir Ital, 2008; 60:535-40.

57. De la Fuente G, Shukri F, Tracy MS, et al.: *Comparative analysis of vagotomy and drainage versus vagotomy and resection procedures for bleeding peptic ulcer disease: Results of 907 patients from the department of veterans affairs national surgical quality improvement program database.* J Am Coll Surg, 2006; 202:78-86.

58. Mathis KL, Farley DR: *Operative management of symptomatic duodenal diverticula.* Am J Surg, 2007; 193:305-11.

59. Walker WE, Cooley DA, Duncan JM, et al.: *The management of aortoduodenal fistula by in situ replacement of the infected abdominal aortic graft.* Ann Surg, 1986; 205:727-32.

60. Kotsis T, Lioupis C, Tzanis A, et al.: *Endovscular repair of a bleeding secondary aortoenteric fistula with acute leg ischemia: A case report and review of the literature*. J Vasc Interv Radiol, 2006; 17:563-67.

61. Sarosi GA Jr, Jaiswal KR, Nwariaku FE, et al.: *Surgical therapy of peptic ulcers in the 21st century: more common than you think*. Am J Surg, 2005; 190:775-79.

62. Ward McQuaid JN, Pease JC, McEwen Smith A, et al.: *Surgery in bleeding peptic ulcers.* Gut, 1960; 1:258-65.

63. Schwesinger WH, Page CP, Sirinek KR, et al.: *Operations for peptic ulcer disease: Paradigm lost*. J Gastrointest Surg, 2001; 5:438-43.

64. Bulut OB, Rasmussen C, Fischer A; *Acute surgical treatment of complicated peptic ulcers with special reference to the elderly.* World J Surg, 1996; 20:574-77.

65. Guinier D, Destrumelle N, Denue PO, et al.: *Technique of antroduodenectomy without ulcer excision as a safe alternative treatment for bleeding chronic duodenal ulcers.* World J Surg, 2009; 33:1010-14

66. Paspatis GA, Konstantinidis K, Chalkiadakis I, et al.: *Changing trends in acute upper gastrointestinal bleeding in Crete, Greece: A population-based study.* Eur J Gastroenterol Hepatol, 2012; 24:102-03.

67. Zittel TT, Jehle EC, Becker HD*: Surgical management of peptic ulcer disease today: Indication, technique and* outcome. Langenbeck's Arch Surg, 2000; 385:84-96.

68. Reuben BC, Stoddard G, Glasgow R, et al.: *Trends and predictors for vagotomy when performing oversew of acute bleeding duodenal ulcer in the United States.* J Gastrointest Surg, 2007; 11:22-28.

69. Thon K, Ohmann C, Hengels KJ, et al.: *Peptic ulcer bleeding: Medical and surgical point of view. Results of a prospective interdisciplinary multicenter observational study. DUSUK Study Group.* Clin Investig, 1992; 70:1061-69.

70. Haffner JF, Jakobsen A, Flatmark AL: *Upper gastrointestinal bleeding in renal transplant recipients: The role of prophylactic gastric surgery.* World J Surg, 1983; 7:738-42.

71. Jamieson GG: *Current status of indications for surgery in peptic ulcer disease.* World J Surg, 2000; 24:256-58.

72. Ishikawa M, Ogata S, Harada M, et al.: *Changes in surgical strategies for peptic ulcers before and after the introduction of H2-receptor antagonists and endoscopic hemostasis*. Surg Today, 1995; 25:318-23.

73. Gustavsson S, Nyrén O: *Time trends in peptic ulcer surgery, 1956 to 1986. A nation-wide survey in Sweden.* Ann Surg, 1989; 210:704-09.

74. Robson AJ, Richards JM, Ohly N, et al.: *The effect of surgical subspecialization on outcomes in peptic ulcer disease complicated by perforation and bleeding.* World J Surg, 2008; 32:1456-461.

75. Paimela H, Oksala NK, Kivilaakso E.: *Surgery for peptic ulcer today. A study on incidence, methods and mortality in surgery for peptic ulcer in Finland between 1987 and 1999*. Dig Surg, 2004; 21:185-91.

76. Bardou M, Youssef M, Toubouti Y, et al.: *Newer endoscopic therapies decrease both re-bleeding and mortality in high risk patients with acute peptic ulcer bleeding: A series of meta-analyses.* Gastroenterology, 2003; 123:239-49.

77. Barkun A, Sabbah S, Enns R, et al.: *The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting.* Am J Gastroenterol, 2004; 99:12382-246.

78. Ohmann C, Imhof M, Roher HD, et al.: *Trends in peptic ulcer bleeding and surgical treatment.* World J Surg, 2000; 24:284-93.

79. Blocksom JM, Tokioka S, Sugawa C: *Current therapy for nonvariceal upper gastrointestinal bleeding.* Surg Endosc, 2004; 18:186-92.

80. Cheng CL, Liu NJ, Lee CS, et al.: *Endoscopic management of Dieulafoy lesions in acute nonvariceal upper gastrointestinal bleeding.* Dig Dis Sc,i 2004; 49:1139-144.

81. Miller AR, Farnell MB, Kelly KA, et al.: *Impact of therapeutic endoscopy on treatment of bleeding duodenal ulcers: 1980-1990.* World J Surg, 1995; 19:89-94.

82. Chiu PW, Lam CY, Lee SW, et al.: *Effect of scheduled second therapeutic endoscopy on peptic ulcer rebleeding: A prospective randomised trial.* Gut, 2003; 52:1403-407.

83. Laine L, McQuaid K*: Endoscopic therapy for bleeding ulcers: an evidence-based approach based on Meta-Analyses of Randomized Controlled Trials.* Clin Gastroenterol Hepatol, 2009; 7:33-47.

84. De Manzoni G, Catalano F, Festini M, Guglielmi A, Lombardo F, Knid R, Rodella L, Ruzzenenti A, Zerman: *Emorragia acuta da ulcera duodenale. Risultati del trattamento endoscopico del primo sanguinamento e delle recidive.* Ann It Chir, 2002; 73:387-96.

85. Scamporino A, Occhigrossi G, Iannetti A, Marenga G, Serafini G, Stagnitti F: *Trattamento endoscopico combinato iniezione di adrenalina e coagulazione con Plasma di Argon (APC) nel sanguinamento da ulcera peptica gastroduodenale.* Ann It Chir, 2001; 72:707-14.

86. Sarin N, Monga N, Adams PD: *Time to endoscopy and outcomes in upper gastrointestinal bleeding.* Can J Gastroenterol, 2000; 23:489-93.

87. Holme JB, Nielsen DT, Funch-Jensen P et al.: *Transcatheter arterial embolization in patients with bleeding duodenal ulcer: An alternative to surgery.* Acta Radiol, 2006; 47:244-47.

88. Farinella E, Ronca P, La Mura F, et al.: *Upper gastrointestinal massive bleeding successfully treated intra-operatively with a collagen and thrombin-based high-viscosity gel for haemostasis. Case report.* G Chir, 2010; 31:186-90.

89. Wong SK, Yu LM, Lau JY, et al.: *Prediction of therapeutic failure after adrenaline injection plus heater probe treatment in patients with bleeding peptic ulcer*. Gut, 2002; 50:322-25.

90. Loffroy R, Guiu B, D'Athis P, et al.: *Arterial embolotherapy for endoscopically unmanageable acute gastroduodenal hemorrhage: Predictors of early rebleeding.* Clin Gastroenterol Hepatol, 2009; 7:515-23.

91. Defreyne L, Vanlangenhove P, De Vos M, et al.: *Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage*. Radiology, 2001; 218:739-48.

92. Poultsides GA, Kim CJ, Orlando R, et al.: *Angiographic embolization for gastroduodenal hemorrhage: Safety, efficacy, and predictors of outcome.* Arch Surg, 2008; 14:457-61.

93. Nawawi O, Young N, So S*: Superselective coil embolization in gastrointestinal haemorrhage: Early experience. Australas Radiol, 2006; 50:21-26.*

94. Laine L, Peterson W: *Bleeding peptic ulcer.* New Engl J Med, 1994; 11:4-14.

95. Leontiadis GI, et al.: *Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding.* BMJ 2005; 330:568.

96. Chen IC, Hung MS, Chiu T, et al.: *Risk scoring system to predict need for clinical intervention for patient with nonvariceal upper gastrointestinal tract bleeding*. Am J Emerg Med 2007; 23:774-49.

97. Hearnshaw SA, Logan RF, Lowe D, et al.: *Acute upper gastrointestinal bleeding in the UK: Patient characteristics, diagnoses and outcomes in the 2007 UK audit.* Gut, 2011; 60:1327-335.

98. So JB, Yam A, Cheah WK, et al.: *Risk factors related to operative mortality and morbidity in patients undergoing emergency gastrectomy.* Br J Surg, 2000; 87:1702-07.

99. Egberts JH, Summa B, Schulz U, et al.: *Impact of preoperative physiological risk profile on postoperative morbidity and mortality after emergency operation of complicated peptic ulcer disease.* World J Surg, 2007; 31:1449-457.

100. Kocer B, Surmeli S, Solak C, et al.: *Factors affecting mortality and morbidity in patients with peptic ulcer perforation*. J Gastroenterol Hepatol, 2007; 22:565-70.

101. Imhof M, Epstein S, Ohmann C, et al.: *Poor late prognosis of bleeding peptic ulcer.* Langenbecks Arch Surg, 2007; 392:587-91.

102. Al-Naamani K, Alzadjali N, Barkun, et al.: *Does blood urea nitrogen level predict severity and high-risk endoscopic lesions in patients with nonvariceal upper gastrointestinal bleeding?* Can J Gastroenterol, 2008; 22:399-403.

103. Imperiale TF, Dominitz JA, Provenzale DT, et al.: *Predicting poor outcome from acute upper gastrointestinal hemorrhage.* Arch Intern Med, 2007; 176:1291-296.

104. Pongprasobchai S, Nimitvilai S, Chasawat J, et al.: *Upper gastrointestinal bleeding e.* World J Gastroenterol 2009; 15:1099-104.

105. Baradarian R, Ramdhaney S, Chapalamadugu R et al.: *Early intensive resuscitation of tiology score for predicting variceal and nonvariceal bleeding patients with upper gastrointestinal bleeding decreases mortality.* Am J Gastroenterol, 2004; 99:619-22.

106. Lim CH: *Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality.* Am J Gastroenterol, 2004; 99:2502-506.

107. Jairath V, Kahan BC, Logan RF et al.: *Red blood cell transfusion practice in patients presenting with acute upper gastrointestinal bleeding: A survey of 815 UK clinicians.* Transfusion, 2011; 51:1940-948.

108. Jairath V, Hearnshaw S, Brunskill SJ et al.: *Red cell transfusion for the management of upper gastrointestinal haemorrhage.* Cochrane Database Syst Rev 2010; 8:CD006613.

109. Towfigh S, Chandler C, Hines OJ et al.: *Outcomes from peptic ulcer surgery have not benefited from advances in medical therapy.* Am Surg, 2002; 68:385-89.

110. Lau JY, Sung JJ, Lee KK et al.: *Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers.* N Engl J Med, 2000; 343:310-16.

111. Lau JY, Leung WK, Wu JC et al.: *Omeprazole before endoscopy in patients with gastrointestinal bleeding.* N Engl J Med, 2007; 356:1631-40.

112. Sreedharan A, Martin J, Leontiadis GI, et al.: *Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding*. Cochrane Database Syst Rev, 2010; 7:CD005415.

113. Graham DY, Hepps KS, Ramirez FC et al.: *Treatment of Helicobacter pylori reduces the rate of bleeding inpeptic ulcer disease.* Scand J Gastroenterol, 1993; 28:939-42.

114. Sadic J, Borgström A, Manjer J, et al.: *Bleeding peptic ulcer - time trends in incidence, treatment and mortality in Sweden.* Aliment Pharmacol Ther, 2009; 30:392-98.

115. Smith BR, Stabile BE: *Emerging trends in peptic ulcer disease and damage control surgery in the H. pylori era.* Am Surg, 2005; 71:797-801.

116. Post PN, Kuipers EJ, Meijer GA: *Declining incidence of peptic ulcer but not of its complications: A nation-wide study in The Netherlands.* Aliment Pharmacol Ther, 2006; 23:1587-593.